PRODUCT MONOGRAPH

CUPRIMINE®

(penicillamine capsules, USP)

THERAPEUTIC CLASSIFICATION

CHELATING AGENT

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Date of Preparation:
June 15, 2005

Control#: 099232

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CHELATING AGENT

ACTION AND CLINICAL PHARMACOLOGY

As a chelating agent, penicillamine removes copper and lead from the body. In copper chelation, from *in vitro* studies which indicate that one atom of copper combines with two molecules of penicillamine, it would appear that one gram of penicillamine should be followed by the excretion of about 200 milligrams of copper; however, the actual amount excreted is about one percent of this. The manner in which lead is chelated is not known. It may be bound in the same way as copper.

Penicillamine also reduces excess cystine excretion in cystinuria. This is done, at least in part, by disulfide interchange between penicillamine and cystine, resulting in formation of penicillamine-cysteine disulfide, a substance that is much more soluble than cystine and is excreted readily.

Penicillamine interferes with the formation of cross-links between tropocollagen molecules and cleaves them when newly formed.

The mechanism of action of penicillamine in rheumatoid arthritis is unknown although it appears to suppress disease activity. Unlike cytotoxic immunosuppressants, penicillamine markedly lowers IgM rheumatoid factor but produces no significant depression in absolute levels of serum immunoglobulins.

Also, unlike cytotoxic immunosuppressants which act on both, penicillamine *in vitro* depresses T-cell activity but not B-cell activity.

In vitro, penicillamine dissociates macroglobulins (rheumatoid factor) although the relationship of the activity to its effect in rheumatoid arthritis is not known.

INDICATIONS AND CLINICAL USE

CUPRIMINE® (penicillamine capsules, USP) is indicated in the treatment of Wilson's disease, chronic lead poisoning, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. Available evidence suggests that CUPRIMINE® is not of value in ankylosing spondylitis. Because of the severe toxicity of this agent, penicillamine should never be used casually.

Wilson's Disease

Treatment has two objectives:

(1) to minimize dietary intake and absorption of copper.
(2) to promote excretion of copper deposited in tissues.

For the second objective, a copper chelating agent is used. Penicillamine is the only one of these agents that is orally effective.

In symptomatic patients, this treatment usually produces marked neurologic improvement, fading of Kayser-Fleisher rings, and gradual amelioration of hepatic dysfunction and psychic disturbances.

Clinical experience to date suggests that life is prolonged with the above regimen.

Noticeable improvement may not occur for one to three months. Occasionally, neurologic symptoms become worse during the initiation of therapy with

CUPRIMINE®. Despite this, the drug should not be discontinued permanently. Although temporary interruption may result in clinical improvement of the neurological symptoms, it carries an increased risk of developing a sensitivity reaction upon resumption of therapy (see PRECAUTIONS).

Treatment of asymptomatic patients has been carried out for over ten years. Symptoms and signs of the disease appear to be prevented indefinitely if daily treatment with CUPRIMINE® can be continued.

Chronic Lead Poisoning - CUPRIMINE® should be considered adjunctive to rigorous control of environmental exposure to lead.

When used in children with chronic lead poisoning, CUPRIMINE® should be used only if the children are asymptomatic, have blood lead levels between 50 and 80 µg/deciliter (1 dL = 100 mL) whole blood, and:

a) have an erythrocyte protoporphyrin level greater than 400 to 500 µg/dL erythrocytes, as determined by a standard free erythrocyte protoporphyrin method (bearing in mind that values differ according to the method used).

b) excrete excessive amounts of δ-aminolevulinic acid (normal = up to 2 mg/M^2/day), or of coproporphyrin (normal = 2 µg/kg/day), or both.

When using CUPRIMINE® to treat chronic lead poisoning in children, it is essential that whole blood lead levels be determined periodically during treatment.

CUPRIMINE® is recommended for use in adults with chronic lead poisoning.

Cystinuria

Conventional treatment is directed at keeping urinary cystine diluted enough to prevent stone formation, keeping the urine alkaline enough to dissolve as much cystine as possible, and minimizing cystine production by a diet low in methionine

(the major dietary precursor of cystine). Patients must drink enough fluid to keep urine specific gravity below 1.010, take enough alkali to keep urinary pH at 7.5 to 8, and maintain a diet low in methionine. This diet is not recommended in growing children and probably is contraindicated in pregnancy because of its low protein content (see PRECAUTIONS).

When these measures are inadequate to control recurrent stone formation, CUPRIMINE® may be used as additional therapy. When patients refuse to adhere to conventional treatment, CUPRIMINE® may be a useful substitute. It is capable of keeping cystine excretion to near normal values, thereby hindering stone formation and the serious consequences of pyelonephritis and impaired renal function that develop in some patients.

Bartter and colleagues depict the process by which penicillamine interacts with cystine to form penicillamine-cysteine mixed disulfide as:

CSSC	+	PS'	⇆	CS'	+ CSSP
PSSP	+	CS'	⇆	PS'	+ CSSP
CSSC	+	PSSP	⇆	2 CSSP	
CSSC	=	cystine			
CS'	=	deprotonated cysteine			
PSSP	=	penicillamine			
PS'	=	deprotonated penicillamine sulfhydryl			
CSSP	=	penicillamine-cysteine mixed disulfide			

In this process, it is assumed that the deprotonated form of penicillamine, PS', is the active factor in bringing about the disulfide interchange.

Rheumatoid Arthritis - Because CUPRIMINE® can cause severe adverse reactions, its use in rheumatoid arthritis should be restricted to patients who have severe, active disease and who have failed to respond to an adequate trial of conventional therapy. Even then benefit-to-risk ratio should be carefully considered. Other measures, such as rest, physiotherapy, salicylates, and corticosteroids, may need to be used in conjunction with CUPRIMINE® (see PRECAUTIONS).

