# Metalcaptase® 300 mg

## 1. NAME OF THE MEDICINAL PRODUCT

Metalcaptase® 300 mg
enteric coated tablets
Active pharmaceutical ingredient: penicillamine

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 enteric coated tablet contains 300 mg penicillamine
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

enteric coated tablet

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Rheumatoid arthritis
- Wilson's disease
- Lead, mercury, copper, and zinc poisoning
- Cystinuria with detected cysteine stones when recurrence of stones cannot be prevented by other methods (methionine-free diet, hyperhydration, alkalisation of urine) as well as in cases of advanced cysteine stone disorders involving special risks (e.g. after nephrectomy).
- There is some evidence that scleroderma may respond to treatment with Metalcaptase 300 mg.

### 4.2 Posology and method of administration

Dosage

Adults

- The daily dose for patients with rheumatoid arthritis is 150 mg penicillamine in the first two weeks, 300 mg in the third and fourth weeks, 450 mg in the fifth and sixth week and 600 mg from the seventh to the sixteenth week. If the effect is insufficient the daily dose is increased after the sixteenth week in 150 mg steps every two weeks according to the same schedule up to a maximum dose of 900 mg, or temporarily to as much as 1 200 mg. After the drug begins to take effect of action, the daily dose is gradually reduced to the individual maintenance dose of 300 to 600 mg of penicillamine.
  For the initiation of treatment and the gradual increase/decrease of the dosage tablets with reduced amount of active substance (150 mg penicillamine) are available.
  The daily dose should be distributed evenly over the day.
- Patients with Wilson's disease should take 10 to 20 mg of penicillamine per kilogram body weight per day.
- An initial daily dose of 4 x 300 mg penicillamine is recommended for patients with heavy metal poisoning. If treatment is prolonged, the daily dose should not exceed 40 mg of penicillamine per kilogram body weight.
- Patients with cystinuria should receive four doses of 225 to 525 mg penicillamine daily, depending on cysteine excretion.

Children and adolescents

- Metalcaptase 300 mg is not suitable for therapy of rheumatoid arthritis in children and adolescents because the amount of the active ingredient is too high. Tablets with a reduced amount of active ingredient are available.
- Wilson's disease: 10 to 20 mg penicillamine per kilogram body weight daily.
- A daily dose of up to 100 mg of penicillamine per kilogram body weight is recommended for patients with heavy metal poisoning. The maximum daily dose of penicillamine in these cases is 1 050 mg.

- Patients with cystinuria should receive 4 doses of 225 to 525 mg penicillamine daily, depending on cysteine excretion.

Method of administration
The drug should be taken on an empty stomach or one hour before or 2 to 3 hours after meals with generous amounts of liquids.

To preserve the gastric acid resistant coating, coated tablets must not be split or chewed.

Metalcaptase 300 mg therapy for rheumatoid arthritis can be discontinued entirely in the case of prolonged remission.

**4.3 Contraindications**
Metalcaptase 300 mg may not be used in the presence of:
- Hypersensitivity to the active pharmaceutical ingredient or to any of the excipients listed in section 6.1,
- Penicillin allergy,
- Renal injuries,
- Bone marrow disorders,
- Systemic lupus erythematodes (SLE) or evidence of antinuclear antibodies in higher titre levels,
- Parenchymal liver disorders,
- Simultaneous gold or chloroquine therapy.

**4.4 Special warnings and precautions for use**
Prior to Metalcaptase 300 mg treatment, analysis of the blood, urine, creatinine, serum transaminases, cholestasis parameters and neurological status is required to identify specific risks.

Blood counts (thrombocyte and leucocyte counts) and urine tests (for proteinuria and erythrocyte sedimentation) should be performed regularly during treatment, every one to two weeks initially and at a maximum interval of four weeks from the third month. If treatment must be discontinued owing to changes in the blood count or the urine findings, patients must still be monitored closely until the findings return to normal.

Serum transaminases and $\gamma$-GT should be monitored at four-week intervals.

The patient should be examined or queried every four weeks to ensure early detection of neurological complications.

Patients known to be prone to allergic reactions (hay fever, eczema, nettle rash, asthma attacks) require especially close monitoring.

Criteria for discontinuing Metalcaptase 300 mg treatment:
Confirmed proteinuria, creatinine exceeding 2 mg %, leucopenia below 3 000/mm³, drop in granulocytes below 1 500/mm³, thrombocytopenia below 120 000/mm³ or a drop to 50 % of initial values, skin symptoms requiring clarification, eye-muscle paralysis, risk-relevant increases in ANA titres and an increase in the biochemical signs of cholestasis or an increase in transaminases.

