√ Nausea, loss of appetite, vomiting and occasional diarrhoea may occur.
√ Thrombophlebitis, pancreatitis, cheilosis, glossitis, gingivostomatitis, and elastosis perforans serpiginosa have been reported, but are rare.
√ There may be reversible impairment of taste.
√ A syndrome closely resembling disseminated erythematosus has been reported.
√ Severe and ultimately fatal glomerulonephritis and intra-alveolar haemorrhage (Goodpasture's syndrome) has occurred rarely.
√ Iron deficiency may develop, especially in menstruating women, and in children, supplemental iron therapy may be required.
√ It has been reported that Penicillamine also can induce a Pemphigus-like disorder, polymyosis and symptoms similar to those of myasthenia gravis.
√ There have been a few reports of increased serum alkaline phosphatase, and positive cephalin flocculation and thymol turbidity tests.
√ Reversible optic neuritis, possibly connected with pyridoxine deficiency.
√ Penicillamine causes an increase in the amount of soluble collagen. In rats, this results in inhibition of normal healing and also a decrease in tensile strength of intact skin. In man, this same abnormality probably is the cause of increased skin friability at sites especially subject to pressure or trauma, such as knees, shoulders, elbows, toes, and buttocks.

Extravasations of blood may occur which may be purpuric, with external bleeding if the skin is broken, or they may appear as vesicles containing dark blood. Neither type is progressive. There is no apparent association with bleeding elsewhere in the body and no associated coagulation defect has been found. Therapy may be continued in the presence of these lesions, although they may disappear if dosage is reduced.

The chelating action of the medicine may cause increased excretion of other heavy metals such as zinc, mercury and gold.

Breast enlargement has been reported as a rare complication of Penicillamine therapy in both women and men. Breast enlargement may resolve with discontinuation of Penicillamine. Some patients required an anti-estrogen medication to decrease breast size. In a few patients breast enlargement was considerable and/or prolonged with poor resolution and others required surgery.

OVERDOSE

The treatment of PENICITIN overdosage is nonspecific and essentially supportive. There is no known antidote.

DRUG INTERACTIONS

PENICITIN potentiates actions of Isoniazid.

STORAGE

Store at a temperature not exceeding 25°C. Protect from light & moisture.

PRESENTATION

5 strips of 10 capsule in a box

For further information please contact:-
SAMARTH LIFE SCIENCES PVT. LTD.
Ram Mandir Road, Goregaon (W),
Mumbai - 400 104.

For the use of a Registered Medical Practitioner or a Hospital or Laboratory only.

PENICILLAMINE CAPSULES USP

PENICITIN

COMPOSITION

Each capsule contains:
Penicillamine IP 250 mg

DESCRIPTION

Penicillamine is a chelating agent used in the treatment of Wilson's disease. It is also used to reduce cystine excretion in cystinuria and to treat patients with severe, active rheumatoid arthritis unresponsive to conventional therapy.

CLINICAL PHARMACOLOGY

It is the stable thiol group that gives Penicillamine its biological activity, making it an effective chelating agent for heavy metals. This enables it to form a soluble mixed disulfide with cysteine and to depolymerise large protein molecules. Penicillamine forms a chelate with copper. If the sulphydryl groups of certain enzymes are blocked by copper, the free sulphydryl group of Penicillamine may in some way be able to reactivate such enzymes, providing a second mechanism of action in Wilson's disease. In cystinuria Penicillamine reduces excess cysteine excretion by interchanging disulfide between Penicillamine and cysteine, resulting in formation of Penicillamine-cysteine disulfide, a substance that is much more soluble than cysteine and is excreted readily. It is not known how Penicillamine acts in producing beneficial effects in rheumatoid arthritis. It might act by interfering with the immune response, chelation of copper, dissociation of macroglobulins, effect on collagen, and antiviral activity.

PHARMACOKINETICS

PENICITIN is readily absorbed from the alimentary tract following oral administration. Up to 80% of the absorbed dose is excreted in the urine mainly as Penicillamine disulfide or as a mixed disulfide. It appears that distribution of PENICITIN is through the water space of the body. Plasma protein binding and tissue binding, especially by the skin, delay final clearance by several weeks. The initial half-life in blood is 20 minutes but this phase lasts for less than one hour. The half-life of the stored Penicillamine is about 90 hours.