CONTRAINDICATIONS

Except for the treatment of Wilson's disease or certain cases of cystinuria, use of penicillamine during pregnancy is contraindicated (see PRECAUTIONS).

Although breast milk studies have not been reported in animals or humans, mothers on therapy with penicillamine should not nurse their infants.

Patients with a history of penicillamine-related aplastic anemia or agranulocytosis should not be restarted on penicillamine (see PRECAUTIONS and ADVERSE REACTIONS).

Because of its potential for causing renal damage, penicillamine should not be administered to rheumatoid arthritis patients with a history or other evidence of renal insufficiency.

CUPRIMINE® (penicillamine capsules, USP) should not be given with chronic lead poisoning when there is x-ray evidence of lead-containing substances in the gastrointestinal tract. Treatment with the drug may be instituted after the gastrointestinal tract has been cleared of these substances. Studies in animals suggest that CUPRIMINE® may be ineffective, and possibly hazardous, if excessive oral ingestion of lead continues during administration of the drug.

Penicillamine should not be used in patients who are receiving gold therapy, antimalarial or cytotoxic drugs, oxyphenbutazone or phenylbutazone because these drugs are also associated with similar serious hematologic and renal adverse reactions. Patients who have had gold salt therapy discontinued due to a major toxic reaction may be at greater risk of serious adverse reactions with penicillamine but not necessarily of the same type.

WARNINGS

The use of penicillamine has been associated with fatalities due to certain diseases such as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome, and myasthenia gravis.

Because of the potential for serious hematological and renal adverse reactions to occur at any time, routine urinalysis, white and differential blood cell count, hemoglobin determination, and direct platelet count must be done every two weeks for at least the first six months of penicillamine therapy and monthly thereafter. Patients should be instructed to report promptly the development of signs and symptoms of granulocytopenia and/or thrombocytopenia such as fever, sore throat, chills, bruising or bleeding. The above laboratory studies should then be promptly repeated.

Leukopenia and thrombocytopenia have been reported to occur in up to five percent of patients during penicillamine therapy. Leukopenia is of the granulocytic series and may or may not be associated with an increase in eosinophils. A confirmed reduction in WBC below 3500 mandates discontinuance of penicillamine therapy. Thrombocytopenia may be on an idiosyncratic basis, with decreased or absent megakaryocytes in the marrow, when it is part of an aplastic anemia. In other cases the thrombocytopenia is presumably on an immune basis since the number of megakaryocytes in the marrow has been reported to be normal or sometimes increased. The development of a platelet count below 100,000, even in the absence of clinical bleeding, requires at least temporary cessation of penicillamine therapy. A progressive fall in either platelet count or WBC in three successive determinations, even though values are still within the normal range, likewise requires at least temporary cessation.

Proteinuria and/or hematuria may develop during therapy and may be warning signs of membranous glomerulopathy which can progress to a nephrotic syndrome. Close observation of these patients is essential. In some patients the proteinuria

disappears with continued therapy; in others, penicillamine must be discontinued. When a patient develops proteinuria or hematuria the physician must ascertain whether it is a sign of drug-induced glomerulopathy or is unrelated to penicillamine.

Rheumatoid arthritis patients who develop moderate degrees of proteinuria may be continued cautiously on penicillamine therapy, provided that quantitative 24-hour urinary protein determinations are obtained at intervals of one to two weeks. Penicillamine dosage should not be increased under these circumstances. Proteinuria which exceeds 1 g/24 hours, or proteinuria which is progressively increasing, requires either discontinuance of the drug or a reduction in the dosage. In some patients, proteinuria has been reported to clear following reduction in dosage.

In rheumatoid arthritis patients penicillamine should be discontinued if unexplained gross hematuria or persistent microscopic hematuria develops.

In patients with Wilson's disease or cystinuria the risks of continued penicillamine therapy in patients manifesting potentially serious urinary abnormalities must be weighed against the expected therapeutic benefits.

When penicillamine is used in cystinuria, an annual x-ray for renal stones is advised. Cystine stones form rapidly, sometimes in six months.

Up to one year or more may be required for any urinary abnormalities to disappear after penicillamine has been discontinued.

Because of rare reports of intrahepatic cholestasis and toxic hepatitis, liver function tests are recommended every six months for the duration of therapy.

Goodpasture's syndrome has occurred rarely. The development of abnormal urinary findings associated with hemoptysis and pulmonary infiltrates on x-ray requires immediate cessation of penicillamine.

Obliterative bronchiolitis has been reported rarely. The patient should be cautioned to report immediately pulmonary symptoms such as exertional dyspnea, unexplained cough or wheezing. Pulmonary function studies should be considered at that time.

Onset of new neurologic symptoms has been reported with CUPRIMINE® (see ADVERSE REACTIONS). Occasionally, neurologic symptoms become worse during initiation of therapy with CUPRIMINE® (see INDICATIONS AND CLINICAL USE). Myasthenic syndrome sometimes progressing to myasthenia gravis has been reported. Ptosis and diplopia, with weakness of the extraocular muscles, are often early signs of myasthenia. In the majority of cases, symptoms of myasthenia have receded after withdrawal of penicillamine.

Most of the various forms of pemphigus have occurred during treatment with penicillamine. Pemphigus vulgaris and pemphigus foliaceus are reported most frequently, usually as a late complication of therapy. The seborrhea-like characteristics of pemphigus foliaceus may obscure an early diagnosis. When pemphigus is suspected, CUPRIMINE® should be discontinued. Treatment has consisted of high doses of corticosteroids alone or, in some cases, concomitantly with an immunosuppressant. Treatment may be required for only a few weeks or months, but may need to be continued for more than a year.

