

PRODUCT MONOGRAPH

PrCUPRIMINE®
Penicillamine Capsules, USP
250 mg

Chelating Agent

Bausch Health, Canada Inc
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Laval, Quebec
H7L 4A8

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PrCUPRIMINE®
Penicillamine Capsules, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Capsules 250 mg	Lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

CUPRIMINE (penicillamine capsules, USP) is indicated for:

- 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 WARNINGS AND 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 mcg/deciliter (1 dL = 100 mL) whole blood, and:

- a) have an erythrocyte protoporphyrin level greater than 400 to 500 mcg/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/M²/day), or of coproporphyrin (normal = 2 mcg/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.

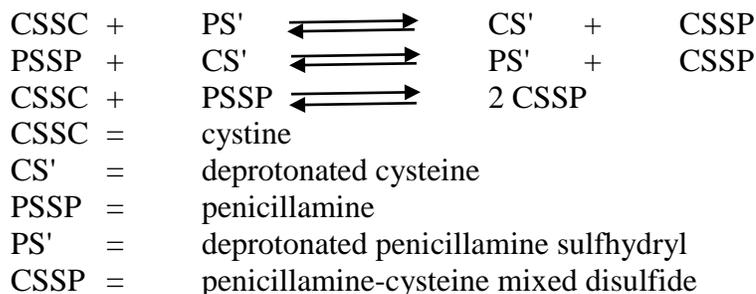
CUPRIMINE is recommended for use in adults with chronic lead poisoning.

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 WARNINGS AND 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:



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 WARNINGS AND PRECAUTIONS).

Geriatrics

Clinical studies of CUPRIMINE are limited in subjects aged 65 and over; they did not include sufficient numbers of elderly subjects aged 65 and over to adequately determine whether they respond differently from younger subjects. Review of reported clinical trials with penicillamine in the elderly (>65 years of age) showed a statistically significant increase in the frequency of minor and serious skin rash and serious abnormality of taste than in younger patients in 1 clinical trial. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drugs.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and careful monitoring of renal function is recommended.

Pediatrics

(see WARNINGS AND PRECAUTIONS, Pediatrics).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING

section of the product monograph.

- Pregnancy. Exceptions to this contraindication include the treatment of Wilson's disease or certain cases of cystinuria. (see WARNINGS AND 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 WARNINGS AND 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 AND PRECAUTIONS

General

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.

Carcinogenesis and Mutagenesis

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.

Endocrine and Metabolism

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.

Gastrointestinal

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.

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.

Genitourinary

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 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.

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.

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.

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

Hepatic/Biliary/Pancreatic

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

Immune

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 reinstated 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 re-administration 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.

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.

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.

Neurologic

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.

Peri-Operative Considerations

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.

Respiratory

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.

Sensitivity/Resistance

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.

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.

Skin

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.

Special Populations

Pregnant Women

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 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.

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 experience¹ 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.

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

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

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.

Nursing Women

See CONTRAINDICATIONS

Pediatrics (< 18 years of age)

The efficacy of CUPRIMINE (penicillamine capsules, USP) in juvenile rheumatoid arthritis has not been established

Geriatrics

See INDICATIONS AND CLINICAL USE and Post-Market Adverse Reactions.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 WARNINGS AND PRECAUTIONS).

Clinical Trial and Post-Market Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 WARNINGS AND 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 WARNINGS AND PRECAUTIONS).

Gastrointestinal side effects are usually reversible following cessation of therapy.

Hematological

Penicillamine can cause bone marrow depression (see WARNINGS AND PRECAUTIONS). 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 AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS); dystonia.

Side effects that have been reported rarely include thrombophlebitis; hyperpyrexia (see PRECAUTIONS); falling hair or alopecia; lichen planus; (see WARNINGS AND PRECAUTIONS); 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 WARNINGS AND PRECAUTIONS).

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

Post-Market Adverse Drug Reactions (since May 2003)

The following adverse reactions have been reported in post-marketing experience since May 2003:

Hepatobiliary disorders: Hepatic failure

Renal and urinary disorders: Renal failure

Vascular disorders: Vasculitis

Skin and Subcutaneous disorders: Yellow nail syndrome.

Geriatrics

In post-marketing surveillance, the most frequently reported serious adverse events seen in geriatric patients (≥ 65 years of age) were related to taste abnormalities, skin and subcutaneous tissue disorders and blood and lymphatic system disorders, including anemia, bone marrow failure, and thrombocytopenia. The frequency of these adverse events in the elderly is greater than in younger patients.

