SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cuprenil 250 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: D-penicillamine.
Each tablet contains 250 mg D-penicillamine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets, pink colour, round shaped, convex on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
- Severe, active rheumatoid arthritis
- Wilson's disease (hepatolenticular degeneration)
- Cystinuria
- Lead poisoning
- Chronic active hepatitis.

4.2 Posology and method of administration
The dosage is determined according to indications. Cuprenil should be taken on an empty stomach at least half an hour before meals.

Posology

Severe, active rheumatoid arthritis, including juvenile forms

- **Adults:** A dose of 125-250mg daily for the initial one month period. Increase by the same amount every 4 to 12 weeks until remission occurs. The minimum maintenance dose to achieve suppression of symptoms should be used and treatment should be discontinued if no benefit is obtained within 12 months.
  
The usual daily maintenance dose is 500-750 mg. No more than 1.5 g of product can be taken a day. The dose should be kept at maintenance level for six months, thereafter, reducing the daily dosage by 125 to 250 mg every 12 weeks is recommended.
- **Elderly:** The initial dose should not exceed 125mg daily for the first month, increasing by similar increments every four to twelve weeks until remission. The daily dosage should not exceed 1 g of product.
- **Children:** The usual maintenance dose is 15 to 20mg/kg of body weight a day. The initial dose should be 2.5 to 5mg/kg/day, and increased every four weeks over a period of three to six months.

Wilson’s disease

- **Adults:** 1.5-2 g daily in divided doses. Upon remission, the daily dose may be reduced to 0.75 -1 g. For patients with a negative copper balance (more copper is lost than received), the lowest
effective dose should be chosen. A daily dose of 2 g daily should not be continued for more than one year.

- **Elderly:** Up to 20 mg per kg body weight daily in divided doses. The daily dose cannot exceed 1 g.
- **Children:** The usual daily dose is 15-20 mg/kg of body weight. It must be divided. The lowest daily dose is 500 mg.

**Cystinuria**

Ideally, establish the lowest effective dose by quantitative amino acid chromatography of urine.

i) Dissolution of cystine stones

**Adults:** 1000–3000 mg daily in divided doses, adjusted to maintain urinary cystine below 200mg/litre.

ii) Prevention of cystine stones

**Adults:** a daily dose of 500mg to 1000mg until the urine cystine level becomes lower than 300mg/l.

**Elderly:** the minimum effective dose until the urine cystine level becomes lower than 200mg/l.

**Children:** a lower effective dose should be determined to maintain urinary cystine levels below 200 mg/l.

**Indication**

During treatment, it is recommended to drink plenty (at least 3 liters per day) of fluids. Since urine is more acidic at night than during the day, the patient should drink 500 ml of water before going to bed and at night. Generally, the more fluids are drunk, the less penicillamine is needed. In order to minimize cystine synthesis, it is recommended to follow a diet that contains little methionine. In following this diet, a low amount of proteins get into the body, so it is not recommended for children and pregnant women.

**Lead poisoning**

- **Adults:** Daily oral dose of 1000-1500mg in divided doses until urinary lead is stabilised at 0.5 mg/day.
- **Elderly:** 20mg per kg body weight daily in divided doses until urinary lead is stabilised at less than 0.5mg/day.
- **Children:** Cuprenil should only be used in cases where blood lead levels <45mcg/dL. A total of 15-20mg/kg/day in 2-3 doses should be used.

**Chronic active hepatitis**

- **Adults:** The initial daily dose is 500mg, in divided doses, increasing gradually over three months to a maintenance dose of 1250mg daily. The concurrent use of corticosteroids is
forbidden. Throughout therapy, liver function tests should be carried out at suitable intervals for the assessment of disease status.

- **Children:** The safety and efficacy of penicillamine in children less than 18 years old with chronic active hepatitis have not been established. No data are available.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Lupus erythematosus.
- Patients with a history of aplastic anaemia or agranulocytosis during treatment with penicillium.
- Due to the potential for renal toxicity, penicillamine should not be used in patients with rheumatoid arthritis and with current or previous renal impairment.
- Should not be used in cases of chronic lead poisoning if a gastrointestinal X-ray shows derivatives containing lead. This medicine should only be used upon removal of the aforementioned derivatives from the gastrointestinal tract. Animal studies show that penicillamine may be ineffective or even dangerous, if too high a quantity of lead gets into the body during its use.
- Concomitant or previous treatment with gold may increase the risk of side effects with penicillamine treatment. Therefore, penicillamine should be used with caution in patients who have previously had adverse reactions to gold and concomitant treatment with gold should be avoided (see Section “Interaction with other medicinal products and other forms of interaction”).

### 4.4 Special warnings and precautions for use

Some patients, treated with penicillamine, may experience aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture syndrome, and myasthenia gravis.

For the first 6 months, every two weeks, and later – each month, a general urine analysis should be performed, and the quantitative blood cell composition and platelet count should be established. Patients should be informed of the signs and symptoms of granulocytopenia and/or thrombocytopenia such as fever, chills, sore throat or easy bruising. Laboratory tests should be repeated in this case.

