PRESCRIBING INFORMATION

[Pr]MYOCHRYSINE®
Sodium aurothiomalate, Solution for injection, Mfr. Std.

10 mg/mL, 25 mg/mL and 50 mg/mL

ATC Code: M01CB01

Disease Modifying Anti-Rheumatic Agent

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NAME OF DRUG

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INDICATIONS

MYOCHRYSINE (sodium aurothiomalate) is indicated in the treatment of both adult and juvenile rheumatoid arthritis.

MYOCHRYSINE may also be of benefit in the treatment of patients with psoriatic arthritis or Felty's syndrome.

It is usually used for treating patients who show evidence of continued or additional disease activity despite conservative drug therapy, e.g. with salicylates or other anti-inflammatory agents. MYOCHRYSINE may induce partial or complete remission of rheumatoid arthritis. In chronic advanced rheumatoid arthritis, it may prevent further damage to affected joints; however, it does not reverse existing damage.

MYOCHRYSINE (sodium aurothiomalate) should be administered only to selected patients who are under the supervision of a physician experienced with chrysotherapy and thoroughly familiar with the toxicity and benefits of the drug.

CONTRAINDICATIONS

MYOCHRYSINE (sodium aurothiomalate) is contraindicated in patients with:
- Known hypersensitivity to gold, or to any ingredient in the formulation including non-medicinal ingredients. For a complete listing, see DOSAGE FORMS, COMPOSITION, AND PACKAGING;
- Blood dyscrasias or a history of agranulocytosis, hemorrhagic diathesis or drug induced granulocytopenia or anemia;
- Renal disease;
- Hepatic dysfunction;

- Systemic lupus erythematosus;
- Significant dermatitis including urticaria or eczema;
- A personal history of serious adverse effects with previous gold therapy, including bone marrow aplasia or other hematological disorders, exfoliative dermatitis, necrotizing enterocolitis or pulmonary fibrosis;
- Pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations);
- Breast-feeding (see WARNINGS AND PRECAUTIONS, Special Populations).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The appearance of clinical effect is slow. It may take at least 8 weeks to become significant and the maximum benefits may not be achieved for at least 6 months.

Note: To reinstitute therapy following mild adverse reactions see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Recommended Adult Dose and Dosage Adjustment

Initial: 10 mg I.M. the first week, 25 mg the second week, then 25 to 50 mg weekly for the next 20 weeks or until toxicity occurs.

At this stage the response to therapy should dictate the future course of treatment. Patients with good to excellent response can go to maintenance therapy. In those with modest improvement a prolonged period of weekly injections may be maintained.

Maintenance: 50 mg I.M. tapered progressively to every 2 to 4 weeks according to clinical response and tolerance, and maintained indefinitely.

Initial Treatment	**Dosage**
Week 1	10 mg I.M.
Week 2	25 mg I.M.
Week 3 to 22, or until toxicity occurs	25 to 50 mg I.M.
Maintenance Treatment	**Dosage**
Every 2-4 weeks	50 mg I.M.

Recommended Pediatric Dose and Dosage Adjustment

10 mg I.M. the first week followed by 1 mg/kg of body weight per week; do not exceed 50 mg per dose. See adult dosage for intervals between injections.

Administration

MYOCHRYSINE (sodium aurothiomalate) should be administered by the intramuscular route

only, preferably in the gluteal muscle.

Warning: It is advisable to inject MYOCHRYSINE immediately after transfer into syringe because exposure to daylight will produce a rapid discoloration of the solution.

DO NOT ADMINISTER the solution if darker than pale yellow.

Because of the possibility of anaphylactic reaction, it is recommended that patients be kept under medical observation for a period of 30 minutes after the administration of the drug.

OVERDOSAGE

Symptoms: are those of heavy metal toxicity; they include pruritus, dermatitis, stomatitis, vague gastrointestinal discomfort, albuminuria with or without a nephrotic syndrome, hematuria, agranulocytosis, thrombocytopenic purpura, and aplastic anemia.

Treatment: Gold therapy should be discontinued promptly and supportive treatments should be given as required for specific complications. Chelation of gold by antidote treatment may be used.

Patients with severe dermatitis may benefit from oral antihistamines, topical corticosteroids or emollients. Major skin lesions and serious blood disorders demand hospital admission.

For the management of severe renal, hematologic, pulmonary enterocolic or generalized pruritic reactions, moderate to high dose corticosteroid therapy (e.g. prednisone 20 - 100 mg daily in divided doses) reportedly is beneficial.

When high-dose corticosteroid therapy is ineffective or substantial adverse reactions to steroids occur, a chelating agent (e.g. dimercaprol) or a drug such as N-acetylcysteine may be used to enhance the elimination of gold.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Each MYOCHRYSINE 1 mL ampoule for I.M. injection contains 10, 25 or 50 mg of sodium aurothiomalate.

Composition

MYOCHRYSINE is a sterile aqueous solution of sodium aurothiomalate. It contains chlorocresol as a preservative.

