Pr Ridaura® (auranofin) 3mg (Antirheumatic Agent)

INDICATIONS AND CLINICAL USE: Ridaura® (auranofin) is indicated in the management of adults with active (classical or definite) rheumatoid arthritis who have not responded to adequate trials of conventional anti-inflammatory therapy. Ridaura® might also be of benefit in patients with psoriatic arthritis. Ridaura® should be considered only when salicylates or other non-steroidal anti-inflammatory drugs, and, when appropriate, steroids, have proven to be inadequate for controlling the symptoms of rheumatoid arthritis.

Ridaura® should be added to an ongoing comprehensive treatment program which includes physical as well as other drug therapy. The usual time to onset of therapeutic response to Ridaura® is 3 to 4 months; some patients require as long as 6 months to show a full clinical response. Ridaura® is not indicated in other arthropathies, such as osteoarthritis.

CONTRAINDICATIONS: Ridaura® (auranofin) is contraindicated in patients with a history of serious gold-induced toxicity including necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis or hypersensitivity. Ridaura® should not be prescribed for patients with progressive renal disease, severe hepatological disorders.

Use in Pregnancy: Ridaura® has been shown to be embryotoxic in rats at dose levels of 5 mg/kg/day or higher and both embryotoxic and teratogenic in rabbits at doses of 0.5 mg/kg/day or higher. Therefore, Ridaura® should not be given to pregnant women. Furthermore, women of childbearing potential should be made aware of the necessity to avoid pregnancy during treatment and for at least six months after because of the slow excretion of gold and its persistence in the body tissues after discontinuation of treatment. Nursing Mothers: Gold is excreted in rodent milk following the administration of auranofin. It is not known whether Ridaura® is excreted in human milk; however, injectable gold appears in the milk of nursing mothers following administration. Therefore, it is recommended that Ridaura® not be given during nursing.

WARNINGS: Ridaura® (auranofin) contains gold and, like other gold-containing drugs, can cause gold toxicity. Danger signs of possible gold toxicity include the following: fall in hemoglobin, leukopenia below 4000 WBC/mm3, granulocytes below 1500/mm3, decrease in platelets below 150,000/mm3, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, it is recommended that white blood cells with differential, platelet count, haemoglobin, urinary protein and renal and liver function be measured prior to Ridaura® therapy to establish a baseline and to identify pre-existing conditions. See CONTRAINDICATIONS. The possibility of adverse reactions should be explained to patients before staring therapy. See INFORMATION FOR PATIENTS. Patients should be advised to report promptly any unusual signs and symptoms occurring during treatment with Ridaura®, such as sore throat or tongue, mouth ulceration, skin rash, easy bruising, purpura, epistaxis, bleeding gums or menorrhagia. When the following adverse reactions occur, Ridaura® therapy may require modification or additional monitoring as outlined below:

Thrombocytopenia: Thrombocytopenia has occurred in approximately 1 - 3% of patients (see ADVERSE REACTIONS) treated with Ridaura®, some of whom developed bleeding. The thrombocytopenia appears to be peripheral in origin in most cases and is usually reversible upon withdrawal of Ridaura®. Its onset bears no relationship to the duration of Ridaura® therapy and its course may be rapid. While patients' platelet counts require monitoring every 2 weeks for the first 3 months and at least monthly thereafter, the occurrence of a precipitous decline in platelets or a platelet count less than 100,000/mm3 or signs and symptoms (e.g., purpura, ecchymoses or petechiae) suggestive of thrombocytopenia indicates a need to immediately withdraw Ridaura® and all other therapies with the potential to cause thrombocytopenia, and to obtain additional platelet counts. No additional Ridaura® should be given unless the thrombocytopenia resolves and further studies show it was not due to gold therapy.

