

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Distamine 125mg Film-coated Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 125mg D-penicillamine.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet.

White, film-coated tablet with a diameter of 8mm, marked “DS” on one face and “125” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- a) Severe active rheumatoid arthritis, including juvenile forms
- b) Wilson’s disease (hepatolenticular degeneration)
- c) Cystinuria – dissolution and prevention of cystine stones
- d) Lead poisoning
- e) Chronic active hepatitis

4.2 Posology and method of administration

For oral administration.

If possible, Distamine should be taken at least half an hour before meals, or on retiring.

a) Rheumatoid arthritis

Adults: 125 to 250mg daily for the first month. Increase by the same amount every four 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. Improvement may not occur for some months. The usual maintenance dose is 500 to 750mg daily. Up to 1500mg daily may be required.

If remission is established and has been sustained for six months, gradual reduction by 125 to 250mg amounts every 12 weeks may be attempted.

The elderly: Increased toxicity has been observed in this patient population regardless of renal function. Initial dose should not exceed 125mg daily for the first month, increasing by a similar increment every four to 12 weeks until the minimum maintenance dose to suppress symptoms is reached. Daily dosage should not exceed 1000mg.

Children: 15 to 20mg/kg/day is considered appropriate in the majority of cases. The initial dose should be lower (2.5 to 5mg/kg/day) and increased at four-weekly intervals over a period of three to six months. Please note that as the smallest available tablet is 125mg, this may not be suitable for children under eight years.

b) Wilson's disease

Adults: 1500 to 2000mg daily in divided doses. Dose may be reduced to 750mg to 1000mg daily when control of the disease is achieved. Patients must be maintained in negative copper balance and the minimum dose of penicillamine required to achieve this should be given.

It is advisable that a dose of 2000mg/day should not be continued for more than a year.

The elderly: 20mg/kg/day in divided doses. Adjust dose to control disease and maintain negative copper balance.

Children: Up to 20mg/kg/day in divided doses. Minimum dose 500mg/day.

c) Cystinuria

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

(i) Dissolution of cystine stones:

Adults: 1000 to 3000mg daily in divided doses.

Urine cystine levels of not more than 200mg/l should be maintained.

(ii) Prevention of cystine stones:

Adults: 500mg to 1000mg on retiring. Fluid intake should be not less than 3 litres/day.

Urine cystine levels of not more than 300mg/l should be maintained.

The elderly: Use the minimum dose to maintain urinary cystine levels below 200mg/l.

Children: No dose range established, but urinary cystine levels must be kept below 200mg/l. The minimum dose of penicillamine required to achieve this should be given.

d) Lead poisoning

Adults: 1000 to 1500mg daily in divided doses until urinary lead is stabilised at less than 0.5mg/day.

The elderly: 20mg/kg/day in divided doses until urinary lead is stabilised at less than 0.5mg/day.

Children: 20mg/kg/day.

e) Chronic active hepatitis

Adults: For maintenance treatment after the disease process has been brought under control with corticosteroids. The initial dose of 500mg daily, in divided doses, should be increased gradually over three months to a maintenance dose of 1250mg 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.

f) Desensitisation

See Section 5.1, "Pharmacodynamic properties".

Renal insufficiency will require more careful monitoring, as follows:

- a) *Rheumatoid arthritis:* Distamine 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.

- b) *Wilson's disease*: It is necessary to maintain patients in negative copper balance even in cases of renal insufficiency. Extra precautions should be taken to monitor the course of such patients for adverse effects.
- c) *Cystinuria*: Renal insufficiency may be present at the onset of therapy. A lower starting dose should be selected, but it will be necessary to give sufficient Distamine to achieve urine cystine levels of not more than 300mg/l. The maintenance dose should be reviewed at intervals of not more than four weeks.

4.3 Contraindications

Hypersensitivity to penicillamine or any of the excipients (see Section 6.1), except in a life-threatening situation, when desensitisation should be attempted (see Section 5.1, "Pharmacodynamic properties").

Agranulocytosis or severe thrombocytopenia due to penicillamine.

Lupus erythematosus.

Lactation.

Persistent proteinuria.

Moderate or severe renal impairment.

4.4 Special warnings and special precautions for use

Full blood counts including platelets, 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 "Undesirable effects").

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

Withdrawal of treatment should be considered if platelets fall below 120,000 or white blood cells below 2,500/mm³, or if three successive falls are noted within the normal range. Treatment may be restarted at a reduced dose when counts return to normal, but should be permanently withdrawn on recurrence of neutropenia or thrombocytopenia.

In patients with normal renal function, urine should be tested weekly at first, and following each increase in dose, then monthly, although longer intervals may be adequate for cystinuria and Wilson's disease. Increasing proteinuria may necessitate withdrawal of therapy.

Care should be exercised in patients with renal insufficiency; modification of dosage may be necessary (see Section 4.2, "Posology and method of administration").

Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions (see Section 4.8 "Undesirable effects").

Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see Section 4.8 “Undesirable effects”).

Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately (see Section 4.8 “Undesirable effects”).

A late rash, described as acquired epidermolysis bullosa and penicillamine dermatopathy, may occur after several months or years of therapy. This may necessitate a reduction in dosage (see Section 4.8 “Undesirable effects”).

Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men (see Section 4.8 “Undesirable effects”). In some patients breast enlargement was considerable and/or prolonged with poor resolution and others required surgery. 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 “Undesirable effects”).

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 “Undesirable effects”).

4.5 Interaction with other medicinal products and other forms of interaction

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

If concomitant oral iron therapy is indicated, this should not be given within two hours of taking penicillamine.

Caution should be observed when anti-inflammatory or other drugs with known propensity for causing renal or marrow injury are taken concurrently with penicillamine.

4.6 Pregnancy and lactation

Usage in pregnancy: The safety of penicillamine for use during pregnancy has not been established. It has been shown to be teratogenic in rats when given in doses several times higher than those recommended for human use.

Lactation: penicillamine is contraindicated in breast-feeding (see Section 4.3 “Contra-indications”).

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 500mg and 2000mg 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 2000mg 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.

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 are usually reversible (see Section 4.4 "Special Warnings and Precautions for Use").

Proteinuria occurs in up to 30% of patients and is partially dose-related (see Section 4.4 "Special Warnings and Precautions for Use").

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (greater than or equal to 1 in 10); common (less than or equal to 1 in 100, less than 1 in 10); uncommon (greater than or equal to 1 in 1,000, less than 1 in 100); rare (greater than or less than 1 in 10,000, less than 1 in 1,000) very rare (less than 1 in 10,000), not known (where no valid estimate of the incidence has been derived).

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

Table 1

Blood and Lymphatic system disorders	
Common:	Thrombocytopenia
Not known:	Neutropenia ⁸ , agranulocytosis ¹ , aplastic anaemia ¹ , haemolytic anaemia
Gastrointestinal disorders:	
Rare:	Mouth ulceration, stomatitis
Not known:	Pancreatitis, Nausea ² , vomiting
General disorders and administration site conditions	
Not known:	Fever ²
Hepatobiliary disorders	
Not known:	Jaundice

Immune system disorders

Rare: Allergic reactions including hypersensitivity

Metabolism and nutrition disorders

Not known: Anorexia²

Musculoskeletal and connective tissue disorders

Not known: Drug induced lupus erythamatosus, myasthenia gravis, polymyositis, rheumatoid arthritis

Nervous system disorders

Not known: Loss of taste⁴

Renal and urinary disorders

Very common: Proteinuria

Rare: Haematuria⁵

Not known: Nephrotic syndrome, glomerulonephritis, Goodpasture's syndrome

Reproductive system and breast disorders

Rare: Breast enlargement⁷

Respiratory, thoracic and mediastinal disorders

Not known: Inflammatory conditions of the respiratory tract such as bronchiolitis, pneumonitis

Skin and subcutaneous tissue disorders

Rare: Alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity

Not known: Rash², urticarial reactions³, dermatomyositis, pemphigus, Stevens-Johnson syndrome, acquired epidermolysis bullosa⁶, penicillamine dermopathy⁶.

Vascular disorders

Not known: Pulmonary haemorrhage

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 "Special Warnings and Precautions for Use").

⁴ Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see Section 4.4 "Special Warnings and Precautions for Use").

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 "Special Warnings and Precautions for Use").

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 "Special Warnings and Precautions for Use").

⁷ Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men (see Section 4.4 “Special Warnings and Precautions for Use”).

⁸ The reaction may occur at any time during treatment and are usually reversible (see Section 4.4 “Special Warnings and Precautions for Use”).

The development of septic arthritis in patients with rheumatoid arthritis has been linked to the use of DMARDs, including penicillamine (see Section 4.4 “Special Warnings and Precautions for Use”).

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 (see Section 4.4 “Special Warnings and Precautions for Use”).

4.9 Overdose

No instances of adverse reactions to an overdose of penicillamine have been recorded and no specific measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: M01C C

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. No fixed dosage regimen. An initial dose of 25mg daily is suggested, to be gradually increased in accordance with the patient’s response. Higher initial doses have been employed in cystinuric patients.

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 10,000mg/kg, but intra-peritoneal injections of a dose of 660mg/kg caused no deaths.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Magnesium stearate
Povidone
Sodium starch glycolate (Type A)

Tablet coating

Glycerol
Titanium dioxide (E171)
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottle with screw cap, containing 100 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Ltd
Avonbridge House
Bath Road
Chippenham
Wiltshire
SN15 2BB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PA 943/3/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th October 1975/ 12th October 2005

10. DATE OF REVISION OF THE TEXT

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