Once instituted for Wilson's disease or cystinuria, treatment with penicillamine should, as a rule, be continued on a daily basis. Interruptions for even a few days have been followed by sensitivity reactions after reinstitution of therapy.

PRECAUTIONS

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

Should drug fever occur in patients receiving penicillamine, stop the drug. In patients with Wilson's disease, trientine hydrochloride (where available) or zinc compounds such as zinc sulfate may be tried. In patients with cystinuria, in whom these alternative agents are inappropriate, penicillamine should be temporarily discontinued until the reaction subsides. Then penicillamine should be reinstituted with a small dose that is gradually increased until the desired dosage is attained. Systemic steroid therapy may be necessary, and is usually helpful, in such patients in whom toxic reactions develop a second or third time.

In the case of drug fever in rheumatoid arthritis patients, because other treatments are available, penicillamine should be discontinued and another therapeutic alternative tried since experience indicates that the febrile reaction will recur in a very high percentage of patients upon readministration of penicillamine.

The skin and mucous membranes should be observed for allergic reactions. Early and late rashes have occurred. Early rash occurs during the first few months of treatment and is more common. It is usually a generalized pruritic, erythematous, maculopapular or morbilliform rash and resembles the allergic rash seen with other drugs. Early rash usually disappears within days after stopping penicillamine and seldom recurs when the drug is restarted at a lower dosage. Pruritus and early rash may often be controlled by the concomitant administration of antihistamines. Less commonly, a late rash may be seen, usually after six months or more of treatment, and requires discontinuation of penicillamine. It is usually on the trunk, is accompanied by intense pruritus, and is usually unresponsive to topical corticosteroid therapy. Late rash may take weeks to disappear after penicillamine is stopped and usually recurs if the drug is restarted.

The appearance of a drug eruption accompanied by fever, arthralgia, lymphadenopathy or other allergic manifestations usually requires discontinuation of penicillamine.

Certain patients will develop a positive antinuclear antibody (ANA) test and some of these may show a lupus erythematosus-like syndrome similar to drug-induced lupus associated with other drugs. The lupus erythematosus-like syndrome is not associated with the hypocomplementemia and may be present without nephropathy. The development of a positive ANA test does not mandate discontinuance of the drug; however, the physician should be alerted to the possibility that a lupus erythematosus-like syndrome may develop in the future.

Some patients may develop oral ulcerations which in some cases have the appearance of aphthous stomatitis. The stomatitis usually recurs on rechallenge but often clears on a lower dosage. Although rare, cheilosis, glossitis and gingivostomatitis have also been reported. These oral lesions are frequently dose-related and may preclude further increase in penicillamine dosage or require discontinuation of the drug.

Hypogeusia (a blunting or diminution in taste perception) has occurred in some patients. This may last two to three months or more and may develop into a total loss of taste; however, it is usually self-limited despite continued penicillamine treatment. Such taste impairment is rare in patients with Wilson's disease.

Patients who are allergic to penicillin may theoretically have cross-sensitivity to penicillamine. The possibility of reactions from contamination of penicillamine by trace amounts of penicillin, has been eliminated now that penicillamine is being produced synthetically rather than as a degradation product of penicillin.

Because of their dietary restrictions, patients with Wilson's disease and cystinuria should be given 25 mg/day of pyridoxine during therapy, since penicillamine increases the requirement for this vitamin. Patients also may receive benefit from a multivitamin preparation, although there is no evidence that deficiency of any vitamin other than pyridoxine is associated with penicillamine. In Wilson's disease, multivitamin preparations must be copper-free.

Rheumatoid arthritis patients whose nutrition is impaired should also be given a daily supplement of pyridoxine. Mineral supplements should not be given, since they may block the response to penicillamine.

Iron deficiency may develop, especially in children and in menstruating women. In Wilson's disease, this may be a result of adding the effects of the low copper diet, which is probably also low in iron, and the penicillamine to the effects of blood loss or growth. In cystinuria, a low methionine diet may contribute to iron deficiency, since it is necessarily low in protein. If necessary, iron may be given in short courses, but a period of two hours should elapse between administration of penicillamine and iron, since orally administered iron has been shown to reduce the effects of penicillamine.

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 may be the cause of increased skin friability at sites especially subject to pressure or trauma, such as shoulders, elbows, knees, toes, and buttocks. Extravasations of blood may occur and may appear as purpuric areas, with external bleeding if the skin is broken, or 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 penicillamine may be continued in the presence of these lesions. They may not recur if dosage is reduced.

Other reported effects probably due to the action of penicillamine on collagen are excessive wrinkling of the skin and development of small, white papules at venipuncture and surgical sites.

The effects of penicillamine on collagen and elastin make it advisable to consider a reduction in dosage to 250 mg/day, when surgery is contemplated. Reinstitution of full therapy should be delayed until wound healing is complete.

Tumorigenicity - Long-term animal carcinogenicity studies have not been done with penicillamine. There is a report that five of ten autoimmune disease-prone NZB hybrid mice developed lymphocytic leukemia after 6 months' intraperitoneal treatment with a dose of 400 mg/kg penicillamine 5 days per week.

Use in Children - The efficacy of CUPRIMINE® (penicillamine capsules, USP) in juvenile rheumatoid arthritis has not been established.

Use in Obstetrics - Penicillamine has been shown to be teratogenic in rats when given in doses 6 times higher than the highest dose recommended for human use. Skeletal defects, cleft palates and fetal toxicity (resorptions) have been reported.

