Auranofin

PRESCRIBING INFORMATION

RIDAURA®

Auranofin Capsules

Only

RIDAURA® (auranofin) contains gold, and, like other gold-containing drugs, can cause gold toxicity, signs of which include: fall in hemoglobin, leucopenia below 4,000 cells/mm³, granulocytopenia below 1,500 cells/mm³, decrease in platelets below 150,000 cells/mm³, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work (See PRECAUTIONS—Laboratory Tests) should be reviewed before writing each RIDAURA prescription. Like other gold preparations, RIDAURA is only indicated for use in selected patients with active rheumatoid arthritis. Physicians planning to use RIDAURA should be experienced with chrysotherapy and should thoroughly familiarize themselves with the toxicity and benefits of RIDAURA.

In addition, the following precautions should be routinely employed:

1. The possibility of adverse reactions should be explained to patients before starting therapy.
2. Patients should be advised to report promptly any symptoms suggesting toxicity. (See PRECAUTIONS—Information for Patients.)

DESCRIPTION

RIDAURA® (auranofin) is available in oral form as capsules containing 3 mg auranofin.

Auranofin is (2,3,4,6-tetra-O-acetyl-1-thio-D-glucopyranosato-5-) triethylphosphine) gold.

Auranofin contains 29% gold and has the following chemical structure:

Each RIDAURA capsule, with opaque brown cap and opaque tan body, contains auranofin, 3 mg, and is imprinted with the product name RIDAURA. Inactive ingredients consist of benzyl alcohol, cellulosic, pectin, saccharin sodium, sodium chloride, color D&C Blue No. 33, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients.

CLINICAL PHARMACOLOGY

The mechanism of action of RIDAURA (auranofin) is not understood. In patients with adult rheumatoid arthritis, RIDAURA may modify disease activity as manifested by synovitis and associated symptoms, and reflected by laboratory parameters such as ESR. There is no substantial evidence, however, that gold diarhoea stools reported in approximately 90% of the patients. This is generally managed by reducing the dosage (e.g., from 8 mg daily to 3 mg) and in only 6% of the patients it is necessary to discontinue RIDAURA (auranofin) permanently. Gold toxicity, including leukopenia, granulocytopenia, thrombocytopenia and aplasia or other severe hematologic disorders.

WARNINGS

Danger signs of possible gold toxicity include fall in hemoglobin, leucopenia below 4,000 cells/mm³, granulocytopenia below 1,500 cells/mm³, decrease in platelets below 150,000 cells/mm³, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea.

Thrombocytopenia has occurred in 1-3% of patients. (See ADVERSE REACTIONS) treated with RIDAURA (auranofin), some of whom developed bleeding. The thrombocytopenia usually appears to be of bone marrow origin 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 platelets are monitored, and should be considered as a warning signal.

Cutaneous Reactions: Dermatitis is the most common reaction to injectable gold therapy. The skin may be involved by synovitis and associated symptoms, and inflammation of the blood throughout treatment. Because they have potentially serious consequences, blood dyscrasias should be constantly watched for through regular monitoring. In case of toxic reactions, blood dyscrasias may be considered as a warning signal.

Mucous Membrane Reactions: Stomatitis, manifested by shallow ulcers on the buccal membranes, on the borders of the tongue, on the palate or in the pharynx. Stomatitis may occur as the only adverse reaction or with a dermatitis. Sometimes diffuse glossitis or gingival desquamation. A metallic taste may precede these oral mucous membrane reactions and should be considered as a warning signal.

Renal Reactions: Gold can produce a nephrotic syndrome or glomerulonephritis with proteinuria and hematuria. These symptoms are easily detected as proteinuria or hematuria, but 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 urinalyses regularly and to discontinue treatment promptly if proteinuria or hematuria develops.

Hematologic Reactions: Blood dyscrasias including leukopenia, granulocytopenia, thrombocytopenia and aplastic anemia have all been reported as reactions to injectable gold and RIDAURA. These reactions may occur separately or in combination at any time during treatment. Because they have potentially serious consequences, blood dyscrasias should be constantly watched for through regular monitoring (at least monthly) of the formed elements of the blood throughout treatment.

Miscellaneous Reactions: Rare reactions attributed to gold include cholestatic jaundice, bone marrow suppression, peripheral neuropathy, partial or complete hair loss, fever. Patients: Patients should be advised of the possibility of toxicity from RIDAURA and of the signs and symptoms that they should report promptly. (Patient information sheets are available.)
Women of childbearing potential should be warned of the potential risks of RIDAURA therapy during pregnancy. (See PRECAU-
TIONS—Pregnancy.)

Laboratory Tests: CBC with differential, platelet count, urinalysis, and renal and liver function tests should be performed prior to RIDAURA (auranofin) therapy to establish a baseline and to identify any preexisting conditions. CBC with differential, platelet count and urinalysis should then be monitored at least monthly; other parameters should be monitored as appropriate.

Drug Interactions: In a single patient report, there is the suggestion that concurrent administration of RIDAURA and phenytoin may have increased phenytoin blood levels.