Proteinuria and (or) hematuria, i.e., warning symptoms of commencing glomerulonephritis, sometimes causing nephrotic syndrome, may occur. These patients should be very closely monitored. In the cases of some patients, proteinuria symptoms go away during treatment, while in the cases of others, for whom the disorder persists, the treatment with penicillamine should be discontinued. If proteinuria and hematuria is observed, the doctor has to determine whether there is a dependency between the glomerular changes and the use of medicine.

If changes are observed in the urine of patients with Wilson’s disease or cystinuria who are treated with penicillamine, the ratio between the danger of the continued use of the product and the treatment benefit must be identified.

In order to observe the occurrence of kidney stones in patients with cystinuria who are being treated with penicillamine, it is recommended that an X-ray examination of the urinary tract be done as early as possible, once a year. Cystine stones can occur very fast, sometimes even within 6 months.
Although there are a low number of cases of drug-induced bile stasis in the liver and toxic liver inflammation reported, while using the medicine, it is recommended that the liver be examined every 6 months. Although obliterative bronchiolitis is rare, patients should be warned to seek prompt medical attention in case of breathlessness after physical load, or if coughing, whistling breath occurs because of unidentified reasons. In this case, you may need to examine lung function. Cases of dangerous myasthenia syndrome, during which myasthenia gravis may even occur, have been reported. Droopy eyelids and double vision due to weakened eye muscles are often the early symptoms of myasthenia gravis. Upon termination of penicillamine use, they usually disappear.

If you get herpes, penicillamine use should be discontinued. Herpes is treated with high doses of corticosteroids, which are administered alone, or sometimes combined with immunosuppressive drugs. Treatment usually lasts for several weeks or months, however, sometimes it is necessary to treat for more than a year.

Precautionary measures
In response to penicillamine administration, patients may experience chills or a rash during the second or third week of treatment. Early allergic reactions with a rash usually disappear within a few days after the discontinuation of drug use, however, they may rarely occur again in cases of using it again when starting at low doses. In the event of itching and a rash, antihistamines may be prescribed. Less frequently, usually after 6 months of use or later, a late allergic reaction, characterized by a rash, may develop. In this case, treatment should be discontinued. If you have rash, chills, joint pain, enlarged lymph nodes or other allergy symptoms, treatment should be discontinued.

Patients with increased sensitivity to penicillin may be allergic to penicillamine (cross-sensitivity occurs). Undesirable effects, previously caused by a very small amount of penicillin left in penicillamine during its production, are not possible, since penicillamine is now synthesized, and not derived by decomposing penicillin. Penicillamine affects the production of collagen and elastin, therefore, the dose should be reduced before surgery, i.e., 250 mg of penicillamine should be used. The usual therapeutic dose is only possible after the surgical wound is fully healed.

4.5 Interaction with other medicinal products and other forms of interaction
Cuprenil increases the need for vitamin B6 in the body. Cuprenil forms complex compounds with heavy metals, therefore, an interval of at least 2 hours should be maintained between taking Cuprenil and iron products. Cuprenil cannot be used together with medicines which result in bone marrow suppression, e.g. gold products and medicines for malaria, cytostatics, oxyfenbutazone or phenylbutazone. Penicillamine is a pyridoxine antagonist and increases its elimination in the urine, which may encourage the occurrence of anemia or peripheral neuritis.

4.6 Fertility, pregnancy and lactation
No controlled clinical studies with pregnant women were conducted. In animal studies, fetuses of rats, subject to 6 times higher than the highest recommended human dose, experienced skeletal defects and a cracked palate.

Use of product for pregnant women, according to indications:
• Wilson's disease. While no birth defects have been observed in children whose mothers were treated with penicillamine during pregnancy, pregnant women should use no more than 1 g of penicillamine a day. If a Caesarean section is planned, no daily dose higher than 250 mg is recommended during the last 6 weeks of pregnancy and after childbirth, until the surgical wound is fully healed.

• Rheumatoid arthritis. Pregnant women with rheumatoid arthritis cannot use the product, as malformations have been observed in children whose mothers were treated with penicillamine for rheumatoid arthritis or cystinuria during pregnancy.

• Cystinuria. Penicillamine is not recommended for pregnant women.

Lactation:
It is not known whether the drug is excreted in breast milk, so penicillamine is not recommended for breastfeeding women.

4.7 Effects on the ability to drive or operate machinery

Cuprenil has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

The frequency of undesirable effects is defined as:
• very common (≥ 1/10)
• common (from ≥ 1/100 to < 1/10)
• uncommon (from ≥ 1/1000 to < 1/100)
• rare (from ≥ 1/10,000 to < 1/1000)
• very rare (< 1/10,000) and not known (cannot be calculated from the available data).