THERAPEUTIC INDICATIONS

In severe, active rheumatoid arthritis, including Still's disease in children. As a chelating agent in the treatment of Wilson's disease and lead poisoning, PENICITIN enhance the urinary excretion of gold and mercury and other heavy metals. In the treatment of cystinuria in cases where high-fluid regimens are not adequate, or in conjunction with them.

DOSAGE & ADMINISTRATION

In all patients receiving PENICITIN it is important that PENICITIN be given on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other drug, food or milk.

In adults

Rheumatoid Disease:

Not more than 250 mg daily for one month, increasing by the same amount at intervals of not less

than one month, until a daily dose of 1500 mg has been reached. The dose should be kept to the lowest which is effective in order to minimise side effects. Many patients respond to a maintenance dose of 750 mg daily, and it may be worthwhile to keep patients on this dosage for several months before deciding on a further increment. Dose of PENICITIN for each individual must be sought by careful monitoring over a period of months. PENICITIN should be given in divided doses.
Therapeutic response to changes in maintenance dosage usually will not become evident for six to eight weeks. There is little point in persevering with PENICITIN if there is no response after six months at a full maintenance dose. In relapse of the therapy, most of the cases will respond to an increase, which should be gradual. Both seronegative and seropositive rheumatoid arthritis usually responds to PENICITIN.

Wilson's disease:
As a chelating agent most adult patients require the medicine in a daily dose of 1500 mg to 2000 mg. Improvement is often slow, though cupruresis is immediate and there may be clinical deterioration at first. Except in the most advanced case, substantial improvement can generally be expected. Patients who are vomiting or unable to swallow should be given parenteral E.D.T.A.

Lead Poisoning:
Patients who are vomiting or who are unable to swallow should be given parenteral E.D.T.A., but all others are best treated by means of PENICITIN in a dose of 250 to 1000 mg daily, in divided doses.

Other heavy metals poisoning:
PENICITIN enhance the urinary excretion of gold, iron, antimony, zinc and mercury.

Cystinuria:
A single 500 mg dose on retiring, following free fluids during the day, may effect stone dissolution in a functioning kidney. 750 to 1000 mg daily in divided doses is generally adequate and it should not be necessary to exceed 2000 mg daily.

Chronic active hepatitis:
Started with 500mg a day gradually increased over three months, to 1250mg a day.

In Children
The dose depends on the weight of the child.

Rheumatoid arthritis:
15mg to 20mg a day for each kilogram of body weight started with a low dose for the first month and increased gradually.

Wilson's disease:
Started with 500mg a day then increased to 20mg a day for each kilogram of body weight.

Cystinuria:
The dose will depend on illness of the child.

Lead poisoning:
20mg a day for each kilogram of body weight.

CONTRAINDICATIONS
Hypersensitivity to Penicillamine. Except in a life-threatening situations, PENICITIN should not be used in patients who are receiving gold therapy or antimalarial drugs.

WARNINGS AND PRECAUTIONS
Physicians planning to use PENICITIN should thoroughly familiarise themselves with potential toxicity and benefits. Each patient should remain constantly under the close supervision of the physician. Patients should be instructed to report promptly fever, sore throat, chills, bruising or bleeding. The skin and mucous membranes should be observed for allergic reactions.

The use of Penicillamine has been associated with fatalities due to aplastic anaemia, agranulocytosis, thrombocytopenia, Goodpasture's Syndrome and myasthenia gravis. Because of the potential for serious haematological and renal adverse reactions to occur at any time, haemoglobin determination, white and differential cell count, direct platelet count and urinalysis should be carried out at weekly intervals for the first four weeks, then at two-weekly intervals for the next five months and monthly thereafter for the duration of therapy. 1. PENICITIN treatment should be withdrawn if the total WBC falls below 3000 per mm^3, neutrophils fall below 2000 or platelets below 120,000, or if a steady decline over three successive tests is observed, even though the counts remain within the normal range.

♦A nephrotic syndrome may develop during therapy, and proteinuria may be a warning sign of its development. In some cases proteinuria disappears with continued therapy; in other cases the medicine must be discontinued. When a patient develops proteinuria, the physician should ascertain that it is a symptom of the nephrotic syndrome and not transitory proteinuria unrelated to Penicillamine. Withdraw treatment if albumin in the urine increases progressively to exceed 2 g per day.

♦If successive tests demonstrate haematuria discontinue PENICITIN treatment immediately.

♦Some patients may experience drug fever, a marked febrile response to PENICITIN usually in the second or third week following initiation of therapy. Drug fever may sometimes be accompanied by a macular cutaneous reaction. If fever, or a reaction in the skin, blood or urine appears, PENICITIN should be discontinued until the reaction subsides. After this, it should be reinstituted in patients with Wilson's disease in a small dose that is gradually increased until full dosage is attained.

