Anti-rheumatic drug/Therapeutic agent for Wilson’s disease/Heavy metal antidote

METALCAPTASE® Capsules 50 mg
METALCAPTASE® Capsules 100 mg
(Penicillamine)

Relative Contraindications
As a general rule, METALCAPTASE is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.

Rheumatoid arthritis
1. Elderly patients. [Serious blood disorders etc. may be induced.]
2. Patients immediately after undergoing surgery. [Serious blood disorders etc. may be induced.]
3. Patients with decreased bone marrow function. [Serious blood disorders etc. may be induced.]
4. Patients whose general condition is poor. [Serious blood disorders etc. may be induced.]
5. Nursing mothers. [See PRECAUTIONS, 6. Use during Pregnancy, Delivery, or Lactation]

WARNING
METALCAPTASE may cause serious blood disorders (e.g., agranulocytosis). Read the PRECAUTIONS section carefully.

Contraindications
METALCAPTASE is contraindicated in the following patients.

Rheumatoid arthritis
1. Patients with blood disorders. [Serious blood disorders such as aplastic anemia may be induced.]
2. Patients with renal disorders. [Serious renal disorders such as nephrosis may be induced.]
3. Patients with systemic lupus erythematosus (SLE). [SLE symptoms may be aggravated.]
4. Growing children with metabolic disorders of the connective tissues. [Abnormalities of the connective tissues may be induced.]
5. Patients receiving gold therapy. [See PRECAUTIONS, 3. Drug Interactions]
6. Women known or suspected to be pregnant. [See PRECAUTIONS, 6. Use during Pregnancy, Delivery, or Lactation]

Wilson’s disease (hepato-lenticular degeneration) and lead/mercury/copper poisoning
1. Patients receiving gold therapy. [See PRECAUTIONS, 3. Drug Interactions]
2. Patients with renal disorders. [Serious renal disorders may be induced.]
3. Patients with systemic lupus erythematosus (SLE). [SLE symptoms may be aggravated.]
4. Growing children with metabolic disorders of the connective tissues. [Abnormalities of the connective tissues may be induced.]
5. Women known or suspected to be pregnant and nursing mothers. [See PRECAUTIONS, 6. Use during Pregnancy, Delivery, or Lactation]

formulations

<table>
<thead>
<tr>
<th>Brand name</th>
<th>METALCAPTASE Capsules 50 mg</th>
<th>METALCAPTASE Capsules 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Penicillamine 50 mg/capsule</td>
<td>Penicillamine 100 mg/capsule</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Corn starch</td>
<td>Corn starch</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate [Capsule shell]</td>
<td>Magnesium stearate [Capsule shell]</td>
</tr>
<tr>
<td></td>
<td>Gelatin</td>
<td>Gelatin</td>
</tr>
<tr>
<td></td>
<td>Titanium oxide</td>
<td>Titanium oxide</td>
</tr>
<tr>
<td></td>
<td>Sodium lauryl sulfate</td>
<td>Sodium lauryl sulfate</td>
</tr>
<tr>
<td></td>
<td>Yellow No. 4</td>
<td>Yellow No. 4</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Hard capsule [Cap]</td>
<td>Hard capsule [Cap]</td>
</tr>
<tr>
<td></td>
<td>Opaque light orange [Body]</td>
<td>Red [Body]</td>
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<tr>
<td>ID code</td>
<td>T650</td>
<td>T651</td>
</tr>
<tr>
<td>Appearance</td>
<td>ca. 305 mg</td>
<td>ca. 305 mg</td>
</tr>
</tbody>
</table>
### INDICATIONS, DOSAGE, AND ADMINISTRATION