Packaging
MYOCHRYSINE 10 mg/mL, 25 mg/mL and 50 mg/mL are supplied in boxes of 5 ampoules.

WARNINGS AND PRECAUTIONS

General
MYOCHRYSINE should be administered with extra caution:
- In patients with a history of enterocolitis or pulmonary fibrosis. An annual x-ray is recommended and attention should be paid to unexplained breathlessness and dry cough.
- In patients with a history of urticaria.
- In patients with a history of eczema.
- In the elderly.
- If phenylbutazone or oxyphenbutazone are administered concurrently.

Carcinogenesis and Mutagenesis
Renal adenoma and adenocarcinoma have been reported in rats after prolonged administration of frequent, high doses of parenteral gold compounds (2 mg/kg/week for 45 weeks followed by 6 mg/kg/day for 47 weeks in one study; 3 mg/kg/day or 6 mg/kg/day for up to 2 years in a second study). The adenomas were similar to those produced in rats by chronic administration of other heavy metals such as lead or nickel. The relevance of these findings to man is unknown. Renal adenomas have not been reported in humans receiving therapeutic doses of sodium aurothiomalate.

Cardiovascular
A vasomotor (nitritoid) reaction may occur within several minutes of a MYOCHRYSINE injection. The nitritoid reaction is characterized by flushing, tachycardia and faintness. When it occurs, caution should be exercised before resuming therapy in patients with compromised cardiovascular status.

Hypersensitivity
Rarely, anaphylactic shock, syncope, bradycardia, thickening of the tongue, difficulty in swallowing and breathing, and angioedema may occur in the minutes that follow the injection of MYOCHRYSINE. If an anaphylactic reaction occurs, treatment should be discontinued.

Special Populations
Pregnant Women
The safety of MYOCHRYSINE in pregnant women and newborns has not been established. However, gold is known to cross the placenta and it can reach significant concentrations in the fetus. Due to the potential for teratogenicity, MYOCHRYSINE is contraindicated in pregnant

women.

Women of Childbearing Potential
Female patients of childbearing potential that are receiving MYOCHRYSINE should be instructed to avoid pregnancy.

Breast-feeding
Parenterally administered gold is excreted in human breast milk and has been detected in the blood of a nursing infant. Although problems in humans have not been documented, the use of MYOCHRYSINE in nursing mothers is not recommended because of the potential for serious adverse effects in the infant.

Geriatrics (≥65 years of age)
This population is more likely to experience vasomotor or nitritoid reactions associated with gold compounds, which are usually transient but there have been isolated reports of associated complications.

Monitoring and Laboratory Tests
Toxic reactions to MYOCHRYSINE are relatively frequent and, in certain cases, may be quite severe. Thus emphasis should be placed on careful clinical and laboratory monitoring and early detection of adverse reactions.

Baseline evaluation should include a biochemical profile to identify any preexisting conditions. Before receiving gold, patients should also have a complete blood cell count with differential, numerical platelet count, hemoglobin determination and urinalysis for protein, white cells, red cells and casts; these tests should be repeated before each injection and patients should have an examination of the skin and buccal mucosa for skin rash, bruising or mouth ulcers.

Patients should be counseled to report the presence or appearance of pruritus, rash, sore throat or tongue, stomatitis, buccal ulceration, easy bruising, purpura, epistaxis, bleeding gums, menorrhagia, unexplained bleeding, diarrhea, pyrexia, indigestion, metallic taste, or unexplained malaise. Because of the potential for serious consequences, blood examinations should be performed throughout treatment. If warranted by blood cell count, patients reporting sore throat, glossitis, buccal ulceration and/or easy bruising or bleeding should be treated for agranulocytosis, aplastic anemia and/or thrombocytopenia.

Dermatitis and lesions of the mucous membranes are common and may be serious; pruritus may precede the early development of a skin reaction. Renal toxicity ranges from mild proteinuria to the nephrotic syndrome; prognosis is usually good. Hematologic reactions have been observed rarely but fatalities have ensued. Other severe toxic manifestations include cholestatic jaundice, enterocolitis and interstitial lung disease.

Presence of albuminuria, pruritis, rash, or eosinophilia, are indication of developing toxicity. If

toxicity develops, MYOCHRYSINE should be discontinued immediately and symptomatic treatment be given as required.

If the reaction to gold therapy is not of a serious type, injections may be cautiously resumed 2 or 3 weeks after the toxic reaction has subsided. In these circumstances, 5 to 10 mg of gold is administered; if the test dose is tolerated, MYOCHRYSINE may be administered cautiously in larger doses on subsequent injections, at a decreased frequency.

Severe reactions are a contraindication to further gold therapy.

ADVERSE REACTIONS

The most frequent adverse reactions with MYOCHRYSINE (sodium aurothiomalate) involve the skin (ranging from simple rash to severe exfoliative dermatitis) and mucous membranes (ulcers) and may affect 30% of patients. Renal effects are next in frequency with proteinuria being observed in 10 to 15% of patients.