♦Liver function tests are advisable every six months during the first year and a half of therapy.

♦PENICITIN increases the requirement of pyridoxine (Vitamin B_6) and in rare cases cause central and peripheral nervous symptoms which could be due to pyridoxine deficiency. Some authorities recommend prophylactic administration of 25 mg pyridoxine daily.

♦When PENICITIN is used in cystinuria, an annual X-ray is advised. Cystine stones form rapidly, sometimes in six months.

♦Cross-allergy to Penicillin and Penicillamine may occur and PENICITIN should be used with caution in the Penicillin-hypersensitive patient.

♦A neurological examination prior to therapy is advisable to distinguish pre-existing neurological disturbances from any which may arise during treatment. Should neurological abnormalities occur (excluding loss of taste), PENICITIN should be withdrawn and other appropriate therapy initiated.

♦Patients being treated with PENICITIN should not be subjected to elective surgical procedures, especially vascular surgery, as Penicillamine has the capacity to interfere with collagen cross-links.

♦Therapy with Penicillamine should, if possible, be discontinued for at least six weeks prior to surgery.

♦Some patients have experienced reversible optic neuritis, possibly related to pyridoxine deficiency. Patients complaining of visual disturbances should undergo a full ophthalmological examination.

The frequency and severity of some of the adverse reactions are greatly reduced by gradual introduction of PENICITIN.

Pregnancy:
PENICITIN can cause cutis laxa in the human foetus. It should not be given during pregnancy if possible because of its affinity for metals and cystine, and its effect on collagen. In severe, untreated Wilson's disease and when stones continue to form in patients with cystinuria, the benefits of therapy with the medicine must be evaluated against the risk. A patient with cystinuria, who was treated with Penicillamine 2 g a day during pregnancy, gave birth to a child with generalised connective tissue defect that may have been caused by Penicillamine

Breast-feeding:
No information is available on concentration of Penicillamine in breast milk.

ADVERSE EFFECTS

√ Penicillamine causes allergic reactions, the most common of which is a maculopapular or erythematous rash early in therapy, and occasionally accompanied by fever, arthralgia or lymphadenopathy and Urticaria

√ Other adverse reactions includes nephrotic syndrome, hepatic dysfunction, falling hair, tinnitus, elevated sedimentation rate, eosinophilia, monocytosis, leukocytosis, thrombocytosis, thrombocytopenia, bone marrow hypoplasia, leukopenia, and granulocytopenia ranging in severity from asymptomatic and reversible to agranulocytosis with fatalities.√

Allegato

AL MINISTERO DELLA SALUTE
USMAF-SASN ……Torino Caselle
UNITA' TERRITORIALE……Torino Caselle

Richiesta di importazione di medicinali ai sensi del D.M. 11/02/1997.

Il sottoscritto Dr. ……..……..……..……

Residente in …… via ……..

Tel. ……

Iscritto nell'Albo dell'Ordine dei Medici-Chirurghi di …..…….

al n. …… cod. regionale ……

chiede di importare il medicinale (contenente il seguente/i principio/i attivo/i):

Penicillamina ……..

nome commerciale: **PENICITIN**

forma farmaceutica: **250 MG**

nella quantità di numero ……..…...confezioni contenenti **50 CPR** di farmaco cadauno.

Prodotto dalla ditta: **Samarth** (specificare il nome dell'azienda).

Precisa che tale medicinale è regolarmente registrato nel Paese di provenienza: **INDIA**

Per il trattamento di ……

Tale medicinale è indispensabile per la cura del Sig. (iniziali o codice) ……

affetto da: ……

Dichiara altresì che il farmaco:

- Non ha valida alternativa terapeutica con altri medicinali registrati in Italia;
- Non contiene sostanze stupefacenti o psicotrope;
- Non è un emoderivato;
- Verrà impiegato sotto la propria responsabilità, dopo aver ottenuto il consenso informato scritto dal paziente;
- Che le generalità del paziente ed i documenti relativi al consenso informato sono custoditi presso il medico curante per la durata prevista dalla normativa vigente.

Particolari condizioni di conservazione del medicinale:
Temperatura (es. -20°C, da 2 a 8°C, <25°C, <30°C, nessuna indicazione): ……
Altro: ……

Luogo e data _____

_____

Timbro e firma leggibile del medico