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Use this drug only when an adequate effect cannot be obtained with anti-inflammatory and analgesic agents and other agents. Usually, penicillamine is administered orally to adult patients at a dose of 100 mg, once to three times a day, on an empty stomach (2 hours after meals). The dosage may be adjusted depending on the patient’s age, weight, symptoms, response and tolerance to the drug, etc. In general, the initial daily dose should be set at 100 mg, and if necessary to increase, the daily dose should be gradually increased by 100 mg at intervals of 4 weeks or more. The maintenance dose should be adjusted to the minimum at which the desired effect can be obtained. In addition, start with a lower dose when resuming administration. Further, if a daily dose of 300 mg shows insufficient effect and greater effect can be expected by increasing the dose, it can be increased up to 600 mg daily while observing the patient’s condition. However, the minimum effective dose should be maintained by decreasing the dose after obtaining the desired effect.</td>
</tr>
<tr>
<td>Wilson’s disease (hepato-lenticular degeneration)</td>
<td>Usually, penicillamine is administered orally to adult patients at a daily dose of 1,000 mg, either in a single dose or in divided doses (several times a day), on an empty stomach (at least 30 minutes before meals). The dosage may be adjusted depending on the patient’s age, symptoms, response and tolerance to the drug, etc. In general, the daily dose should be adjusted to a range of 600–1,400 mg. The dosage regimen (e.g., continuous administration, intermittent administration, dosage titration regimen, etc.) should be individualized.</td>
</tr>
<tr>
<td>Lead/mercury/copper poisoning</td>
<td>In adults: Usually, penicillamine is administered orally at a daily dose of 1,000 mg in divided doses (several times a day) on an empty stomach (at least 30 minutes before meals). The dosage may be adjusted depending on the patient’s age, symptoms, response and tolerance to the drug, etc. In general, the daily dose should be adjusted to a range of 600–1,400 mg. The dosage regimen (e.g., continuous administration, intermittent administration, dosage titration regimen, etc.) should be individualized. In children: Usually, penicillamine is administered orally at a daily dose of 20–30 mg/kg in divided doses (several times a day) on an empty stomach (at least 30 minutes before meals).</td>
</tr>
</tbody>
</table>

The dosage may be adjusted depending on the patient’s age, symptoms, response and tolerance to the drug, etc.; however, the total daily dose of penicillamine should not exceed 1,000 mg (i.e., the usual adult daily dose).

### Special Precautions for Dosage and Administration

**For patients with rheumatoid arthritis:**

- **Start with a low dose (i.e., 100 mg of penicillamine/day).** If a higher dose is required **judging by rheumatic activity**, the daily dose should be gradually increased at intervals of 4 weeks or more, with close monitoring of the patient’s condition. When a satisfactory therapeutic response is obtained, the dose should then be reduced gradually to the **lowest effective maintenance level** (preferably below 200 mg), because this drug is often effective even at lower doses after the achievement of therapeutic response. **In general, a daily dose in excess of 600 mg penicillamine provides little added benefit.**
- **Since the onset of clinical response to penicillamine is delayed (4 weeks or more are usually required), it is recommended not to stop any current medication(s), such as anti-inflammatory and analgesic agents; continuous co-administration is desirable until a satisfactory response occurs.**
- **If no clinical response is observed even after continuous administration of penicillamine for 6 months, METALCAPTASE therapy should be discontinued.**

### PRECAUTIONS

1. **Special Precautions for Use**

   METALCAPTASE should be administered with caution in the following patients.

   - **Rheumatoid arthritis**
     
     1. Patients with a past history of blood disorders. [Perform regular blood tests, since blood disorders may be induced. (See 2. Important Precautions)]
     2. Patients with a past history of renal disorders. [Perform regular renal function tests such as tests for urinary protein, since renal disorders may be induced. (See 2. Important Precautions)]
     3. Patients with liver disorders. [Monitor liver function test values, since liver function abnormalities may be induced.]
     4. Patients with known hypersensitivity to penicillin antibiotics.
     5. Patients receiving immunosuppressive therapy. [See 3. Drug Interactions]

   - **Wilson’s disease (hepato-lenticular degeneration) and lead/mercury/copper poisoning**
     
     1. Patients with a past history of blood disorders. [Perform regular blood tests, since blood disorders may be induced.]
     2. Patients with a past history of renal disorders. [Perform regular renal function tests such as tests for urinary protein, since renal disorders may be induced.]
     3. Patients with liver disorders. [Monitor liver function test values, since liver function abnormalities may be induced.]
     4. Patients with known hypersensitivity to penicillin antibiotics.
     5. Elderly patients. [Serious blood disorders etc. may be induced.]
     6. Patients receiving immunosuppressive therapy. [See 3. Drug Interactions]
2. Important Precautions

**Rheumatoid arthritis**

(1) METALCAPTASE should be used only for intractable rheumatoid arthritis that cannot be controlled by anti-inflammatory and analgesic agents, gold compounds, etc., because serious side effects have been reported with the use of penicillamine.

(2) Prior to starting METALCAPTASE therapy, possible major side effects and precautions (including those for dosage and administration) should be explained to the patient. In addition, the patient should be instructed to notify the physician immediately if symptoms such as pharyngeal pain, fever, or purpura occur.

