

PRODUCT MONOGRAPH

CILAMIN CAPSULES

Each hard gelatin capsule of Cilamin contains:

Penicillamine IP – 250 mg

Hard Gelatin Capsule

Wilson's disease – Chelating agent

Manufactured By:

Panacea Biotec Limited.

Malpur, Baddi, Tehsil Nalagarh,

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CILAMIN CAPSULES

Each hard gelatin capsule of CILAMIN contains:

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Approved Indications
Oral	Hard Gelatin Capsule Penicillamine IP – 250 mg	CILAMIN is an chelating agent indicated for: - Wilson's disease

INDICATIONS AND CLINICAL USE:

CILAMIN which is in **hard gelatin capsule** form is indicated in the management of: Wilson's disease, Cystinuria & Rheumatoid Arthritis

Clinical Use in special population:

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Penicillamine is directly mutagenic to *S. typhimurium* strain TA92 in the Ames test; mutagenicity is enhanced by kidney postmitochondrial subcellular fraction 9. Penicillamine does not induce gene mutations in Chinese hamster V79 cells.

Penicillamine induces sister-chromatid exchanges and chromosome aberrations in cultivated mammalian cells. No studies on the effect of Penicillamine on fertility are available.

Pregnancy

Pregnancy Category D

Pediatric Use

The efficacy of Penicillamine in juvenile rheumatoid arthritis has not been established.

Geriatric Use

Clinical studies of Penicillamine 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 suggest greater risk than in younger patients for overall skin rash and abnormality of taste. 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.

CONTRAINDICATIONS:

CILAMIN is contraindicated in patients with a history of Penicillamine-related aplastic anemia or agranulocytosis should not be restarted on Penicillamine. 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.

Pregnancy and Lactation

Except for the treatment of Wilson's disease or certain patients with cystinuria, use of Penicillamine during pregnancy is contraindicated.

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

WARNING AND PRECAUTIONS:

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.

Wilson's disease — Continued treatment with CILAMIN throughout pregnancy protects the mother against relapse of the Wilson's disease, and that discontinuation of CILAMIN has deleterious effects on the mother, which may be fatal.

If CILAMIN is administered during pregnancy to patients with Wilson's disease, it is recommended that the daily dosage be limited to 750 mg. If cesarean section is planned the daily dose should be reduced to 250 mg, but not lower, for the last six weeks of pregnancy and postoperatively until wound healing is complete.

Cystinuria — If possible, CILAMIN should not be given during pregnancy to women with cystinuria. 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 mother must be evaluated against the risk to the fetus.

Rheumatoid Arthritis — CILAMIN 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.

ADVERSE EFFECTS:

More common

- Fever
- joint pain
- lesions on the face, neck, scalp, and/or trunk
- skin rash, hives, or itching
- swollen and/or painful glands
- ulcers, sores, or white spots on lips or in mouth
- Diarrhea
- lessening or loss of sense of taste
- loss of appetite
- nausea or vomiting
- stomach pain (mild)

Less common

- Bloody or cloudy urine
- shortness of breath, troubled breathing, tightness in chest, or wheezing
- sore throat and fever with or without chills
- swelling of face, feet, or lower legs
- unusual bleeding or bruising
- unusual tiredness or weakness
- weight gain

Rare

- Abdominal or stomach pain (severe)
- blisters on skin
- bloody or black, tarry stools
- chest pain
- coughing or hoarseness
- dark urine

- difficulty in breathing, chewing, talking, or swallowing
- eye pain, blurred or double vision, or any change in vision
- general feeling of discomfort or illness or weakness
- lower back or side pain
- muscle weakness
- painful or difficult urination
- pale stools
- pinpoint red spots on skin
- redness, tenderness, itching, burning, or peeling of skin
- red or irritated eyes
- red, thick, or scaly skin
- ringing or buzzing in the ears
- spitting blood
- yellow eyes or skin

DRUG INTERACTIONS:

- CILAMIN and multivitamin with minerals should not be taken orally at the same time. Products that contain magnesium, aluminum, calcium, iron, and/or other minerals may interfere with the absorption of CILAMIN and reduce its effectiveness. You should take multivitamin with minerals at least 2 hours before or 2 hours after the CILAMIN dose.
- Reduced absorption of CILAMIN in the presence of food. The effectiveness of the antibiotic may be reduced. CILAMIN should be administered one hour before or two hours after meals and at least one hour apart from any other drug, food, or milk. This will make it easier for your body to absorb the medication.

DOSAGE AND ADMINISTRATION:

Dosage schedule:

a) Composition : –

Each CILAMIN capsule contains:

Penicillamine IP – 250 mg

b) Dosage Form – Hard Gelatin Capsule

Administration: - The usual recommended dose of CILAMIN is 1 to 4 times daily. Take each dose with a full glass of water (8 ounces or 240 milliliters). Should be taken on an empty stomach. (Take on an empty stomach 1 hr before or 2 hr after meals, & at least 1 hr apart from any other drug, food, milk, antacid, Zn- or Fe-containing prep.)