Infections and infestations:
Rare: chronic bronchitis

Blood and lymphatic system disorders:
Common: thrombocytopenia, lymphadenopathy
Uncommon: neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia

Immune system disorders
Common: hypersensitivity reaction

Eye disorders
Rare: inflammation of the eye nerve

Ear and labyrinth disorders:
Rare: tinnitus

Respiratory disorders, thoracic and mediastinal disorders:
Rare: chronic bronchitis

Gastrointestinal disorders:
Common: stomatitis
Rare: pancreatitis, stomach ulcer relapse

Liver and biliary tract disorders:
Rare: cholestasis

Skin and connective tissue disorders:
Common: hives, erythema, itching
Rare: exfoliative dermatitis, toxic epidermal necrolysis (Lyell’s syndrome), pemphigus.

Musculoskeletal and connective tissue disorders:
Common: arthralgia.
Rare: myasthenia gravis, lupus band.

Renal and urinary tract disorders:
Common: glomerulonephritis, urinary tract infection.
Rare: Goodpasture syndrome.

General disorders:
Uncommon: pyrexia.

Reporting of suspected adverse reactions
The reporting of suspected adverse reactions after use 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 by completing the form and sending it by post to the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, e-mail: adr@urpl.gov.pl.

4.9 Overdose
No reports of serious poisoning with penicillamine have been received so far, but the therapeutic dose can cause various side effects.
During treatment, especially at the beginning, you may experience an acute hypersensitivity reaction. In patients with a known hypersensitivity to penicillins, a cross-hypersensitivity reaction is possible.
Aid measures. Treatment is symptomatic.
Allergic reaction. Penicillamine should be discontinued and the use of corticosteroids should be started, with later treatment with penicillamine started again at a low dose, which is gradually increased until the desired therapeutic effect occurs.
Iron and vitamin B6 deficiency. It is necessary to eliminate iron and vitamin B6 deficiency.
Dysgeusia. The recommended daily dose is 5-10 mg copper, i.e., 5-10 drops of 4% copper sulfate pentahydrate solution. It should be taken divided into two doses.
In case of patients with Wilson's disease, the use of copper products is prohibited.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group - specific antirheumatic agents, ATC code - M01 CC01.

Cuprenil is a medicine which forms complex compounds by actively binding with metal ions. It binds to metals, mostly copper, mercury, lead and iron, and forms stable soluble complex compounds, which are excreted in the urine.
It is not exactly known how penicillamine affects rheumatoid arthritis, but it is thought that the drug increases lymphocyte activity. It significantly reduces the concentrations of rheumatoid factor (IgM) and immunoglobulin complexes in the plasma and joint fluids, and has almost no effect on the general plasma concentration of immunoglobulin. In vitro, penicillamine inhibits T lymphocyte activity and does not affect B lymphocytes.
Cuprenil is the most suitable medicine for Wilson’s disease (hepatolenticular degeneration). This disease is caused by a disorder in copper metabolism, because of which, copper starts accumulating in various organs: kidneys, brain, liver, eyeballs. The drug reduces the absorption of copper from food and promotes its
removal from tissue. In addition, this product is an effective treatment measure in cases of acute poisoning with lead or other heavy metals (iron, mercury, copper).

Penicillamine is used to treat urinary stone disease. In the bodies of patients with cystinuria, penicillamine forms a complex compound, penicillin cysteine disulfide, which is more soluble than cystine and easily excreted through the kidneys. Because of these changes, cystine concentration in urine is significantly reduced, and it is very important for the prevention of cystine stones. If properly treated, cystine stones gradually dissolve.

5.2 Pharmacokinetic properties
Penicillamine with heavy metal ions forms chelates – persistent complex compounds, which are soluble in water and excreted in urine. The product is well absorbed from the gastrointestinal tract. Following oral administration of penicillamine, the highest blood concentration is reach in approximately 2 hours. Cuprenil metabolism is two-phase: during the first phase, its half-life takes 1 hour, while during the second phase – 5 hours. Penicillamine penetrates into almost all tissues. Within 48 hours, approximately 80% of a dose is removed with urine and faeces.

5.3 Preclinical safety data
Administered penicillamine causes minimal toxic effects. Its LD50 in mice is 5000 mg/kg of body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Potato starch,
Lactose monohydrate,
Povidone,
Talc,
Magnesium stearate.

Coating:
Hypermellose,
Macrogol 4000,
Titanium dioxide (E171),
Lacquer containing azorubine (E122).

6.2 Incompatibilities
There is a lack of information on physical and chemical incompatibility of the drug in cases of mixing it with other medicinal products.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the temperature under 25°C.

6.5 Nature and contents of container
PVC/Al foil blisters in a carton box.
2 blisters, 15 tablets in each (30 tablets, in total).  
The container is made of polyethylene/polypropylene with a cap.  
100 tablets in each container.

6.6   Special precautions for disposal

No special requirements.

7.   MARKETING AUTHORITY HOLDER

Teva Pharmaceuticals Polska Sp. zo.o.  
Ul. Emilii Plater 53  
00-113 Varšuva  
Lenkija

8.   MARKETING AUTHORISATION NUMBER(S)

942  
R/1262

9.   DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION


10.  DATE OF REVISION OF THE TEXT

Stamp: /2013 10 24/