(3) Prior to starting METALCAPTASE therapy, laboratory tests (blood counts, renal and liver function tests, etc.) must be performed.

During the therapy, closely observe the clinical symptoms and perform laboratory tests (such as blood tests and urinalysis) regularly at a frequency of once every 1–2 weeks for the initial 2 months of therapy and once every 2–4 weeks thereafter. Further, special attention should be paid to white blood cell (WBC) counts, platelet counts, and urinary protein. METALCAPTASE should be discontinued and appropriate therapeutic action taken if any of the following abnormalities are observed.

<table>
<thead>
<tr>
<th>Decreased WBC</th>
<th>Fewer than 3,000/mm$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased platelets</td>
<td>Fewer than 100,000/mm$^3$</td>
</tr>
<tr>
<td>Proteinuria, hematuria</td>
<td>Persistent proteinuria, a tendency for an increase in urinary protein excretion, or hematuria</td>
</tr>
</tbody>
</table>

Since blood disorders can occur and worsen rapidly, blood test results should be carefully monitored to detect early signs of abnormalities during treatment, especially in outpatients. Pay particular attention to the WBC and platelet counts. If these values show a tendency to decrease over time, even if they are still within the normal range, reduction or withdrawal of METALCAPTASE should be considered.

**Lead/mercury/copper poisoning**

(1) In patients with serious lead poisoning, METALCAPTASE can be used as an adjunctive treatment after initial therapy with an intravenous chelating agent. In contrast, the drug can be used as monotherapy in asymptomatic patients with blood lead levels of 40–60 µg/dL or higher. If the blood lead levels decrease to below 40–60 µg/dL, withdrawal of METALCAPTASE should be considered. However, because it has been reported for other chelating agents that the decreased blood lead levels can rise again after stopping administration, the blood lead levels should be regularly monitored for an additional 1–2 weeks. If a rebound increase is observed, METALCAPTASE administration can be resumed.

Children are more susceptible to lead poisoning than adults and their central nervous system is sensitive to the damaging effects of lead; hence, if a child is persistently exposed to lead, even at low levels, there is an increased risk of encephalopathy. Keep the lead-exposed child under close medical supervision.

(2) When considering the use of METALCAPTASE to treat poisoning with heavy metals other than lead, mercury or copper, the risk/benefit ratio should be carefully assessed, because, for example, there are no generally accepted criteria regarding the blood levels of these heavy metals for determining when drug therapy should be initiated and discontinued.

(3) Prior to administering this product, renal function testing (serum creatinine etc.) must be conducted, since a sufficient volume of urine is necessary to excrete heavy metals and to obtain the desired effects. In addition, testing should be performed regularly (once every 1–2 weeks) during treatment. If a decline in renal function is observed, combined treatment with METALCAPTASE and hemodialysis should be considered.

(4) Serious side effects have been reported with the use of METALCAPTASE, and it is likely that the incidence of side effects increases as the dose increases; accordingly, the product should be administered to patients if, and only if, its therapeutic benefits are judged to outweigh its potential risks. It should be started after careful consideration and continued under close medical supervision.

3. Drug Interactions

(1) Co-administration contraindicated

METALCAPTASE must not be administered concomitantly with the following drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms, and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold compounds (Aurothiomalate, auranofin, etc.) [SHIOSOL] [RIDAURA]</td>
<td>Concomitant use with penicillamine may cause serious blood disorders.</td>
<td>Mechanism unknown</td>
</tr>
</tbody>
</table>

(2) Precautions for co-administration

Caution should be exercised when considering the concomitant use of METALCAPTASE with the following drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms, and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive agents</td>
<td>Side effects may be aggravated.</td>
<td>Mechanism unknown</td>
</tr>
<tr>
<td>Oral iron preparations (Sodium ferrous citrate, ferrous sulfate, etc.)</td>
<td>These medications may reduce the effects of penicillamine when used concomitantly. If the use of these medications is necessary, avoid simultaneous administration with penicillamine.</td>
<td>The absorption of penicillamine is reduced when administered simultaneously. (See PHARMACOKINETICS)</td>
</tr>
<tr>
<td>Antacids containing magnesium or aluminum (Magnesium hydroxide, aluminum hydroxide)</td>
<td></td>
<td>The mechanism may involve zinc chelation with penicillamine, leading to decreased absorption of penicillamine.</td>
</tr>
<tr>
<td>Oral preparations containing zinc</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Adverse Reactions

**Rheumatoid arthritis**

A total of 3,274 adverse reactions were encountered in 2,171 (26.8%) of 8,110 patients treated with penicillamine for rheumatoid arthritis. The most common adverse reactions included rash in 729 cases, pruritus in 553 cases, renal function disorders in 326 cases, dysgeusia in 114 cases, and abdominal pain in 109 cases. [Results of pre-approval clinical trials and post-marketing clinical experience studies]

**Wilson’s disease (hepato-lenticular degeneration)**

No clinical studies have been performed to determine the incidence of adverse reactions to penicillamine in patients with Wilson’s disease.

