SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Penicillamine 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg penicillamine.

Excipient with known effects: Each tablet contains 96 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

A round, white normal biconvex film coated tablet embossed with 'PC 250' on one side and marked 'G' on reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Severe active rheumatoid arthritis including juvenile forms.
2. Wilson's disease (hepatolenticular degeneration) in adults and children (0 to 18 years).
3. Cystinuria – dissolution and prevention of cystine stones in adults and children (0 to 18 years).
4. Lead poisoning in adults and children (0 to 18 years).
5. Chronic active hepatitis in adults.

4.2 Posology and method of administration

Posology

a) Rheumatoid Arthritis

Adults

A daily dose of 125 - 250 mg per day is recommended for the first month, increasing by the same amount every four to twelve weeks until remission occurs. The minimum maintenance dose to achieve suppression of symptoms should be used and treatment should be discontinued if no improvement occurs within 12 months. Improvement may not occur for some months. The usual maintenance dose is 500 mg to 750 mg daily. However, up to 1500 mg daily may be required.

Reduction in maintenance dosage by 125 mg to 250 mg every 12 weeks may be attempted after a period of 6 months continuous remission.

Elderly

The initial dose should not exceed 125 mg daily for the first month, increasing by similar increments every four to twelve weeks until the minimum maintenance dose to supress symptoms is reached. Daily dosage should not exceed 1000 mg (see section 4.4).

Paediatric population

The usual maintenance dose is 15 to 20 mg/kg/day. The initial dose should be lower (2.5 to 5 mg/kg/day) and increased every four weeks over a period of three to six months.

Patients with Renal impairment

Penicillamine therapy should be initiated at a low dose with intervals between dose increase of at least twelve weeks. Fortnightly monitoring for toxicity is mandatory throughout treatment for rheumatoid arthritis.

b) Wilsons Disease

Patients must be maintained in negative copper balance and the minimum dose of Penicillamine required to achieve this should be given.

Adults

1500 mg to 2000 mg daily in divided doses. Dose reduction may be attempted when remission occurs, decreasing to 750 mg to 1000 mg per day. It is advisable that a dose of 2000 mg per day should not be continued for more than 12 months.

Elderly

20 mg/kg/day in divided doses adjusting the dose minimal level necessary to control disease.

Paediatric population

20 mg/kg/day in two or three divided doses, given 1 hour before meals. For older children (>12 years) the usual maintenance dose is 750 mg to 1000 mg daily.

Patients with Renal impairment

Extra precautions should be taken to monitor for adverse effects in patients with Wilson's disease and renal insufficiency.

c) Cystinuria

The lowest effective dose should be used and this is determined by quantitative amino acid chromatography of urine.

(i) Dissolution of cystine stones

Adults

1000 mg to 3000 mg daily, in divided doses. Cystine levels in urine should not exceed 200 mg/litre.

(ii) Prevention of cystine stones

Adults

500 mg to 1000 mg at bedtime. Maintenance of adequate fluid intake (not less than 3 litres/day is important). Cystine levels in the urine should not exceed 300 mg/litre.

Elderly

Use the minimum dose to maintain urinary cystine levels below 200 mg/litre.

Paediatric population

20 to 30 mg/kg/day in two or three divided doses, given 1 hour prior to meals, adjusted to maintain urinary cystine level below 200 mg/litre.

Patients with Renal impairment

If renal insufficiency is present at the onset of therapy, the starting dose should be lower, but it will be necessary to give sufficient Penicillamine to achieve urine cystine levels of not more than 300 mg/litre. The maintenance dose should be reviewed at intervals of not more than four weeks.

d) Lead Poisoning

Adults

1000 mg to 1500 mg daily, in divided doses until urinary lead is stabilised at less than 0.5 mg per day.

Elderly

20 mg/kg/day in divided doses until lead levels in the urine is stabilised at less than 0.5 mg per day.

Paediatric population

Penicillamine should only be used in cases where blood lead levels <45 mcg/dL. A total of 15 – 20 mg/kg/day in 2 – 3 doses should be used.

e) Chronic active hepatitis

Adults

For maintenance treatment after the disease process has been brought under control with corticosteroids. The initial dose of 500 mg daily in divided doses, should be increased gradually over three months to a maintenance dose of 1250 mg daily. During this period, the dose of corticosteroids should be phased out. Throughout therapy, liver function tests should be carried out periodically to assess the disease status.

Elderly

Not recommended.

Paediatric population

The safety and efficacy of penicillamine in children less than 18 years with chronic active hepatitis has not been established. No data are available.

Method of administration

For oral administration.

Penicillamine should be taken on an empty stomach at least half an hour before meals in adults and one hour before meals in paediatric patients, or on retiring.

As the smallest available tablet is 125 mg, this might not be suitable for very young children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Agranulocytosis, aplastic anaemia or severe thrombocytopenia due to penicillamine.

Lupus erythematosus.

Moderate or severe renal impairment.

4.4 Special warnings and precautions for use

Full blood and platelet counts should be performed and renal function should be assessed prior to treatment with penicillamine.