DRUG INTERACTIONS

Drug-Drug Interactions

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.

Drug-Food Interactions

See DOSAGE AND ADMINISTRATION

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Penicillamine may cause alteration of the biodistribution of technetium Tc-99m gluceptate.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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.

Recommended Dose and Dosage Adjustment

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 mcg 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/M²/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 mcg/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 mcg/dL, or until urinary lead excretion remains below 500 mcg/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 250 mg which is thereafter increased at one to three-month intervals, by 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 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 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 250 mg/day at approximately three-month intervals may be attempted.

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.

Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

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 $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in fruit juice twice a day. (Do not give copper to patients with Wilson's disease.)

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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-cystine 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.

STORAGE AND STABILITY

Store at 15-30°C. Keep container tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

- D & C Yellow 10,
- Gelatin,
- Lactose,
- Magnesium stearate,
- Titanium dioxide

Capsules CUPRIMINE 250 mg have an ivory opaque cap and an ivory opaque body imprinted radially with ATON 705 and CUPRIMINE respectively. Available in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

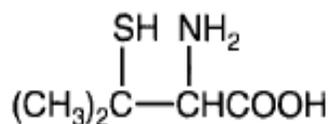
Proper name: penicillamine

Chemical name: 3-mercapto-D-valine

Molecular formula: C₅H₁₁NO₂S

Molecular mass: 149.21 g/mol

Structural formula:



Physicochemical properties

Description: Penicillamine is a white or practically white, crystalline powder

Solubility: 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:

$$[\alpha]_{\text{D}}^{25} = -63^\circ \pm 5^\circ \quad (C = 1, 1\text{N NaOH}).$$

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.

CLINICAL TRIALS

Information not available.

DETAILED PHARMACOLOGY

General Pharmacology

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

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 hyperesthetic 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.

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.

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.

MICROBIOLOGY

Information not available.

TOXICOLOGY

Acute Toxicity (LD₅₀)

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 fasciculata. 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.

BIBLIOGRAPHY

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. Brooks PM. Pharmacokinetics of D-penicillamine, *Aust. N.Z. J. Med* 1982; 12(5): 554.
4. Chisolm JJ Jr. Treatment of Lead Poisoning. *Mod Treatment* 1971;8:593-612.
5. Chisolm JJ Jr, Brown DH. Micro-Scale Photofluorometric Determination of "Free Erythrocyte Porphyrin" (Protoporphyrin IX). *Clin Chem* 1975;21:1669-82.
6. Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated Antineutrophil Cytolasmic Antibody-positive Vasculitis. *Arthritis Rheum* 2000;43(2):405-13.
7. 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;1:216-8.
8. Dixon A St J, Davies J, Dormandy TL, Hamilton EBD, Holt PJJ, 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.
9. Dubost JJ, Fraysse, P, Ristori JM, Rampon S. Yellow Nail Syndrome with Bronchiectasis Following D-penicillamine Therapy for Rheumatoid Arthritis. Report of two Cases. *Sem Hop* 1988;64(23):1548-51.
10. Frimpter GW. Medical Management of Cystinuria. *Am J Med Sci* 1968;255:348-57.
11. Garcia-Porrúa C, Gonzalez-Gay MA, Bouza P. D-penicillamine-induced Crescentic Glomerulonephritis in a Patient with Scleroderma. *Nephron* 2000;84(1):101-2.
12. 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.
13. Henkin RI, Keiser HR, Jaffe IA, Sternlieb I, Scheinberg IH. Decreased Taste Sensitivity after D-Penicillamine Reserved by Copper Administration, *Lancet* 1967;2:1268-71.