There are no controlled studies on the use of penicillamine in pregnant women. Although normal outcomes have been reported, characteristic congenital cutis laxa and associated birth defects have been reported in infants born of mothers who received therapy with penicillamine during pregnancy. Penicillamine should be used in women of childbearing potential only when the expected benefits outweigh the possible hazards. Women on therapy with penicillamine who are of childbearing potential should be apprised of this risk and followed closely for early recognition of pregnancy.

Wilson's Disease - Reported experience[1] shows that continued treatment with penicillamine throughout pregnancy protects the mother against relapse of the Wilson's disease, and that discontinuation of penicillamine has deleterious effects on the mother.

If penicillamine is administered during pregnancy to patients with Wilson's disease, it is recommended that the daily dosage be limited to 1 g. If cesarean section is planned, the daily dosage should be limited to 250 mg during the last six weeks of pregnancy and postoperatively until wound healing is complete.

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[1] Scheinberg IH, Sternlieb I. N Engl J Med 1975;293:1300-1302.

Cystinuria - If possible, penicillamine should not be given during pregnancy to women with cystinuria (see CONTRAINDICATIONS). There are reports of women with cystinuria on therapy with penicillamine who gave birth to infants with generalized connective tissue defects who died following abdominal surgery. If stones continue to form in these patients, the benefits of therapy to the mothers must be evaluated against the risk to the fetus.

Rheumatoid Arthritis - Penicillamine should not be administered to rheumatoid arthritis patients who are pregnant and should be discontinued promptly in patients in whom pregnancy is suspected or diagnosed.

There is a report that a woman with rheumatoid arthritis treated with less than one gram a day of penicillamine during pregnancy gave birth (cesarean delivery) to an infant with growth retardation, flattened face with broad nasal bridge, low set ears, short neck with loose skin folds, and unusually lax body skin.
Nursing Mothers - See CONTRAINDICATIONS.

ADVERSE REACTIONS

Penicillamine is a drug with a high incidence of untoward reactions, some of which are potentially fatal. Therefore, it is mandatory that patients receiving penicillamine therapy remain under close medical supervision throughout the period of drug administration (see PRECAUTIONS).

Reported incidences (%) for the most commonly occurring adverse reactions in **rheumatoid arthritis** patients are noted, based on 17 representative clinical trials reported in the literature (1270 patients).

Allergic - Generalized pruritus, early and late rashes (5%), pemphigoid-type reactions, and drug eruptions which may be accompanied by fever, arthralgia, or lymphadenopathy have occurred (see PRECAUTIONS). Some patients may show

a lupus erythematosus-like syndrome similar to drug-induced lupus produced by other pharmacological agents (see WARNINGS and PRECAUTIONS).

Urticaria and exfoliative dermatitis have occurred.

Thyroiditis has been reported; hypoglycemia in association with anti-insulin antibodies has been reported. These reactions are extremely rare.

Some patients may develop a migratory polyarthralgia, often with objective synovitis (see DOSAGE AND ADMINISTRATION).

Gastrointestinal - Anorexia, epigastric pain, nausea, vomiting, or occasional diarrhea may occur (17%).

Isolated cases of reactivated peptic ulcer have occurred, as have hepatic dysfunction and pancreatitis. Intrahepatic cholestasis and toxic hepatitis have been reported rarely. There have been a few reports of increased serum alkaline phosphatase, lactic dehydrogenase, and positive cephalin flocculation and thymol turbidity tests.

Some patients may report a blunting, diminution, or total loss of taste perception (12%); or may develop oral ulcerations. Although rare, cheilosis, glossitis, and gingivostomatitis have been reported (see PRECAUTIONS).

Gastrointestinal side effects are usually reversible following cessation of therapy.

Hematological - Penicillamine can cause bone marrow depression (see WARNINGS). Leukopenia (2%) and thrombocytopenia (4%) have occurred. Fatalities have been reported as a result of thrombocytopenia, agranulocytosis, aplastic anemia, and sideroblastic anemia.

Thrombotic thrombocytopenic purpura, hemolytic anemia, red cell aplasia, monocytosis, leukocytosis, eosinophilia, and thrombocytosis have also been reported.

Renal - Patients on penicillamine therapy may develop proteinuria (6%) and/or hematuria which, in some, may progress to the development of the nephrotic syndrome as a result of an immune complex membranous glomerulopathy (see WARNINGS).

Central Nervous System - Tinnitus, optic neuritis and peripheral sensory and motor neuropathies (including polyradiculoneuropathy, i.e., Guillain-Barré Syndrome) have been reported. Muscular weakness may or may not occur with the peripheral neuropathies. Visual and psychic disturbances; mental disorders; and agitation and anxiety have been reported.

Neuromuscular - Myasthenia gravis (see PRECAUTIONS); dystonia.

Other - Side effects that have been reported rarely include thrombophlebitis; hyperpyrexia (see PRECAUTIONS); falling hair or alopecia; lichen planus; (see WARNINGS); polymyositis; dermatomyositis; mammary hyperplasia; elastosis perforans serpiginosa; toxic epidermal necrolysis; anetoderma (cutaneous macular atrophy); and Goodpasture's syndrome, a severe and ultimately fatal glomerulonephritis associated with intra-alveolar hemorrhage (see WARNINGS). Fatal renal vasculitis has also been reported. Allergic alveolitis, obliterative bronchiolitis, interstitial pneumonitis and pulmonary fibrosis have been reported in patients with severe rheumatoid arthritis, some of whom were receiving penicillamine. Bronchial asthma also has been reported.