OVERDOSE:

Seek emergency medical attention.

Symptoms of a CILAMIN overdose are not known.

ACTION AND CLINICAL PHARMACOLOGY:

Penicillamine is a chelating agent recommended for the removal of excess copper in patients with Wilson's disease. 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.

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.

In rheumatoid arthritis, the onset of therapeutic response to CUPRIMINE (Penicillamine) 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 all patients receiving Penicillamine, it is important that CUPRIMINE (Penicillamine) 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, milk, antacid, zinc or iron-containing preparation. This permits maximum absorption and reduces the likelihood of inactivation by metal binding in the gastrointestinal tract.

Pharmacokinetics:

Penicillamine is absorbed rapidly but incompletely (40-70%) from the gastrointestinal tract, with wide interindividual variations. Food, antacids, and iron reduce absorption of the drug. The peak plasma concentration of Penicillamine occurs 1-3 hours after ingestion; it is approximately 1-2 mg/L after an oral dose of 250 mg. The drug appears in the plasma as free Penicillamine, Penicillamine disulfide, and cysteine-Penicillamine disulfide. When prolonged treatment is stopped, there is a slow elimination phase lasting 4-6 days.

More than 80% of plasma Penicillamine is bound to proteins, especially albumin and ceruloplasmin. The drug also binds to erythrocytes and macrophages. A small fraction of the dose is metabolized in the liver to S-methyl-D-Penicillamine. Excretion is mainly renal, mainly as disulfides.

STORAGE AND HANDLING:

CILAMIN capsules should be stored below 25 ° C. Protect from light and moisture. Keep the medicine out of reach of children.

DOSAGE FORM– Hard gelatin capsule

COMPOSITION –

Each CILAMIN capsule contains:

Penicillamine IP – 250 mg

PACKAGING – 10 capsules /strip

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

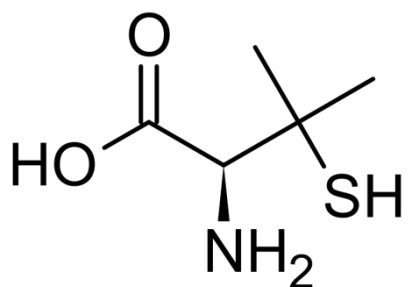
Drug Substance

Common Name: Penicillamine

Chemical Name:

-2-amino-3-methyl-3-sulfanyl-butanoic acid

Penicillamine has the following chemical structure:



The molecular weight is 149.212g/mol. The molecular formula is C₅H₁₁NO₂S

PART III: PATIENT INFORMATION

CILAMIN Capsules

This leaflet is a summary and will not tell you everything about the combination. Contact your doctor or pharmacist if you have any questions about the drug

Generic Name: Penicillamine (Pronunciation: pen ih SILL ah meen)

- **What is Penicillamine?**
- **What are the Indications and Usage of Penicillamine?**
- **What are the contraindications of Penicillamine?**
- **What are the storage conditions of Penicillamine?**
- **What are the drug interactions of Penicillamine?**
- **What are the adverse reactions of Penicillamine?**
- **What happens if I overdose Penicillamine?**
- **What happens if I miss a dose of Penicillamine?**
- **What should I discuss with my healthcare provider before receiving Penicillamine?**
- **How is Penicillamine given?**
- **Where can I get more information?**

What is Penicillamine?

Penicillamine is a chelating agent. It attaches to other chemicals in the body, which aids in their removal.

Penicillamine is used to remove excess copper associated with Wilson's disease. It is also used to reduce cystine in the urine and to treat severe rheumatoid arthritis.

Indications and Usage

CILAMIN which is in **hard gelatin capsule** form is indicated in the management of: Wilson's disease, Cystinuria & Rheumatoid Arthritis

Contraindications

CILAMIN is contraindicated in patients with a history of Penicillamine-related aplastic anemia or agranulocytosis should not be restarted on Penicillamine. Because of its potential for causing renal damage, CILAMIN should not be administered to rheumatoid arthritis patients with a history or other evidence of renal insufficiency.

Pregnancy and Lactation

Except for the treatment of Wilson's disease or certain patients with cystinuria, use of CILAMIN during pregnancy is contraindicated.

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

Storage and Handling

CILAMIN capsules should be stored below 25 ° C. Protect from light. Keep the medicine out of reach of children.