Carcinogenesis/Mutagenesis: 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 the frequency 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 1.0 mg/kg/day and 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) and rats given auranofin at doses of 1, 3 and 9 mg/kg/day (42 times the human dose) had an increase above controls in the incidence of resorptions and a decrease in litter size and weight linked to maternal toxicity. No such effects were found in rats given 2.5 mg/kg/day (21 times the human dose). Pregnant mice given auranofin at a dose of 5 mg/kg/day (42 times the human dose) had no teratogenic effects. There are no adequate and well-controlled RIDAURA studies in pregnant women.

Nursing Mothers: Nursing during RIDAURA therapy is not recommended. Following auranofin administration to rats in late gestation, gold is excreted in milk. Following the administration of injectable gold, gold appears in the milk of nursing women; human data on auranofin are not available.

Pediatric Use: RIDAURA (auranofin) is not recommended for use in pediatric patients because its safety and effectiveness have not been established.

ADVERSE REACTIONS

The adverse reactions incidences listed below are based on observations of 1) 4,784 RIDAURA-treated patients in clinical trials (2,474 U.S., 2,310 foreign), of whom 2,729 were treated more than one year and 573 for more than three years; and 2) postmarketing experience. The highest incidence is during the first six months of treatment; however, reactions can occur after many months of therapy. With rare exceptions, all patients were on concomitant nonsteroidal anti-inflammatory therapy; some of them were also taking low dosages of corticosteroids.

Reactions occurring in more than 1% of RIDAURA-treated patients

Gastrointestinal: loose stools or diarrhea (67%); abdominal pain (14%); nausea with or without vomiting (10%); constipation; anorexia; flatulence; dyspepsia; dysgeusia.

Dermatological: rash (24%); pruritus (17%); hair loss; urticaria.

Mucous Membrane: stomatitis (13%); conjunctivitis*; glossitis.

Hematological: anemia; leukopenia; thrombocytopenia; eosinophilia.

Renal: proteinuria*; hematuria.

Hepatic: elevated liver enzymes.

*Reactions marked with an asterisk occurred in 0.1-1% of the patients. The other reactions listed occurred in less than 0.1%.

Reactions occurring in less than 1% of RIDAURA-treated patients

Gastrointestinal: dysphagia; gastrointestinal bleeding*; melena; positive stool for occult blood*; ulcerative enterocolitis.

Dermatological: angioedema.

Mucous Membrane: gingivitis.

Hematological: aplastic anemia; neutropenia; agranulocytosis; pure red cell aplasia; pancyclopenia.

Hepatic: jaundice.

Respiratory: interstitial pneumonitis.

Neurological: peripheral neuropathy.

Ocular: gold deposits in the lens or cornea unassociated clinically with eye disorders or visual impairment.

†Reactions marked with a dagger occurred in 0.1-1% of the patients. The other reactions listed occurred in less than 0.1%.

Reactions reported with injectable gold preparations, but not with RIDAURA (auranofin)

(based on clinical trials and on postmarketing experience)

Cutaneous Reactions: generalized exfoliative dermatitis.

Incidence of Adverse Reactions for Injectable Gold and RIDAURA Injectable Gold 18 Comparative Trials

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<thead>
<tr>
<th>RIDAURA Injectable Gold</th>
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<tbody>
<tr>
<td>Coadministration</td>
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<tr>
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<tr>
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<td>No</td>
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<td>Total</td>
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<td>1435 (445)</td>
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<td>Incidence</td>
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<td>0.9%</td>
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OVERDOSAGE

The usual oral LD₅₀ for auranofin is 310 mg/kg in adult mice and 265 mg/kg in adult rats. The minimum lethal dose is 10 mg/kg.

In case of acute overdosage, immediate induction of emesis or gastric lavage and appropriate supportive therapy are recommended.

RIDAURA overdosage experience is limited. A 50-year-old female, previously on 1 mg RIDAURA daily, took 27 mg (9 capsules) daily for 10 days and developed an encephalopathy and peripheral neuropathy. RIDAURA was discontinued and she eventually recovered.

There has been no experience with treating RIDAURA overdosage with modalities such as chelating agents. However, they have been used with injectable gold and may be considered for RIDAURA overdosage.

DOSE AND ADMINISTRATION

Usual Adult Dosage: The usual adult dosage of RIDAURA (auranofin) is 6 mg daily, given either as 3 mg twice daily or 6 mg once daily. Initiation of therapy at dosages exceeding 6 mg daily is not recommended because it is associated with an increased incidence of diarrhea. Auranofin propagation is inadequate after six months, an increase to 9 mg (3 mg three times daily) may be tolerated. If response remains inadequate after a three-month trial of 9 mg daily, RIDAURA therapy should be discontinued. Safety at dosages exceeding 9 mg daily has not been studied.

Transferring from Injectable Gold: In controlled clinical studies, patients previously using gold have been transferred to RIDAURA (auranofin) by discontinuing the injectable agent and starting oral therapy with RIDAURA, 6 mg daily. When patients are transferred to RIDAURA, they should be informed of its adverse reaction profile, in particular the gastrointestinal reactions. (See PRECAU-
TIONS—Information for Patients.) At six months, control of severe activity of patients transferred to RIDAURA and those maintained on the injectable agent was not different. Data beyond six months are not available.