**Lead/mercury/copper poisoning**

No clinical studies have been performed to determine the incidence of adverse reactions to penicillamine in patients with heavy metal poisoning.

(1) Clinically significant adverse reactions

1) Pancreatitis (0.05%), leukopenia (0.79%), granulocytopenia (0.05%), agranulocytosis (incidence unknown), eosinophilia (0.02%), aplastic anemia (0.04%), anemia (hypochromic anemia, hemolytic anemia, etc.) (0.64%), thrombocytopenia (1.07%), thrombotic thrombocytopenic purpura (Moschowitz syndrome) (incidence unknown), nephrotic syndrome (membranous nephropathy etc.) (0.09%): Since pancreatitis, leukopenia, granulocytopenia, agranulocytosis, eosinophilia, aplastic anemia, anemia (hypochromic anemia, hemolytic anemia, etc.), thrombocytopenia, thrombotic thrombocytopenic purpura (Moschowitz syndrome), and/or nephrotic syndrome (membranous nephropathy etc.) may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of METALCAPTASE should be taken. (See 2. Important Precautions)

2) Alveolitis (incidence unknown), interstitial pneumonia/PIE (pulmonary infiltrates with eosinophilia) syndrome (incidence unknown), obliterative bronchiolitis (incidence unknown): Since alveolitis, interstitial pneumonia/PIE syndrome, and/or obliterative bronchiolitis may occur, patients should be closely monitored. If any abnormalities (fever, cough, dyspnea, abnormal chest X-ray, eosinophilia, etc.) are observed, METALCAPTASE should be discontinued and appropriate therapeutic action (e.g., corticosteroid therapy) taken.

3) Goodpasture’s syndrome (incidence unknown): Since Goodpasture’s syndrome may occur, patients should be closely monitored. If any abnormal urinalysis findings are observed accompanied by pulmonary abnormalities (hemoptysis, abnormal chest X-ray, etc.), METALCAPTASE should be discontinued immediately.

4) Agenesis (0.43%), optic neuritis (incidence unknown): Since agenesis and/or optic neuritis may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.

5) Systemic lupus erythematosus (SLE)-like symptoms (0.02%), pemphigus-like syndrome (0.27%), myasthenia gravis (0.06%): Since SLE-like symptoms, pemphigus-like syndrome, and/or myasthenia gravis may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.

6) Neuritis (0.02%), polyneuritis including Guillain-Barre syndrome (incidence unknown): Since neuritis or polyneuritis including Guillain-Barre syndrome may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.

7) Polymyositis (0.06%), muscle paresis (incidence unknown): Since polymyositis or muscle paresis may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.

8) Polyangiitis (incidence unknown), allergic vasculitis (incidence unknown), thrombophlebitis (incidence unknown): Since myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated microscopic polyangiitis causing diverse abnormalities in the lung and kidney, allergic vasculitis (leukocytoclastic vasculitis), thrombophlebitis, etc. may occur, patients should be closely monitored. If any abnormalities are observed, METALCAPTASE should be discontinued immediately and appropriate therapeutic action taken.

9) Cholestatic hepatitis (incidence unknown): Since cholestatic hepatitis has been reported in rheumatoid arthritis patients receiving penicillamine, it is highly recommended to perform periodic liver function tests during treatment.