**4.5 Interaction with other medicinal products and other forms of interaction**
Indomethacin can cause elevated penicillamine levels in the plasma.

In combination with azathioprine, Metalcaptase 300 mg tolerance is reduced.

Preparations containing iron should be taken at least two hours before or after Metalcaptase 300 mg. Taking them concurrently reduces penicillamine absorption (by as much as 70 %). The same applies to antacids containing magnesium or aluminium and to sucralfate.

Prolonged Metalcaptase 300 mg therapy may lead to a deficiency of vitamin $B_6$ making supplements (80 to 160 mg per day) necessary.

Therapy with preparations containing gold in the prehistory of patients undergoing penicillamine treatment increases the risk of bone marrow injury.

Concurrent therapy with cytotoxic drugs, phenylbutazone or oxyphenbutazone increases the risk of bone marrow and kidney injury.

**4.6 Fertility, pregnancy and lactation**

Effective contraceptive measures should be ensured when treating women of child-bearing age. Metalcaptase 300 mg may not be used to treat rheumatic arthritis during pregnancy. For other diseases, treatment with Metalcaptase 300 mg should only be continued if no other therapy with a better benefit/risk ratio in this regard is available.

Nursing should be discontinued during treatment with Metalcaptase 300 mg (see also section 5.3d, "Reproductive toxicity").

**4.7 Effects on ability to drive and use machines**

None known so far.

**4.8 Undesirable effects**

Metalcaptase 300 mg treatment entails many side effects, some of them severe.
The following frequency details are used as a base for the assessment of the side effects:

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|---|---|
| Very common | (≥ 1/10) |
| Common | (≥ 1/100 to < 1/10) |
| Uncommon | (≥ 1/1 000 to < 1/100) |
| Rare | (≥ 1/10 000 to < 1/1 000) |
| Very rare | (< 1/10 000) |

Blood and lymphatic system disorders

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| Common | bone marrow disorders (leucopenia, thrombocytopenia, aplastic anaemia), involving the danger of agranulocytosis and even panmyelopathy. |
| Very rare | Disregarding of damage to the bone marrow can be fatal in isolated cases, although a benign outcome can usually be expected if side effects are detected early and the therapy is immediately discontinued. |

Immune system disorders

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| Common | skin symptoms, mostly allergic in nature (various forms of exanthema, erythema, urticaria, papulohaemorrhagic skin lesions, purpura), on rare occasions accompanied by fever. |
| Uncommon | myasthenic syndrome (mainly ocular myasthenia) and the clinically latent humoral antinuclear antibody syndrome as an indication of the risk of induction of autoimmune disorders. |
| Very rare | systemic lupus erythematodes. |

Metabolism and nutrition disorders

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| Very common | generally harmless gustatory disorders that can be reversed by reducing the dosage or discontinuing treatment (from hypogeusia to ageusia). |
| Very rare | intrahepatic cholestasis, increased formation of insulin antibodies.<br>Only a few isolated case reports have referred to significant effects on the blood sugar level, however. |

Nervous system disorders

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| Very rare | neuritis nervi optici.<br>It should be noted that neurological symptoms may be aggravated (irreversibly in some cases) when patients with Wilson's disease are treated. If this occurs, penicillamine therapy should be discontinued. |

Respiratory, thoracic and mediastinal disorders

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| Very rare | reversible pulmonary infiltrates, chronic progressive lung mutations (comparable to fibrosing alveolitis) |

Gastrointestinal disorders

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| Very common | gastric intolerance, loss of appetite, nausea, retching, less often diarrhea |
| Uncommon | gastric or intestinal bleeding. |
| Very rare | provocation of ulcerous colitis. |

Skin and subcutaneous tissue disorders

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| Common | mucosal complications (buccal or lingual ulceration) |
| Very rare | Disregarding damage to skin (pemphigus) can be fatal in isolated cases, although a benign outcome can usually be expected if side effects are detected early and the therapy is immediately discontinued. |
| Very rare | pseudoxanthoma elasticum, elastosis perforans serpiginosa or lichen planus. Blunt injuries to the skin of patients receiving high doses may cause blood blisters at the pressure or contusion site which later form papules or plaques. Hirsutism, hair loss. |
| Very rare | Xanthochromia of the nails. |

Musculoskeletal, connective tissue and bone disorders

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| Very rare | polymyositis, dermatomyositis. |

Renal and urinary disorders

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| Common | Proteinuria, sometimes accompanied by haematuria, as a symptom of kidney damage (immunocomplex nephritis). It can develop into a nephrotic syndrome at any time. |
| Very rare | Disregarding of damage to the kidneys can be fatal in isolated cases, although a benign outcome can usually be expected if side effects are detected early and the therapy is immediately discontinued. |

Reproductive system and breast disorders

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| Very rare | mammary enlargement after sustained treatment. |

Investigations

Testing for ketone bodies (nitroprusside test) may yield false positive results.