14. Herranz L, Rovira A, Grande C, Suarez A, Martinez-Ara J, Pallardo LF, Gomez-Pan A. Autoimmune Insulin Syndrome in a Patient with Progressive Systemic Sclerosis Receiving Penicillamine. *Horm Res* 1992; 37(1-2):78-80.
15. Hinkle GH, Basmadjian GP, Peek C, Barker KK, Ice RD. Effects of Concurrent Drug Therapy on Technetium Tc-99m Gluceptate Biodistribution. *Am J Hosp Pharm* 1982; 39:1930-1933
16. Huskisson EC, Hart FD. Penicillamine in the Treatment of Rheumatoid Arthritis. *Ann Rheum Dis* 1972;31:402-4.
17. 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;33:532-5.
18. Ilchyshyn A, Vickers CFH. Yellow Nail Syndrome Associated with Penicillamine Therapy. *Acta Derm Venereol.* (Stockh) 1983;63:554-5.
19. Jaffe IA. D-Penicillamine. *Bull Rheum Dis* 1977-78;28:6.
20. Kean WF, Anastassiades, TP, Dwosh, IL, Ford, PM, Kelly, WG, Dok, CM. Efficacy and Toxicity of D-Penicillamine for Rheumatoid Disease in the Elderly. *J Am Geriatric Soc.* 1982; 30(2):94-100.
21. Kean, WF, Bellarny, N, Lock, CJL, Adachi, J. Bio-Inorganic Effects of D-Penicillamine in Children and in the Elderly. *Clin. Invest. Med.* 1984;7(1):77-83.
22. Lehuédé G, Toussirot E, Despaux J, Michel F, Wendlin D. Yellow Nail Syndrome Associated with Thiol Compound Therapy for Rheumatoid Arthritis. *Joint Bone Spine* 2002;69(4):406-8.
23. Lotz M, Potts JT, Bartter FC. Rapid, Simple Method for Determining Effectiveness of D-Penicillamine Therapy in Cystinuria. *Br Med J* 1965;2:521.
24. Lubach D, Marghescu S. Yellow Nail Syndrome Caused by D-penicillamine. *Der Hautarzt* 1979;30:547-9.
25. MacDonald WB, Fellers FX. Penicillamine in the Treatment of Patients with Cystinuria. *J Am Med Assoc* 1966;197: 396-402.
26. Mathieson PW, Peat DS, Short A, Watts RA, . Coexistent Membranous Nephropathy and ANCA-positive Crescentic Glomerulonephritis in Association with Penicillamine. *Nephrol Dial Transplant* 1996;11(5):863-6.

27. Mjølnerod OK, Rasmussen Dommerud SA, Gjerluldsen ST. Congenital Connective-Tissue Defect Probably due to D-Penicillamine Treatment in Pregnancy. *The Lancet* 1971; 1:673.
28. 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;193-5.
29. Nanke Y, Akama H, Terai C, Kamatani N. Rapidly Progressive Glomerulonephritis with D-penicillamine. *Am J Med Sci* 2000;320(6):398-402.
30. Netter P, Bannwarth B, Pere P, Nicolas A, Clinical Pharmacokinetics of D-penicillamine, *Clin Pharmacokinet* 1987; 13(5): 317-333.
31. Osman M A, Patel RB, Schuna A, Sundstrom WR ,Welling P G. Reduction in Oral Penicillamine Absorption by Food, Antacid, and Ferrous Sulfate, *Clin Pharmacol Ther* 1983; 33(4): 465-470.
32. Reuner U, Kunath B. 37-Years Treatment of Wilson Disease. *Z Gastroenterol* 2001;39(3):259.
33. 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.
34. 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.
35. Scheinberg IH, Sternlieb I. The Long-Term Management of Hepatolenticular Degeneration (Wilson's Disease). *Am J Med* 1960;29:316-33
36. Scheinberg IH, Sternlieb I. Pregnancy in Penicillamine-Treated Patients with Wilson's Disease. *N Engl J Med* 1975;293:1300-2.
37. 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.
38. Sternlieb I, Scheinberg IH. Prevention of Wilson's Disease in Asymptomatic Patients. *N Engl J Med* 1968; 278:352-9.
39. Sternlieb I, Scheinberg IH. Penicillamine Therapy for Hepatolenticular Degeneration. *J Am Med Assoc* 1967; 189:748-54.

40. Walshe JM. Treatment of Wilson's Disease with Penicillamine. *Lancet* 1960;1:188-92.
41. Walshe JM, Yealland M. Chelation Treatment of Neurological Wilson's Disease. *Q J Med* 1993;86(3):197-204.
42. Wiesner RH, Carlson GL, Dickson ER, Go VLW. The Pharmacokinetics of D-penicillamine in Health and Primary Biliary Cirrhosis (PBC). *Gastroenterology* 1980;79(5, Part 2): 1066.

PART III: CONSUMER INFORMATION**PrCUPRIMINE®
Penicillamine Capsules, USP**

This leaflet is part III of a three-part "Product Monograph" published when CUPRIMINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CUPRIMINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

CUPRIMINE (penicillamine capsules, USP) is indicated in the treatment of:

- Wilson's disease (a disease which causes the body to retain copper);
- chronic lead poisoning,
- cystinuria (buildup of cystine stones in the kidneys and bladder), and
- severe, active rheumatoid arthritis which fails to respond to conventional treatment.