Increased skin friability, excessive wrinkling of skin, and development of small white papules at venipuncture and surgical sites have been reported (see PRECAUTIONS).

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There are no known instances of acute poisoning with penicillamine. In therapeutic doses, however, it may cause a wide variety of adverse reactions. Penicillamine may cause acute sensitivity reactions early in therapy. Cross sensitivity with penicillin may exist.

Treatment

In general, treatment is symptomatic.

Allergic Reactions

Discontinue penicillamine promptly and treat the patient with glucocorticoids, followed by reinstitution of penicillamine in small doses that are increased gradually to the desired amount.

Iron and Pyridoxine Deficiencies

Iron and pyridoxine supplementation.

Impairment of Taste

5-10 mg of copper a day can be administered as 5-10 drops of a 4% solution of $CuSO_4 5H_2O$ in fruit juice twice a day. (Do not give copper to patients with Wilson's disease.)

DOSAGE AND ADMINISTRATION

Physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special dosage considerations, and therapeutic benefits. Penicillamine should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to report promptly any symptoms suggesting toxicity.

In all patients receiving penicillamine, it is important that CUPRIMINE® (penicillamine capsules, USP) 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. This permits maximum absorption and reduces the likelihood of inactivation by metal binding.

Wilson's Disease - Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. The urine must be collected in copper-free glassware, and should be quantitatively analyzed for copper before, and soon after, initiation of therapy with CUPRIMINE®.

Determination of 24-hour urinary copper excretion is a greatest value in the first week of therapy with penicillamine. In the absence of any drug reaction, a dose between 0.75 and 1.5 g that results in an initial 24-hour cupruresis of over 2 mg should be continued for about three months, by which time the most reliable method of monitoring maintenance treatment is the determination of free copper in the serum. This equals the difference between quantitatively determined total copper and ceruloplasmin-copper. Adequately treated patients will usually have less than 10 µg free copper/dL of serum. It is seldom necessary to exceed a dosage of 2 g/day. If the patient is intolerant to therapy with CUPRIMINE®, alternative treatment is trientine hydrochloride (where available) or zinc compounds such as zinc sulfate.

In patients who cannot tolerate as much as 1 g/day initially, initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug and may help to reduce the incidence of adverse reactions.

Chronic Lead Poisoning - CUPRIMINE® should be given when the gastrointestinal tract is empty of lead - containing substances. It may be given to children by dissolving the contents of the capsules no longer than five minutes before administration in a small amount of chilled purée de fruits or fruit juice.

For **children**, the recommended dosage is 30 to 40 mg/kg/day, or 600 to 750 mg/M^2/day, not to exceed 750 mg a day. CUPRIMINE® may be given to children as a single dose or in two divided doses at least two hours before meals. Treatment should be continued until blood lead levels remain below 40 µg/dL whole blood for two consecutive months and at least one of the following is achieved:

a. erythrocyte protoporphyrin level decreases to less than three to five times the average normal level
b. excretion of δ-aminolevulinic acid decreases to upper limit of normal
c. excretion of coproporphyrin decreases to upper limit of normal.

For **adults**, the recommended dosage is 900 to 1500 mg a day, in three divided doses for one to two weeks, followed by 750 mg a day in divided doses until blood lead levels are reduced to 60 µg/dL, or until urinary lead excretion remains below 500 µg/L for two consecutive months. All doses should be given at least two hours before meals.

Cystinuria - It is recommended that CUPRIMINE® be used along with conventional therapy. By reducing urinary cystine, it decreases crystalluria and stone formation. In some instances, it has been reported to decrease the size of, and even to dissolve, stones already formed.

The usual dosage of CUPRIMINE® in the treatment of cystinuria is 2 g/day for adults, with a range of 1 to 4 g/day. For children, dosage can be based on 30 mg/kg/day. The total daily amount should be divided into four doses. If four equal doses are not feasible, give the larger portion at bedtime. If adverse reactions necessitate a reduction in dosage, it is important to retain the bedtime dose.

Initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug and may help to reduce the incidence of adverse reactions.

In addition to taking CUPRIMINE®, patients should drink copiously. It is especially important to drink about a pint (½ liter) of fluid at bedtime and another pint (½ liter) once during the night when urine is more concentrated and more acid than during the day. The greater the fluid intake, the lower the required dosage of CUPRIMINE®.

Dosage must be individualized to an amount that limits cystine excretion to 100-200 mg/day in those with no history of stones, and below 100 mg in those who have had stone formation and/or pain. Thus, in determining dosage, the inherent tubular defect, the patient's size, age and rate of growth, and his diet and water intake all must be taken into consideration.

The standard nitroprusside cyanide test has been reported useful as a qualitative measure of the effective dose. Add 2 mL of freshly prepared 5% sodium cyanide to 5 mL of a 24-hour aliquot of protein-free urine and let stand ten minutes. Add 5 drops of freshly prepared 5% sodium nitroprusside and mix. Cystine will turn the mixture magenta. If the result is negative, it can be assumed that cystine excretion is less than 100 mg/g creatinine.

Although penicillamine is rarely excreted unchanged, it also will turn the mixture magenta. If there is any question as to which substance is causing the reaction, a ferric chloride test can be done to eliminate doubt: Add 3% ferric chloride dropwise

to the urine. Penicillamine will turn the urine an immediate and quickly fading blue. Cystine will not produce any change in appearance.

Rheumatoid Arthritis - In rheumatoid arthritis, the onset of therapeutic response to CUPRIMINE® may not be seen for two or three months. In those patients who respond, however, the first evidence of suppression of symptoms such as pain, tenderness, and swelling is generally apparent within three months. The optimum duration of therapy has not been determined. If remissions occur, they may last from months to years, but usually require continued treatment.