Proteinuria: Proteinuria has developed in approximately 3 - 9% of patients (see ADVERSE REACTIONS) treated with Ridaura®. Urinalysis should be performed every 2 weeks for the first 3 months and at least monthly thereafter. If clinically significant proteinuria or microscopic hematuria is found, Ridaura® and all other therapies with the potential to cause proteinuria or microscopic hematuria should be stopped immediately. There has been no experience with the concomitant use of Ridaura® and penicillamine, chloroquine/hydroxychloroquine, immunosuppressive agents (e.g., cyclophosphamide, azathioprine, or methotrexate) or high doses of corticosteroids and therefore, such use cannot be recommended.

PRECAUTIONS General: The potential benefits of using Ridaura® (auranofin) in patients with inflammatory bowel disease, skin rash or history of bone marrow depression, should be weighed against: 1) the potential risks of gold toxicity on organ systems previously compromised or with decreased reserve, and, 2) the difficulty in quickly detecting and correctly attributing the toxic effect. The following adverse reactions have been reported with the use of gold preparations and require modification of Ridaura® treatment or additional monitoring. See ADVERSE REACTIONS for the approximate incidence of those reactions specifically reported with Ridaura®. Gastrointestinal reactions reported with gold therapy include diarrhea/loose stools, nausea, vomiting, anorexia and abdominal cramps. The most common reaction to Ridaura® is diarrhea/loose stools reported in approximately 47% of patients. This is generally manageable by reducing the dosage (e.g., from 6 mg daily to 3 mg). In 4% of the patients it has been necessary to discontinue Ridaura® permanently. Ulcerative enterocolitis is a rare serious gold reaction. Therefore, patients with gastrointestinal symptoms should be monitored for the appearance of gastrointestinal bleeding. Dermatitis is the most common reaction to parenteral gold therapy and the second most common reaction to Ridaura®. Any eruption especially if pruritic that develops during treatment should be considered a gold reaction until proven otherwise. Pruritus often exists before dermatitis becomes apparent, and therefore should be considered to be a warning signal of a cutaneous reaction. Gold dermatitis may be aggravated by exposure to sunlight; an actinic rash may develop. The most serious form of cutaneous reaction reported with parenteral gold is generalized exfoliative dermatitis.

In patients with psoriatic arthritis who were involved in all clinical trials with Ridaura®, 5/438 (1.1%) Ridaura®-treated patients and 2/183 (1.1%) placebo-treated patients had an exacerbation of their psoriasis requiring withdrawal.

Stomatitis, another common gold reaction, may be manifested by shallow ulcers on the buccal membranes, on the borders of the tongue, and on the palate or in the pharynx. Stomatitis may occur as the only adverse reaction or with a dermatitis. Sometimes diffuse glossitis or gingivitis develops. A metallic taste may precede these oral mucous membrane reactions and should be considered a warning signal. Ridaura®, as other gold preparations, can produce a nephrotic syndrome or glomerulitis with proteinuria and hematuria. These renal reactions are usually relatively mild and subside completely if recognized early and treatment is discontinued. They may become severe and chronic if treatment is continued after the onset of the reaction. Therefore, it is important to perform urinalysis regularly and to discontinue treatment promptly if proteinuria or hematuria develops. Blood dyscrasias including leukopenia, granulocytopenia and thrombocytopenia have all been reported as reactions to injectable gold and Ridaura®. These reactions may occur separately or in combination at any time during treatment. In addition, a case of pure red cell aplasia has been reported as a reaction Ridaura®. Because these reactions have potentially serious consequences, blood dyscrasias should be constantly watched for through monitoring of the formed elements of the blood, every 2 weeks for the first 3 months and at least monthly thereafter.

There have been some reports of gold deposits in the lens or corneas of patients treated with Ridaura®. These deposits have not led to any eye disorders or any degree of visual impairment, and have cleared within 3-6 months of cessation of therapy. Initial and periodic ophthalmic examinations are recommended in patients being treated with auranofin.