CUPRIMINE is not effective in the treatment of ankylosing spondylitis (chronic arthritis which affects the spine).

What it does:

Penicillamine is a chelating agent that binds and removes copper and lead from the body. Penicillamine also reduces excess cystine excretion in cystinuria. The mechanism of action of penicillamine in rheumatoid arthritis is not known although it appears to suppress disease activity.

When it should not be used:

Do not use CUPRIMINE if you:

- are allergic to penicillamine or to any ingredient in the formulation. (See: What the important nonmedicinal ingredients are);
- have severe kidney problems;
- have had blood or bone marrow problems because of treatment with penicillamine;
- are breast-feeding or intend to breast-feed;
- are pregnant. (CUPRIMINE may be used in the treatment of Wilson's disease in pregnant women. Please consult your health care professional.);
- receive gold therapy, antimalarial or anti-cancer drugs, phenylbutazone and oxyphenbutazone;
- have evidence of lead in the gastrointestinal tract.

What the medicinal ingredient is:

Penicillamine

What the important nonmedicinal ingredients are:

D & C Yellow 10, Gelatin, Lactose, Magnesium Stearate, and Titanium Dioxide.

What dosage forms it comes in:

Capsules. Each capsule contains 250 mg penicillamine. CUPRIMINE 250 mg are ivory opaque capsules imprinted radially with "ATON 705" on cap and "CUPRIMINE" on body. All capsules contain white to almost white powder.

WARNINGS AND PRECAUTIONS

BEFORE you use CUPRIMINE talk to your doctor or pharmacist if you think any of the following applies to you:

- If you have any medical problems now or have had in the past, especially kidney problems or blood diseases;
- If you are having or planning to have any type of surgery;
- If you are allergic to penicillin as you may also be allergic to penicillamine;
- If you have a muscle disease (i.e., myasthenia gravis);
- If you are pregnant or intending to become pregnant;
- If you are breast-feeding or intending to breast-feed.

Reduction of vitamin B6 and iron in the body may occur during treatment with CUPRIMINE.

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor about any medication that you are using or plan to use, including any medicine obtained without a prescription, vitamins or mineral supplements.

You should not take CUPRIMINE if you are receiving:

- gold therapy;
- antimalarial medication;
- cytotoxic medication (anti-cancer drugs);
- antacid, iron;
- oxyphenbutazone or phenylbutazone.

PROPER USE OF THIS MEDICATION**Usual dose:**

It is important to take CUPRIMINE as directed by your doctor. CUPRIMINE must be taken on an empty stomach, at least one hour before a full meal or two hours after a full meal. Avoid taking any medication, food or milk within at least one hour after taking CUPRIMINE. Take with a full glass of water and drink plenty of water while taking this medication.

Overdose:

If you take more than the dose prescribed by your physician, contact your physician or pharmacist immediately.

Missed Dose

If you miss a dose, do not take a double dose. The next dose should be taken as usual.

If you need any explanations or further information, ask your physician or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side-effects.

The most common side effects are loss of appetite, stomach pain, nausea, vomiting, diarrhea, loss of sensitivity, taste change or loss of taste perception, mouth or tongue infections.

Some patients may also experience allergic reactions (such as swelling, severe trouble breathing, itching, or rashes).

Some patients may also experience easy bleeding or bruising, blood in the urine.

Other side effects include: fatigue, weight gain, joint pain; blisters, hives, fever; yellowing of skin and eyes, ringing in the ear, foggy vision and/or decreased vision sharpness, agitation, anxiety, hair loss, and muscular weakness.

Tell your physician or pharmacist promptly about these or any other unusual symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Allergic Reactions (swelling, severe trouble breathing, itching, rashes).			√
	Easy bleeding or bruising, blood in the urine.			√
	Loss of appetite, stomach pain, nausea, vomiting, diarrhea.	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and
	Loss of sensitivity, taste change or loss of taste perception, mouth or tongue infections	√	
Uncommon	Fatigue, weight gain, joint pain		√
	Blisters, hives, fever		√
	Yellowing of skin and eyes		√
	Ringing in the ear, foggy vision and/or decreased vision sharpness, agitation, anxiety, hair loss, muscular weakness		√

This is not a complete list of side effects. For any unexpected effects while taking CUPRIMINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15-30°C. Keep container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to

Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp> or obtained by contacting the sponsor, Bausch Health, Canada Inc. at: 1-800-361-4261

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