Monitoring of blood and platelet counts should be carried out at appropriate intervals, together with urinalysis for detection of haematuria and proteinuria (see section 4.8). Urinalysis should be carried out weekly at first, and following each increase in dose, then monthly, although longer intervals may be adequate for cystinuria and Wilson's disease. Increasing or persistent proteinuria may necessitate withdrawal of therapy.

During the first eight weeks of therapy full blood counts should be carried out weekly or fortnightly and also in the week after any increase in dose, otherwise monthly thereafter. In cystinuria or Wilson's disease, longer intervals may be adequate.

If platelets fall below 120,000 per mm^3 or white blood cells below 2,500 per mm^3, or if three consecutive falls are noted within the normal range, withdrawal of treatment should be considered. When counts return to normal, treatment may be restarted at a reduced dosage,

but should be permanently withdrawn on recurrence of leucopenia or thrombocytopenia. Penicillamine may potentiate the bone marrow suppression caused by clozapine.

Care should be taken and dosage modified, if needed, in patients with renal impairment (see section 4.2).

Especially careful monitoring is necessary in older people since increased toxicity has been observed in this patient population regardless of renal function.

Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage (see section 4.5).

Penicillamine should be used with caution in patients who have had adverse reactions to gold.

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 4.5).

Penicillamine should not be used in patients who are receiving concurrently antimalarial drugs such as hydroxychloroquine phosphate, chloroquine. These drugs having similar hematologic and renal adverse reactions, could act synergistically when used together with penicillamine (See section 4.5).

If concomitant oral iron, digoxin or antacid therapy is indicated, this should not be given within two hours of taking penicillamine (see section 4.5).

Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions (see section 4.8).

Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see section 4.8).

Haematuria is rare, but if it occurs in the absence of renal stones or other known causes, treatment should be stopped immediately (see section 4.8).

A late rash, described as acquired epidermolysis bullosa and penicillamine dermopathy, may occur after several months or years of therapy. This may necessitate a reduction in dosage (see section 4.8).

Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men (see section 4.8). Danazol has been used successfully to treat breast enlargement which does not regress on drug discontinuation.

The use of DMARDs, including penicillamine, has been linked to the development of septic arthritis in patients with rheumatoid arthritis, although rheumatoid arthritis is a stronger predictor for the development of septic arthritis than the use of a DMARD (see section 4.8).

Deterioration of the neurological symptoms of Wilson’s disease (dystonia, rigidity, tremor, dysarthria) have been reported following introduction of penicillamine in patients treated for this condition. This may be a consequence of mobilisation and redistribution of copper from the liver to the brain (see section 4.8).

Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement of this vitamin (see section 4.5).

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant use of iron or antacids: oral absorption of penicillamine may be reduced by concomitant administration of iron or antacid (see section 4.4).

Concomitant use of digoxin: oral absorption of digoxin may be reduced by concomitant administration of penicillamine (see section 4.4).

Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage (see section 4.4).

Concomitant use of antimalarial drugs such as hydroxychloroquine phosphate, chloroquine: These drugs having similar hematologic and renal adverse reactions, could act synergistically when used together with penicillamine. (see section 4.4).

Concomitant use of gold: concomitant use is not recommended (see section 4.4).

Concomitant use of clozapine: penicillamine may potentiate the blood dyscrasias seen with clozapine (see section 4.4).

Concomitant use of zinc: oral absorption of penicillamine may be reduced by concomitant administration of zinc; absorption of zinc may also be reduced by penicillamine.

Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of penicillamine for use during pregnancy has not been established (see section 5.3).

Wilson's disease: There have been several cases of reversible cutis laxa in infants born to mothers taking penicillamine throughout pregnancy. Although there have been no controlled studies on the use of penicillamine during pregnancy, two retrospective studies have reported the successful delivery of 43 normal infants to 28 women receiving between 500 mg and 2000 mg of penicillamine daily. There are also anecdotal reports both of congenital abnormalities and of successful outcomes in patients who have remained on penicillamine during pregnancy. If treatment with penicillamine is to be continued following a risk-benefit analysis, consideration should be given to reducing the dose of penicillamine to the lowest effective dose.

Cystinuria: Whilst normal infants have been delivered, there is one report of a severe connective tissue abnormality in the infant of a mother who received 2000 mg penicillamine daily throughout pregnancy. Whenever possible, penicillamine should be withheld during pregnancy, but if stones continue to form, the benefit of resuming treatment must be weighed against the possible risk to the foetus.

Rheumatoid arthritis or chronic active hepatitis: Penicillamine should not be administered to patients who are pregnant, and therapy should be stopped when pregnancy is diagnosed or suspected, unless considered to be absolutely essential by the physician.

Breast-feeding

Due to the lack of data on the use in breast-feeding patients and the possibility that penicillamine may be transmitted to newborns through breast milk, penicillamine should only be used in breast-feeding patients when it is considered absolutely essential by the physician.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most common of all side-effects are thrombocytopenia and proteinuria.

Thrombocytopenia occurs commonly. The reaction may occur at any time during treatment and is usually reversible.

Proteinuria occurs in up to 30% of patients and is partially dose-related (see section 4.4).