The severe adverse reactions are those affecting the bone marrow (agranulocytosis, thrombocytopenia and aplastic anemia), exfoliative dermatitis, enterocolitis, liver failure, anaphylactoid reactions and nephropathy; these are rare but may be fatal. It has been proposed that serious reactions may be the result of failure to discontinue therapy when earlier less serious symptoms occur. Close patient monitoring will not eliminate untoward effects but may help reduce their severity (see WARNINGS AND PRECAUTIONS).

The following adverse reactions have been reported:

Skin and subcutaneous tissue disorders: Pruritus and rash (30%) ranging from simple erythema to exfoliative dermatitis and dermatitis bullous, alopecia, and mucous membrane lesions (20%) including stomatitis. Irreversible skin pigmentation (chrysiasis) affecting the skin and mucous membranes can occur in sun-exposed areas after prolonged treatment with MYOCHRYSINE.

Blood and lymphatic system disorders: Leukopenia (2%), thrombocytopenia (1 - 3%), pancytopenia, eosinophilia (see WARNINGS AND PRECAUTIONS), neutropenia, agranulocytosis and aplastic anemia.

Renal and urinary disorders: Proteinuria (10 - 15%), nephrotic syndrome, acute renal failure. Albuminuria may indicate developing toxicity.

Hypersensitivity: Anaphylactic/anaphylactoid reactions, symptoms of which may include weakness, flushing, hypotension, tachycardia, dyspnoea, palpitations, abdominal pain, shock

and possibly collapse.

Gastrointestinal disorders: Metallic taste, diarrhea, and enterocolitis.

Hepatobiliary disorders: Hepatotoxicity with cholestatic jaundice may occur early in the course of treatment, and subsides after discontinuation.

Nervous system disorders: Rare reactions include encephalitis, encephalopathy, peripheral neuropathy with or without fasciculation and Guillain-Barré syndrome.

Respiratory, thoracic and mediastinal disorders: Pulmonary infiltrates, pulmonary fibrosis.

General disorders and administration site conditions: Vasomotor (nitritoid) reactions (see WARNINGS AND PRECAUTIONS).

Visual system disorders: Corneal gold deposits have been noted in some patients.

A transient flare of articular inflammation appearing within 24 hours of injection and lasting 2 or 3 days has also been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Salicylates: Concurrent gold administration may exacerbate aspirin-induced hepatic dysfunction.

Phenylbutazone or oxyphenbutazone: Extra caution should be exercised if phenylbutazone or oxyphenbutazone are administered concurrently with MYOCHRYSINE due to an increased risk of hematological reactions.

Penicillamine: The concurrent use of D-penicillamine or other drugs with potential bone marrow toxicity may increase the potential for serious hematologic and/or renal adverse reactions. Gold salts should not be used concomitantly with penicillamine.

Angiotensin-converting enzyme inhibitors: Caution is needed in patients treated concomitantly with MYOCHRYSINE and angiotensin-converting enzyme inhibitors due to an increased risk of severe anaphylactoid reaction in these patients.

ACTIONS AND CLINICAL PHARMACOLOGY

Sodium aurothiomalate exhibits anti-inflammatory, antiarthritic and immunomodulating effects. The predominant clinical effect of MYOCHRYSINE (sodium aurothiomalate) appears to be suppression of the synovitis in the active stage of the rheumatoid disease. The precise

mechanism of action is unknown but it has been suggested that the drug may act by inhibiting cell-mediated and humoral immune mechanisms. Additional modes of action include alteration or inhibition of various enzyme systems, suppression of phagocytic activity of macrophage and polymorphonuclear leukocytes, and alteration of collagen biosynthesis.

The metabolic fate of sodium aurothiomalate in humans is unknown but it is believed not to be broken down to elemental gold. It is very highly bound to plasma proteins. Sixty to 90% is excreted very slowly by the renal route while 10 to 40% is eliminated in the feces mostly via biliary secretion. The biologic half-life of gold following a single 50 mg dose of parenteral gold has been reported to range from 6 to 25 days. It increases following successive weekly doses.

STORAGE AND STABILITY

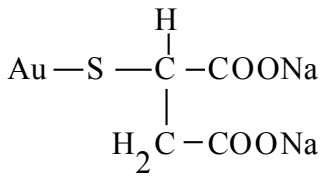
Store between 15 and 30°C. Protect from light.

<u>DO NOT USE</u> a darkened solution (more than pale yellow).

PHARMACEUTICAL INFORMATION

Chemical Name: sodium aurothiomalate (or gold sodium thiomalate) is mercaptosuccinic acid monogold (1+) sodium salt.

Structural Formula: Mixture of monosodium and disodium salts of (2RS)-2-(aurosulphanyl)butanedioic acid



Molecular Formula: $C_4H_4AuNaO_4S + C_4H_3AuNa_2O_4S$

Molecular Mass: 390.1 + 368.09

Gold Content: 44.5 - 46% (dried substance)

Description: Fine pale yellow hygroscopic powder; metallic taste. Very soluble in water; practically insoluble in alcohol and ether. The pH of a 10% aqueous solution is 6.0 to 7.0.

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