In patients with rheumatoid arthritis, it is important that CUPRIMINE® be given on an empty stomach, at least one hour before meals and at least one hour apart from any other drug, food, or milk. This permits maximum absorption and reduces the likelihood of inactivation by metal binding.

When treatment with CUPRIMINE® has been interrupted because of adverse reactions or other reasons, the drug should be reintroduced cautiously by starting with a lower dosage and increasing slowly.

Initial Therapy -The recommended dosage regimen in rheumatoid arthritis begins with a single daily dose of 125 mg to 250 mg which is thereafter increased at one to three month intervals, by 125 mg to 250 mg/day, as patient response and tolerance indicates. If a satisfactory remission of symptoms is achieved, the dose associated with the remission should be continued (see **Maintenance Therapy**). If there is no improvement and there are no signs of potentially serious toxicity after two to three months of treatment with doses of 500-750 mg/day, increases of 125 mg to 250 mg/day at two to three month intervals may be continued until a satisfactory remission occurs (see **Maintenance Therapy**) or signs of toxicity develop (see WARNINGS and PRECAUTIONS). If there is no discernible improvement after three to four months of treatment with 1000 to 1500 mg of penicillamine/day, it may be assumed the patient will not respond and CUPRIMINE® should be discontinued.

Maintenance Therapy - The maintenance dosage of CUPRIMINE® must be individualized, and may require adjustment during the course of treatment. Many patients respond satisfactorily to a dosage within the 500-750 mg/day range. Some need less.

Changes in maintenance dosage levels may not be reflected clinically or in the erythrocyte sedimentation rate for two to three months after each dosage adjustment.

Some patients will subsequently require an increase in the maintenance dosage to achieve maximal disease suppression. In those patients who do respond, but who evidence incomplete suppression of their disease after the first six to nine months of treatment, the daily dosage of CUPRIMINE® may be increased by 125 mg to 250 mg/day at three-month intervals. It is unusual in current practice to employ a dosage in excess of 1 g/day, but up to 1.5 g/day has sometimes been required.

Management of Exacerbation - During the course of treatment some patients may experience an exacerbation of disease activity following an initial good response. These may be self-limited and can subside within twelve weeks. They are usually controlled by the addition of nonsteroidal anti-inflammatory drugs, and only if the patient has demonstrated a true "escape" phenomenon (as evidenced by failure of the flare to subside within this time period) should an increase in the maintenance dose ordinarily be considered.

In the rheumatoid patient, migratory polyarthralgia due to penicillamine is extremely difficult to differentiate from an exacerbation of the rheumatoid arthritis. Discontinuance or a substantial reduction in dosage of CUPRIMINE® for up to several weeks will usually determine which of these processes is responsible for the arthralgia.

Duration of Therapy - The optimum duration of therapy with CUPRIMINE® in rheumatoid arthritis has not been determined. If the patient has been in remission

for six months or more, a gradual, stepwise dosage reduction in decrements of 125 mg to 250 mg/day at approximately three month intervals may be attempted.

Concomitant Drug Therapy - CUPRIMINE® should not be used in patients who are receiving gold therapy, antimalarial or cytotoxic drugs, oxyphenbutazone, or phenylbutazone (see CONTRAINDICATIONS). Other measures, such as salicylates, other non-steroidal anti-inflammatory drugs, or systemic corticosteroids, may be continued when penicillamine is initiated. After improvement commences, analgesic and anti-inflammatory drugs may be slowly discontinued as symptoms permit. Steroid withdrawal must be done gradually, and many months of treatment with CUPRIMINE® may be required before steroids can be completely eliminated.

Dosage Frequency - Based on clinical experience, dosages up to 500 mg/day can be given as a single daily dose. Dosages in excess of 500 mg/day should be administered in divided doses.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

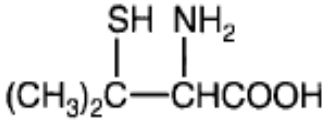
Proper name: penicillamine

Chemical Name: 3-mercapto-D-valine

Chemical Structure: $C_5H_{11}NO_2S$

Structural Formula:

.



Molecular Weight: 149.21

Description:

Penicillamine is a white or practically white, crystalline powder, freely soluble in water, slightly soluble in alcohol, and insoluble in ether, acetone, benzene, and carbon tetrachloride. Although its configuration is D, it is levorotatory as usually measured:

$$[\alpha]_D25° = -63° \pm 5° \text{ (C = 1, 1N NaOH).}$$

It reacts readily with formaldehyde or acetone to form a thiazolidine-carboxylic acid.

Methodology for determining the bioavailability of penicillamine is not available; however, penicillamine is known to be very soluble substance.

II. COMPOSITION

Each capsule contains either 125 mg or 250 mg of penicillamine, and the following non-medicinal ingredients:

D & C Yellow 10,
gelatin,
lactose,
magnesium stearate,
and titanium dioxide.

The 125 mg capsule also contains iron oxide.

AVAILABILITY OF DOSAGE FORMS

Capsules CUPRIMINE® 250 mg have an ivory opaque cap and an ivory opaque body imprinted radially with MSD 602 and CUPRIMINE respectively. Available in bottles of 100.

Capsules CUPRIMINE® 125 mg have a gray opaque cap and an ivory opaque body imprinted radially with MSD 672 and CUPRIMINE respectively. Available in bottles of 100.

PHARMACOLOGY

General Pharmacology

D-penicillamine was tested both *in vivo* and *in vitro* for general pharmacologic effects and had little or no activity.