(2) Other adverse reactions

The following adverse reactions may occur. If any abnormalities related to these adverse reactions are observed, appropriate measures such as reduction of the dosage or withdrawal of METALCAPTASE should be instituted.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-psychiatric</td>
<td>5% &gt;</td>
<td>≥ 0.1%</td>
</tr>
<tr>
<td>Sensory</td>
<td>Dizziness, headache</td>
<td>Perceptual disturbance, eyelid ptosis</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Abdominal pain, stomatitis/ angular stomatitis, anorexia, nausea, vomiting, diarrhea, peptic ulcer, glossitis, dyspepsia, dry mouth</td>
<td>Gastritis, chelitis, melena, gingivitis, constipation</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Incidence</td>
<td>Erythema nodosum, erythema multiforme, disturbance of wound healing, elastosis perforans</td>
</tr>
<tr>
<td></td>
<td>≥ 5%</td>
<td>Nail abnormality</td>
</tr>
<tr>
<td></td>
<td>Incidence</td>
<td>5% &gt;</td>
</tr>
<tr>
<td></td>
<td>Rash, pruritus</td>
<td>Alopecia, dermatitis, purpura, redness, subcutaneous hemorrhage</td>
</tr>
</tbody>
</table>

Dermatologic reactions (incidence unknown): Since dermatologic reactions have been observed in penicillamine-treated patients, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.

Other adverse reactions (incidence unknown): Since other adverse reactions have been observed in penicillamine-treated patients, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of METALCAPTASE should be taken.
### Hepato-biliary
- Hepatic function disorder (increased AST [GOT], increased ALT [GPT], etc.)
- Jaundice

### Renal
- Renal function disorder (proteinuria, hematuria, increased BUN, increased creatinine)
- Nephritis

### Blood
- Epistaxis, lymphopenia, leukocytosis

### Blood vessels
- Capillary fragility

### Immunoglobulin
- Decreased immunoglobulins (IgA, IgG, IgM)*

### Musculo-skeletal
- Arthralgia, myalgia

### Others
- Edema, fever, malaise, pharyngitis
- Asthenia, palpitations, weight loss, weight gain, pain, vulvar erosion
- Vitamin B6 deficiency**, breast hypertrophy, urinary incontinence

* If any abnormal results are found in immunoglobulin tests, appropriate measures such as withdrawal of METALCAPTASE should be taken.

** It is recommended to use vitamin B6 concomitantly.

### 5. Geriatric Use

**Rheumatoid arthritis**

As a general rule, avoid using METALCAPTASE for treating rheumatoid arthritis in elderly patients. (See RELATIVE CONTRAINdications)

**Wilson’s disease (hepato-lenticular degeneration) and lead/mercury/copper poisoning**

Because elderly patients are more likely to have decreased physiological functions, caution should be exercised in the administration of this product for treating Wilson’s disease and heavy metal poisoning.

### 6. Use during Pregnancy, Delivery, or Lactation

1. It has been reported that penicillamine may produce teratogenic effects in human fetuses; accordingly, METALCAPTASE must not be used in women known or suspected to be pregnant, especially for treating rheumatoid arthritis (see CONTRAINdications). However, if penicillamine is required to control Wilson’s disease and heavy metal poisoning in this patient group, then the product should be administered if, and only if, its therapeutic benefits are judged to outweigh its potential risks (see RELATIVE CONTRAINdications).

2. The safety of METALCAPTASE in breast-fed infants has not been established; accordingly, avoid using this product in nursing mothers. If its use is unavoidable, nursing mothers should discontinue breast-feeding during METALCAPTASE therapy.

### 7. Pediatric Use

**Rheumatoid arthritis and Wilson’s disease (hepato-lenticular degeneration)**

Safety in pediatric patients has not been established; accordingly, METALCAPTASE should be administered to pediatric patients only if its therapeutic benefits are judged to outweigh its potential risks.

**Lead/mercury/copper poisoning**

Safety in premature infants, neonates, and babies has not been established; accordingly, METALCAPTASE should be administered to premature infants, neonates, or babies only if its therapeutic benefits are judged to outweigh its potential risks.

### 8. Precautions concerning Use

When METALCAPTASE is provided in a press-through package (PTP) sheet (a blister sheet), instruct the patient to remove each capsule from the package sheet prior to swallowing. It has been reported that, if a small part of the package is mistakenly swallowed along with a capsule, its sharp corners may penetrate and eventually perforate the esophageal mucosa, leading to serious complications (e.g., mediastinitis).