Drug Interactions:

- CILAMIN and multivitamin with minerals should not be taken orally at the same time. Products that contain magnesium, aluminum, calcium, iron, and/or other minerals may interfere with the absorption of CILAMIN and reduce its effectiveness. You should take multivitamin with minerals at least 2 hours before or 2 hours after the CILAMIN dose.
- Reduced absorption of CILAMIN in the presence of food. The effectiveness of the antibiotic may be reduced. CILAMIN should be administered one hour before or two hours after meals and at least one hour apart from any other drug, food, or milk. This will make it easier for your body to absorb the medication.

Do not take CILAMIN if you are taking any of the following medicines:

- a gold-therapy product such as auranofin, aurothioglucose, or gold sodium thiomalate ;
- an antimalarial medicine such as quinine, mefloquine , chloroquine , hydroxychloroquine ,primaquine, or pyrimethamine ;
- a cancer chemotherapy medicine; or
- phenylbutazone.

Like Penicillamine, the medications listed above can affect the blood and the kidneys. Combined with Penicillamine, any of these medicines can be very dangerous.

Before taking CILAMIN, tell your doctor if you are taking digoxin. CILAMIN may decrease the effects of digoxin, and your doctor may want to adjust your dosage or monitor your therapy.

Many other drugs, especially antacids and vitamin and mineral supplements, can decrease the effects of CILAMIN. Do not take any medicines or over-the-counter drugs or supplements within 1 hour of a CILAMIN dose.

Drugs other than those listed here may also interact with Penicillamine. Talk to your doctor and pharmacist before taking any prescription or over-the-counter medicines.

Adverse Reactions:

More common

- Fever
- joint pain
- lesions on the face, neck, scalp, and/or trunk
- skin rash, hives, or itching
- swollen and/or painful glands
- ulcers, sores, or white spots on lips or in mouth
- Diarrhea
- lessening or loss of sense of taste
- loss of appetite
- nausea or vomiting
- stomach pain (mild)

Less common

- Bloody or cloudy urine
- shortness of breath, troubled breathing, tightness in chest, or wheezing
- sore throat and fever with or without chills
- swelling of face, feet, or lower legs
- unusual bleeding or bruising
- unusual tiredness or weakness
- weight gain

Rare

- Abdominal or stomach pain (severe)
- blisters on skin

- bloody or black, tarry stools
- chest pain
- coughing or hoarseness
- dark urine
- difficulty in breathing, chewing, talking, or swallowing
- eye pain, blurred or double vision, or any change in vision
- general feeling of discomfort or illness or weakness
- lower back or side pain
- muscle weakness
- painful or difficult urination
- pale stools
- pinpoint red spots on skin
- redness, tenderness, itching, burning, or peeling of skin
- red or irritated eyes
- red, thick, or scaly skin
- ringing or buzzing in the ears
- spitting blood
- yellow eyes or skin

Overdosage

Seek emergency medical attention.

Symptoms of a CILAMIN overdose are not known.

What happens if I miss a dose?

Take the missed dose on an empty stomach as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed and take only your next regularly scheduled dose. Do not take a double dose of this medication unless otherwise directed by your doctor. If you have missed several doses in a row, do not take any more doses without first talking to your doctor.

What should I discuss with my healthcare provider before taking CILAMIN?

You cannot take CILAMIN if you have taken it in the past and it has damaged your blood cells.

Before taking CILAMIN, tell your doctor if you have kidney disease or any other serious illness. You may not be able to take CILAMIN, or you may require a lower dose or special monitoring during therapy.

Penicillamine may cause birth defects in an unborn baby. However, it has also been used during pregnancy with no evidence of defects. CILAMIN should not be used during pregnancy except to treat Wilson's disease and some cases of cystine in the urine. Do not take this medication without first talking to your doctor if you are pregnant.

It is not known whether Penicillamine passes into breast milk. Since Penicillamine may harm a nursing infant, breast-feeding is not recommended during treatment with this medication.

How should I take CILAMIN?

The usual recommended dose of CILAMIN is 1 to 4 times daily exactly as directed by your doctor. If you do not understand these instructions, ask your pharmacist, nurse, or doctor to explain them to you.

Take each dose with a full glass of water.

CILAMIN must be taken on an empty stomach, at least 1 hour before or 2 hours after a full meal, and at least 1 hour before or after any other drug, food, or milk. Taking CILAMIN with anything else in the stomach greatly decreases its effectiveness.

Do not stop taking CILAMIN without first talking to your doctor. Stopping therapy may cause your body to react abnormally when therapy is restarted. If you do stop taking the medication, do not restart without first talking to your doctor. You may need special monitoring.

Your doctor may want you to take a vitamin and mineral supplement during treatment with CILAMIN. CILAMIN may reduce vitamin B6 and iron in the body. Follow your doctor's instructions.

Store CILAMIN at room temperature away from moisture and heat.

Where can I get more information?

Your pharmacist has additional information about CILAMIN written for health professionals that you may read.