A. Central Nervous System (CNS) Effects

D-penicillamine had no behavioural or CNS activity in a battery of screening tests in mice at a dose of 4 to 324 mg/kg. The compound had no analgesic effect at an oral dose of 128 mg/kg in rats made hyperesthesic with brewer's yeast. In two schedules of reinforcement in rats, D-penicillamine had no significant effect on responding in a chained schedule or on a schedule of continuous reinforcement.

B. Gastrointestinal Effects

D-penicillamine produced only a slight inhibition of titratable acidity in dogs with chronic gastric fistula at an oral dose of 16 to 21 mg/kg, gastric volume was not changed. Vomiting occurred in 3 of 5 dogs during these studies. At a dose of 32 mg/kg p.o., the compound had no effect in gastric secretion in pylorus-ligated rats. D-penicillamine (30 mg/kg p.o.) had no protective effect against stress-induced ulcers in rats.

C. Studies for Cardiovascular and Renal Activity

D-penicillamine caused an increase in 5-hour electrolyte excretion only in 1 of 3 experiments at an oral dose of 100 mg/kg p.o. and was considered inactive. In renal hypertensive rats, D-penicillamine was inactive orally (80 mg/kg) or intraperitoneally (40 mg/kg) in lowering systolic blood pressure. The compound had no significant protective effect against arrhythmia produced by experimental coronary infarction in dogs, or ouabain mortality in rabbits. Penicillamine was essentially inactive *in vitro* in preventing collagen-induced platelet aggregation in samples of human and guinea pig blood. D-penicillamine had no fibrinolytic activity *in vitro* as measured by lysis of human fibrin clots.

Three samples of D-penicillamine had negligible penicillin activity as measured by inhibition of *S. lutea*. D-penicillamine had no inhibitory effect on carbonic anhydrase *in vitro* and had no effect on dopamine B-hydroxylase *in vitro* in mice as measured by heart and brain norepinephrine or dopamine concentration.

TOXICOLOGY

Acute Toxicity (LD_{50})

Species - Strain	Sex	Route	LD_{50}(g/kg)
Mouse-Carworth Farms - CF_1	F	p.o.	10.8
	F	i.v.	5.27
Rat - Charles River Wistar	M	p.o.	14.00
	F	p.o.	10.5
	M	i.p.	3.51
	F	i.p.	3.34
Rabbit	F	i.v.	>0.8

Subacute Toxicity

Administration for 1-4 weeks of an average dose of D-penicillamine 50 mg/kg to rats or of a high dose of 250 mg/kg did not produce any noteworthy inhibition of RNA synthesis in cell nuclei or affect cell-free protein synthesis while the L-isomer at the same doses produced a dose-dependent inhibition.

Rabbits with experimental allergic arthritis following 40 days of combined treatment with D-penicillamine at 30 mg/kg plus vitamin B complex showed signs of inhibition of the maturation of myelopoiesis in the bone marrow. In addition, slight toxic changes in the liver and severe renal lesions resembling membranous proliferative glomerulonephritis were observed.

Subacute oral studies in the dog were complicated by emesis. Pathologic changes related to treatment were not observed at an oral dose of 25 mg/kg b.i.d. for 14

weeks. The intravenous administration of 1 to 10 doses of 50 to 600 mg/kg/day were not tolerated resulting in ptyalism, emesis, total anorexia, weight loss, and death or sacrifice. There were no pathologic changes related to treatment.

Chronic Toxicity

In oral chronic toxicity studies, male and female rats were given D-penicillamine at doses of 25, 125, 500, and 625 mg/kg/day for six months. Additional groups of animals at the same dosage levels were given pyridoxine as a supplement in the diet since D-penicillamine causes pyridoxine deficiency in animals. Pyridoxine supplementation prevented this deficiency as determined by tryptophan challenge. Rats at the highest dosage level developed abdominal hernias, softening of the bone (which was not related to calcium content), discolouration of the scrotum, and a friable, easily injured skin. These effects have been attributed to an increase in soluble collagen with a corresponding decrease in tensile strength. There was a decrease in body weight gain at the high dose level. In earlier studies, a reversible prolongation of bleeding time was observed in subacute studies in rats.

Male and female rhesus monkeys were given oral doses of D-penicillamine of 30, 60, 90, and 180 mg/kg/day for 6 months.

In Drug Week 4, marked signs of toxicity developed in one-third of the monkeys treated with 60, 90, or 180 mg/kg/day. Signs of toxicity included anorexia, pale extremities, watery stools, edema, increased ESR, marked elevations in serum urea nitrogen, hypoalbuminemia, decreases in serum sodium and chloride, muscle weakness, and hyperkalemia. Monkeys with severe toxicity were killed in Drug Week 4 and dosing was discontinued for 9 days at these dose levels. An additional monkey treated with 90 mg/kg/day died in Drug Week 16 after showing the above signs. Survivors in groups 90 and 180 mg/kg/day showed soft stools, weight loss, anemia, leukopenia, hypogammaglobulinemia, and decrease in alkaline phosphatase activity. Pathology studies showed treatment related changes in non-survivors of tubular nephrosis in the kidney, depletion of lymphoid elements in the spleen, lymph nodes and thymus, erythroid atrophy and myeloid hyperplasia of the

bone marrow and hypertrophy of adrenal zona fasiculata. The incidence and degree of renal tubular necrosis contributed to the poor condition or death of these animals. These monkeys also had greater amounts of IgG deposition in the glomeruli.

Surviving monkeys showed hyperplasia of the lymphoid elements in the spleen, lymph node, thymus, and bone marrow. Focal lymphoid cellular infiltration occurred in several organs at all dose levels.