**PHARMACOKINETICS**

### 1. Blood levels$^{1,2}$

Following oral administration of a single dose of 200 mg to healthy adults under fasting conditions, the pharmacokinetic parameters of penicillamine were as follows:

<table>
<thead>
<tr>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>AUC (µg·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td>0.62</td>
<td>1.8</td>
<td>2.3</td>
</tr>
</tbody>
</table>

[n = 12]

Following oral administration of a single dose of 500 mg to healthy adults (non-Japanese subjects) after overnight fasting, immediately after breakfast, immediately after ingestion of an iron preparation during overnight fasting, and immediately after ingestion of an antacid (containing magnesium hydroxide and aluminum hydroxide) during overnight fasting in a four-way crossover design, the pharmacokinetic parameters of penicillamine were as follows:

<table>
<thead>
<tr>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>AUC (µg·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After overnight fasting</td>
<td>3.05</td>
<td>3.8</td>
<td>2.1</td>
</tr>
<tr>
<td>After breakfast</td>
<td>1.51</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Concomitantly with an iron preparation</td>
<td>1.00</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Concomitantly with an antacid</td>
<td>1.72</td>
<td>3.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

[n = 6]

No significant differences were found among the four groups in the T1/2. In contrast, the Cmax and AUC values in the three groups taking penicillamine after breakfast, with an iron preparation, and with an antacid were significantly lower than those in the group taking penicillamine alone after overnight fasting.
2. Distribution

Animal studies: When 20 mg/kg of 14C-penicillamine was administered orally to rats, it was rapidly distributed throughout the entire body (except for the central nervous system) after administration. The radioactivity levels were high in the aorta, cartilage, skin and Achilles tendon, but low in the muscle and fat tissue. It was also found that penicillamine formed disulfide bonds with plasma proteins in vivo, and that the extent of binding of 14C-penicillamine to plasma proteins was increased with time and reached almost 100% at 24 hours after administration.

3. Metabolism and excretion

When a single 200-mg oral dose of penicillamine was administered to healthy adults, the major metabolite in the urine was identified as penicillamine-cysteine disulfide, and minor amounts of penicillamine disulfide were also detected; 35.2% of the dose was excreted in the urine within 24 hours of administration.

**CLINICAL STUDIES**

The results of pre-approval clinical trials, including double-blind and open-label studies, are as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>66.1% (489/740)</td>
</tr>
</tbody>
</table>

**PHARMACOLOGY**

**Rheumatoid arthritis**

1. Effect on the induction of antigenicity

Penicillamine has been shown to exhibit the following actions in vitro: (a) inhibition of the denaturation of human γ-globulin, (b) an inhibitory action on collagenase activity in human synovial fluid, and (c) a stabilizing action on lysosomal membranes in cultured fibroblasts derived from rat carrageen granuloma. It is believed that these actions can directly or indirectly contribute to preventing biological components from acquiring antigenicity.

2. Effect on intramolecular disulfide bonds

Owing to its SH group, penicillamine acts to dissociate S-S bonds in immune complexes (including rheumatoid factor) in patients with rheumatoid arthritis.

3. Effect on immune response

It is reported that penicillamine affects T-lymphocyte function and may act as an immunomodulator involved in the immune response.

**Wilson’s disease (hepatolenticular degeneration) and lead/mercury/copper poisoning**

In patients with Wilson’s disease, two molecules of penicillamine bind one molecule of serum copper to form a soluble chelate, leading to enhanced excretion of copper in the urine. As serum copper concentrations are reduced, copper is deposited in various tissues and organs is released into the bloodstream, thus preventing excessive accumulation of copper in organs such as the brain, liver, kidney and cornea.

In rats treated with heavy metals (lead, mercury), penicillamine increases the excretion of heavy metals in the urine, thereby facilitating their removal from the body.

**DESCRIPTION**

Generic name: Penicillamine
Chemical name: 3-Mercapto-D-valine
Structural formula:

\[
\begin{align*}
\text{CH}_3
\text{H} & \\
\text{HS} & \text{C} \cdots \text{C} \cdots \text{COOH} & \\
\text{CH}_3 \text{NH}_2 & 
\end{align*}
\]

Molecular formula: C,H,N,O,S
Molecular weight: 149.21

**Physicochemical properties:**

Penicillamine is a white crystalline powder with a slightly peculiar smell. It tastes slightly sweet initially, but has an unpleasant aftertaste. It is freely soluble in water and slightly soluble in 95% ethanol.

Melting point: Approx. 195 °C (decomposition)

Optical rotation: [α]D 20° ~ -60° ~ -67°

**PACKAGING**

<table>
<thead>
<tr>
<th>METALCAPTASE</th>
<th>Pack with 100 capsules (PTP/blister pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsules 50 mg</td>
<td></td>
</tr>
<tr>
<td>Capsules 100 mg</td>
<td></td>
</tr>
</tbody>
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Revised in December 2009: No changes to the WARNING, CONTRAINDICATIONS, RELATIVE CONTRAINDICATIONS, or PRECAUTIONS sections