Surgical and medical procedures

Metalcaptase 300 mg therapy should be interrupted in patients undergoing surgery because of the possible influence on collagenous and elastic tissue, or the dose should be reduced six weeks prior to major surgery and kept low until wound healing is completed.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

## 4.9 Overdose

No case of overdose has been reported. A single acute accidental or intentional overdose therefore requires no special action apart from gastrolavage. If penicillamine has already been absorbed, excretion can be accelerated by forced diuresis or dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Antirheumatic, antidote to heavy metal poisoning.

Pharmacotherapeutic group: Specific antirheumatic, ATC code: M01CC01

Penicillamine is a chelating agent. The free electron pairs of nitrogen and sulphur in combination with the COOH group serve to bind the heavy metals. (Treatment of heavy metal intoxication and Wilson's disease). Penicillamine leads to the cleavage of autologous disulphide. This can result in gradual dissolution of cysteine stones in cystinuria patients.

Long-term therapy with penicillamine can modify the course of rheumatoid arthritis even to the point of remission. The mode of action has not been adequately explained. In animal experiments, inflammation models have shown no effect. Its potency may be due to an immunosuppressive effect (reduction of T-lymphocytes in synovial tissue).

### 5.2 Pharmacokinetic properties

Penicillamine is absorbed only incompletely (40 to 50 %) when administered orally. Maximum blood levels are reached after one to two hours. For the most part penicillamine is present in plasma as a disulphide or mixed disulphide together with cysteine. It is excreted almost exclusively through the kidneys in the form of penicillamine disulphide, cysteine-penicillamine disulphide and, in small amounts, as S-methyl penicillamine. The terminal elimination half-life is four to six hours.

### 5.3 Preclinical safety data

a) Acute toxicity

see section 4.9 „overdose“

b) Chronic toxicity / subchronic toxicity

In studies of the chronic toxicity of penicillamine, toxic effects were observed in rats (dose: 540 mg/kg body weight) and dogs (dose: 240 mg/kg body weight) in the form of proteinuria, glomerulonephritis and skin changes.

c) Mutagenic and carcinogenic potential

In vitro studies have indicated that penicillamine has a clear mutagenic effect. This finding has not been confirmed yet by in vivo studies in animals and humans. However induction of mutations by long-term, high-dose administration of penicillamine cannot be ruled out.

No long-term studies of the drug's tumour-generating potential in animals are available.

d) Reproductive toxicity

Penicillamine is embryotoxic in rats and mice, and in high doses it produces teratogenic effects in the skeleton and organs of rats. Several cases of connective tissue defects have been described in humans and traced to the interaction of penicillamine with collagens and elastin. Central nervous system injuries have also occurred. Although no connection between deformity and dose has been demonstrated with certainty, daily doses exceeding 500 mg should be avoided in pregnant women if possible.

It is not known whether penicillamine passes into human milk.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Calcium behenate, calcium hydrogen phosphate-dihydrate, cellulose (microcrystalline and powder), copovidon, dimeticon, macrogol 6 000, cornstarch, poly (methacrylic acid-co-methylmethacrylate) (1:1), triacetin, methacrylic acid-ethylacrylate-copolymer (1:1), polysorbate 80, hydrogenated castor oil, highly disperse silicondioxide, talc, titaniumdioxide.

### 6.2 Incompatibilities
None known so far.

### 6.3 Shelf life
The shelf life is five years.

Do not use the medicinal product after the expiry date.

The expiry date is printed on the carton.

### 6.4 Special precautions for storage
Do not store above 25 °C!

Keep out of the reach and sight of children!

### 6.5 Nature and contents of container
Package with 50 enteric coated tablets in blisters
Package with 100 enteric coated tablets in blisters

### 6.6 Special precautions for disposal and other handling
No special requirements.

## 7. MARKETING AUTHORISATION HOLDER
**HEYL** Chem.-pharm. Fabrik
GmbH & Co. KG
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## 8. MARKETING AUTHORISATION NUMBER
6812873.00.00

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 11.02.1999
Date of latest renewal: 09.07.2009

## 10. DATE OF REVISION OF THE TEXT
December 2014

## 11. PRESCRIPTION STATE
By prescription only