An 11-week study in monkeys of a comparison of synthetically-derived and D-penicillamine derived from fermentation, yielded results similar to the 27-week study. No differences in toxicity were observed between synthetically-derived material and material derived by fermentation.

Tumorigenicity

Long-term animal carcinogenicity studies have not been done with penicillamine. There is a report that five of ten autoimmune disease-prone NZB hybrid mice developed lymphocytic leukemia after 6 months' intraperitoneal treatment with a dose of 400 mg/kg penicillamine 5 days per week.

Teratogenicity

Penicillamine has been shown to be teratogenic in rats when given in doses several times higher than the highest dose recommended for human use. Skeletal defects, cleft palates and fetal toxicity (resorptions) have been reported.

REFERENCES

1. Andrews FM, Golding DN, Freeman AM, Golding JR, Day AT, Hill AGS, Camp AV, et al. Controlled Trial of D(-)Penicillamine in Severe Rheumatoid Arthritis. Lancet 1973;1:275-80.

2. Bartter FC, Lotz M, Thier S, Rosenberg LE, Potts JT. Cystinuria. Combined Clinical Staff Conference at the National Institutes of Health. Ann Intern Med 1965; 62:796-822.

3. Chisolm JJ Jr. Treatment of Lead Poisoning. Mod Treatment 1971;8:593-612.

4. Chisolm JJ Jr, Brown DH. Micro-Scale Photofluorometric Determination of "Free Erythrocyte Porphyrin" (Protoporphyrin IX). Clin Chem 1975;21:1669-82.

5. Crawhall JC, Scowen EF, Thompson CJ, Watts RWE. Dissolution of Cystine Stones during D-Penicillamine Treatment of a Pregnant Patient with Cystinuria. Br Med J 1967;1:216-18.

6. Dixon A St J, Davies J, Dormandy TL, Hamilton EBD, Holt PJL, Mason RM, Thompson M, Weber JCP, Zutshi DW. Synthetic D(-)Penicillamine in Rheumatoid Arthritis: Double-Blind Controlled Study of a High and Low Dosage Regimen. Ann Rheum Dis 1975;34:416-21.

7. Frimpter GW. Medical Management of Cystinuria. Am J Med Sci 1968;255:348-57.

8. Goldstein NP, Tauxe WN, McCall JT, Randall RV, Gross JB. What Wilson's Disease and its Treatment Have Taught us about the Metabolism of Copper. Observations in 27 cases. Med Clin North Am 1968;52:989-1001.

9. Henkin RI, Keiser HR, Jaffe IA, Sternlieb I, Scheinberg IH. Decreased Taste Sensitivity after D-Penicillamine Reserved by Copper Administration, Lancet 1967;2:1268-1271.

10. Huskisson EC, Hart FD. Penicillamine in the Treatment of Rheumatoid Arthritis. Ann Rheum Dis 1972;31:402-404.

11. Huskisson EC, Gibson TJ, Balme HW, Berry H, Burry HC, Grahame R, Hart FD, et al. Trial Comparing D-Penicillamine and Gold in Rheumatoid Arthritis. Preliminary Report. Ann Rheum Dis 1974;33:532-35.

12. Jaffe IA. D-Penicillamine. Bull Rheum Dis 1977-78;28:6.

13. Lotz M, Potts JT, Bartter FC. Rapid, Simple Method for Determining Effectiveness of D-Penicillamine Therapy in Cystinuria. Br Med J 1965;2:521.

14. MacDonald WB, Fellers FX. Penicillamine in the Treatment of Patients with Cystinuria. J Am Med Assoc 1966;197: 396-402.

15. Mjolnerod OK, Rasmussen Dommerud SA, Gjerluldsen ST. Congenital Connective-Tissue Defect Probably due to D-Penicillamine Treatment in Pregnancy. The Lancet 1971; 1:673.

16. Morell AG, Windsor J, Sternlieb I, Scheinberg IH. Measurement of the Concentration of Ceruloplasmin in Serum by Determination of its Oxidase Activity. In: Sunderman FW, Sunderman FW Jr, eds. Laboratory Diagnosis of Liver Diseases. St. Louis, Warren H. Green, Inc., 1968;193-95.

17. Sassa S, Granick JL, Granick S, Kappas A, Levere RD. Studies in Lead Poisoning - I. Microanalysis of Erythrocyte Protoporphyrin Levels by Spectrofluorometry in the Detection of Chronic Lead Intoxication in the Subclinical Range. Biochem Med 1973;8:135-48.
II. Correlation Between the Ratio of Activated to Inactivated-Aminolevulinic Acid Dehydratase of Whole Blood and the Blood Lead Level. Biochem Med 1973;8:149-59.

18. Scheinberg IH, Sternlieb I. The Long-Term Management of Hepatolenticular Degeneration (Wilson's Disease). Am J Med 1960;29:316-33

19. Scheinberg IH, Sternlieb I. Pregnancy in Penicillamine-Treated Patients with Wilson's Disease. N Engl J Med 1975;293:1300-1302.

20. Solomon L, Abrams G, Dinner M, Berman L. Neonatal Abnormalities Associated with D-Penicillamine Treatment During Pregnancy. N Engl J Med 1977;296:54-5.

21. Sternlieb I, Scheinberg IH. Prevention of Wilson's Disease in Asymptomatic Patients. N Engl J Med 1968; 278:352-59.

22. Sternlieb I, Scheinberg IH. Penicillamine Therapy for Hepatolenticular Degeneration. J Am Med Assoc 1967; 189:748-54.

23. Walshe JM. Treatment of Wilson's Disease with Penicillamine. Lancet 1960;1:188-92.