Rare reactions attributed to gold include cholestatic jaundice; gold bronchitis and interstitial pneumonitis and fibrosis; peripheral neuropathy; partial or complete hair loss; fever. The safety and effectiveness of Ridaura® in children under age 16 have not yet been established. Consequently, use in this age group cannot be recommended. In a 24-month study in rats, animals treated with auranofin at 0.4, 1.0 or 2.5 mg/kg/day orally (3, 8 or 21 times the human dose) or gold sodium thiomalate at 2 or 6 mg/kg injected twice weekly (4 or 12 times the human dose) were compared to untreated control animals. There was a significant increase in instances of renal tubular cell karyomegaly and cytomegaly and renal adenoma in the animals treated with 1.0 or 2.5 mg/kg/day of auranofin and 2 or 6 mg/kg twice weekly of gold sodium thiomalate. Malignant renal epithelial tumors were seen in the 2.5 mg/kg/day auranofin and in the 6 mg/kg twice weekly gold sodium thiomalate-treated animals. In a 12-month study, rats treated with auranofin at 23 mg/kg/day (192 times the human dose) developed adenomas of the renal tubular epithelium, whereas those treated with 3.6 mg/kg/day (30 times the human dose) did not. Drug Interactions: One report suggests that, in a single patient, concurrent administration of Ridaura® and phenytoin was associated with increased phenytoin blood levels.

ADVERSE REACTIONS: The adverse reactions listed below are based on observations on 4784 rheumatoid arthritis patients treated with Ridaura® (auranofin) of whom 2729 were treated for more than 1 year and 573 for more than 3 years. The overall incidence of adverse reactions was 62%, of whom 18.6% discontinued therapy. The most common adverse reactions were diarrhea (47%), rash (24%) pruritus (17%), abdominal pain (14%) and stomatitis (13%). More serious adverse reactions were anemia (1.6%), leukopenia (1.9%), thrombocytopenia (0.9%) and proteinuria (5.0%). The highest incidence was during the first 6 months of treatment. However, reactions can occur at any time throughout the course of therapy. Clinical trials were conducted assessing Ridaura® in the treatment of 438 psoriatic arthritis patients. The nature and incidence of adverse reactions were similar to those observed in rheumatoid arthritis patients, Loose stools or diarrhea (47%); abdominal pain (14%); nausea with or without vomiting (10%); anorexia*; flatulence*; constipation and dysgeusia, Rash (24%); pruritus (17%); hair loss; urticarial, Stomatitis (13%); conjunctivitis*; glossitis, Anemia; leukopenia; thrombocytopenia; eosinophilia, Proteinuria*; hematuria, Elevated liver enzymes, Weight loss

Gastrointestinal bleeding; melena; positive stool for occult blood; dysphagia (<0.1%); ulcerative enterocolitis (<0.1%) Angioedema (<0.1%) Gingivitis, Neutropenia; agranulocytosis (<0.1%), aplastic anemia (<0.1%), Membranous glomerulonephritis (<0.1%), nephrotic syndrome (<0.1%), Jaundice (<0.1 %), Interstitial pneumonitis (<0.1%), Peripheral neuropathy (<0.1%) (* Reactions marked with an asterisk occurred in 3-9% of the patients. The other reactions listed occurred in 1-3%)

DOSAGE AND ADMINISTRATION: The usual adult starting dosage is 6 mg per day. This dose may be given: twice a day: one 3 mg capsule with breakfast and one with the evening meal OR once a day: two 3 mg capsules with breakfast OR two 3 mg capsules with the evening meal. Ridaura® (auranofin) should be discontinued in those patients in whom no response is observed after 4 months administration. In those patients in whom a partial response is observed after 4 months, Ridaura® may be continued at 6 mg/day, or the dose may be increased to 9 mg/day (one 3 mg capsule 3 times a day), for an additional 2 months. Ridaura® should be discontinued in patients in whom a satisfactory clinical response has not occurred after 6 months treatment. Daily dosages above 9 mg are not recommended.

AVAILABILITY OF DOSAGE FORMS: Capsules -Each Ridaura® package contains a bottle of 60 tan and brown opaque Ridaura® capsules 3 mg, monogrammed Ridaura, and a package insert packed in an outer carton.

A full Product Monograph is available on request