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000), very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

The incidence and severity of some of the adverse reactions, noted below, varies according to the dosage and nature of the disease under treatment.

Blood and lymphatic system disorders	
Common:	Thrombocytopenia.
Not known:	Neutropenia [8], agranulocytosis [1], aplastic anaemia [1], haemolytic anaemia, leucopenia.
Immune system disorders	
Rare:	Allergic reactions including hypersensitivity.
Metabolism and nutrition disorders	
Not known:	Anorexia [2].
Nervous system disorders	
Not known:	Loss of taste [4].
Vascular disorders	
Not known:	Pulmonary haemorrhage, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Not known:	Inflammatory conditions of the respiratory tract such as bronchiolitis, pneumonitis, yellow nail syndrome.
Gastrointestinal disorders	
Rare:	Mouth ulceration, stomatitis.

Not known:	Pancreatitis, nausea [2], vomiting.
Hepatobiliary disorders	
Not known:	Cholestatic jaundice.
Skin and subcutaneous tissue disorders	
Rare:	Alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity.
Not known:	Rashes [2], urticarial reactions [3], dermatomyositis, pemphigus, Stevens-Johnson syndrome, acquired epidermolysis bullosa [6], penicillamine dermopathy [6].
Musculoskeletal and connective tissue disorders	
Not known:	Drug induced lupus erythematosus, myasthenia gravis, polymyositis, rheumatoid arthritis.
Renal and urinary disorders	
Very common:	Proteinuria.
Rare:	Haematuria [5].
Not known:	Nephrotic syndrome, glomerulonephritis, Goodpasture's syndrome.
Reproductive system and breast disorders	
Rare:	Breast enlargement [7].
General disorders and administration site conditions	
Not known:	Fever [2].

[1.] Deaths from agranulocytosis and aplastic anaemia have occurred.
[2.] Nausea, anorexia, fever and rash may occur early in therapy, especially when full doses are given from the start.
[3.] Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions (see section 4.4).
[4.] Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see section 4.4).
[5.] Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately (see section 4.4).
[6.] A late rash, described as acquired epidermolysis bullosa and penicillamine dermopathy, may occur after several months or years of therapy (see section 4.4).
[7.] Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men (see section 4.4).
[8.] The reaction may occur at any time during treatment and are usually reversible (see section 4.4).

The development of septic arthritis in patients with rheumatoid arthritis has been linked to the use of DMARDs, including penicillamine (see section 4.4).

Deterioration of the neurological symptoms of Wilson's disease (dystonia, rigidity, tremor, dysarthria) have been reported following the introduction of penicillamine in patients treated for this condition (see section 4.4).

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There are no reported cases of undesirable reactions to penicillamine overdosage and no special treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antirheumatic drugs, ATC code: M01CC01

1. Penicillamine is used to treat severe active rheumatoid arthritis not adequately controlled by NSAID therapy.
2. Penicillamine is a chelating agent which aids the elimination from the body of certain heavy metal ions, including copper, lead and mercury, by forming stable soluble complexes with them that are readily excreted by the kidney.
3. It is used in the treatment of Wilson's disease (hepatolenticular degeneration), in conjunction with a low copper diet, to promote the excretion of copper.
4. It may be used to treat asymptomatic lead intoxication.
5. Penicillamine is used as an adjunct to diet and urinary alkalinisation in the management of cystinuria. By reducing urinary concentrations of cystine, penicillamine prevents the formation of calculi and promotes the gradual dissolution of existing calculi.
6. Desensitisation. Should the physician deem it necessary to attempt to desensitise a patient to penicillamine, it should be noted that this formulation is not suitable for this purpose.

5.2 Pharmacokinetic properties

Penicillamine is a thiol-group containing chelating agent, variably absorbed from the gastrointestinal tract. The drug undergoes a rapid distribution phase, followed by a slower elimination phase.

Penicillamine is strongly plasma-protein bound. Most penicillamine is bound to albumin but some is bound to α-globulins or ceruloplasmin.

Penicillamine is not extensively metabolised in man.

About 80% of the absorbed dose is excreted rapidly in the urine, mostly as mixed disulphides. Some of the dose is excreted as a penicillamine copper complex and some as the S-methyl derivative.

5.3 Preclinical safety data

Penicillamine has been shown to be teratogenic in rats when given in doses several times higher than those recommended for human use.

There is no known LD50 value for penicillamine. In studies some rats died after oral administration of 10,000 mg/kg, but intra-peritoneal injections of a dose of 660 mg/kg caused no deaths.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains:

Povidone
Lactose
Sodium starch glycollate
Magnesium stearate

The film-coat contains:

Hydroxypropyl methylcellulose	(E464)
Titanium dioxide	(E171)
Polyethylene glycol	
Carnauba wax	

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a cool, dry place below 25°C.

6.5 Nature and contents of container

Penicillamine Tablets are available in polypropylene containers with polyethylene caps (with optional polyethylene ullage filler) 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited
T/A Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL

8. MARKETING AUTHORISATION NUMBER

PL 04569/0186

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4th December 1987 / 20th May 1998

10 DATE OF REVISION OF THE TEXT

11/02/2026