

RIDAURA

auranofin

Presentation

Tablet containing auranofin 3mg, pale yellow, film-coated, bevel-edged, square tiltab.

Clinical Particulars

Therapeutic indications

RIDAURA is indicated in the management of adults with active progressive rheumatoid arthritis only when non-steroidal anti-inflammatory drugs have been found to be inadequate alone to control the disease, i.e. when second-line therapy is required.

Because RIDAURA cannot repair the damage already caused by chronic rheumatoid arthritis, it is likely to be of significant benefit when therapy is initiated in the early stages of the disease; however, it can also provide benefit to patients with substantial joint damage. RIDAURA is not indicated in non-rheumatoid arthropathies such as osteoarthritis.

Posology and method of administration

Adults:

The usual adult dosage is 6mg per day. This dose may be given in a single administration of two 3mg tablets in the morning with breakfast. It can also be given in two administrations of one 3mg tablet in the morning and one in the evening with meals.

RIDAURA may be co-prescribed with anti-inflammatory drugs/analgesics as part of a comprehensive treatment program. Such concomitant therapy may be necessary especially during the first weeks of RIDAURA therapy, before full benefit of RIDAURA is seen. RIDAURA has also been used successfully with low dose (less than 10mg) corticosteroid therapy.

For adult patients who have not shown satisfactory response to RIDAURA therapy with 6mg/day after 4-6 months, the daily dosage may be increased to 9mg/day by giving one RIDAURA tablet three times a day with meals. Daily dosages above 9.0mg are not recommended because of insufficient experience in human studies.

Uses in children.

The usual paediatric dosage of RIDAURA is 0.15mg/kg/day, given either once a day or as a divided dose twice a day, up to a maximum of 6mg daily.

In children who have an adequate response after 4 months, an increase to 0.2mg/kg/day, up to a maximum of 9mg/daily, may be tolerated.

Safety at doses exceeding 0.2mg/kg/day (or 9mg daily) has not been studied.

Absorption of gold from RIDAURA tablets is rapid but incomplete (see Pharmacokinetic Properties). Although mean blood gold levels are proportional to dose, no correlation between blood gold levels and safety or efficacy has been established. Dosage adjustments should therefore depend on monitoring clinical response and adverse events rather than on monitoring blood gold concentrations.

Use in Elderly

Dosage as above. As with all medicines, extra caution should be undertaken with administration to the elderly.

Clinical studies have shown that patients may be safely transferred to RIDAURA from injectable gold salt therapy without the need for overlap or a washout period.

Contraindications

Auranofin is contraindicated in patients with:

- progressive renal disease
- severe active hepatic disease
- history of hypersensitivity to gold compounds or excipients.

Although not necessarily reported in association with RIDAURA, do not use in patients with a history of any of the following gold-induced disorders; necrotising enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe blood dyscrasias.

Special Warnings and Special Precautions for Use

In general, auranofin is less toxic than parenteral gold therapy and patients who have discontinued parenteral therapy because of an adverse reaction do not show similar reactions with auranofin. However, the physician should be familiar with the following precautions for gold therapy:

Before commencing gold therapy:

- medical conditions that may mask signs of toxicity should be adequately controlled
- baseline results for leukocyte and platelet counts, haemoglobin, and tests for proteinuria / haematuria should be determined
- the patient should be advised of the slow onset of action
- the patient should be alerted to report promptly any symptoms of gold toxicity particularly rash, mucositis, diarrhoea which persists for several days or interferes with daily activities, haematuria or other unusual bleeding/bruising
- patients should be cautioned to minimise exposure to ultraviolet light

Once therapy has begun:

- leukocyte and platelet counts, haemoglobin and tests for proteinuria / haematuria should be monitored on a monthly basis

If signs of gold toxicity are discovered, auranofin and/or concomitant therapy with the potential to cause the symptoms should cease. Once the symptoms resolve, or another cause is established, auranofin may be cautiously reinstated, beginning with a lower dose than that at cessation of therapy. Auranofin therapy should not be reinstated if the reaction was either clinically serious or indicative of hypersensitivity.

Auranofin should be used with caution in patients with:

- renal impairment
- hepatic dysfunction
- previous serious toxicity to parenteral gold salts or to heavy metals other than gold
- inflammatory bowel disease
- history of atopy
- history of, or therapy likely to result in, bone marrow suppression
- Auranofin has not been coadministered with other disease modifying agents such as penicillamine, levamisole and chloroquine / hydrochloroquine and, therefore, concomitant use cannot be recommended

Interaction with other Medicaments and other forms of Interaction

Specific experience of interactions with auranofin is lacking. However, the theoretical potential for interaction with gold therapy, both oral and parenteral, should be considered. Concomitant therapy with metal antagonists and potentially nephrotoxic or haemotoxic medicines should be administered with caution. Such medicines include penicillamine, aminoglycosides, amphotericin B, penicillins, phenylbutazone, phenytoin, sulfonamides, NSAIDs, acyclovir and alcohol.

Drugs affecting GI motility and those which are highly protein-bound may alter the absorption and binding, respectively, of auranofin (see Pharmacokinetic properties).

Pregnancy and lactation

Pregnancy:

Adequate human data on use during pregnancy are not available, and animal studies have shown adverse effects on pregnancy or embryo-foetal development. Use during pregnancy should be restricted to those cases where the potential benefit to the mother outweighs the potential risk to the foetus. The prolonged elimination of gold from the body after discontinuance of treatment (6 months) should be considered in treating women of childbearing potential.

Lactation:

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been identified.

Undesirable Effects

Adverse reactions reported during clinical studies with auranofin were largely gastrointestinal and mucocutaneous in nature.

Dermatologic:

Skin rashes may occur during auranofin therapy. They are usually mild, but have necessitated discontinuation of auranofin therapy in some cases. Pruritus, stomatitis and conjunctivitis have also been reported. Greater than normal hair loss has occurred in some patients on auranofin therapy.

Gastrointestinal:

Loose stools or diarrhoea, usually mild and transient, have been reported relatively frequently. If it becomes more severe or prolonged, then symptomatic treatment may be of benefit. Discontinuation of auranofin therapy is rarely necessary. When necessary a temporary reduction in dose should be considered. Abdominal pain/cramps, nausea and other gastrointestinal symptoms may occur in association with loose stools and diarrhoea.

Haematologic:

Transient decreases in haemoglobin and haematocrit have occurred in a few patients in the early phases of therapy. Similar decreases in haemoglobin and haematocrit were seen in patients in controlled clinical studies receiving placebo or injectable gold. In addition, a case of pure red cell aplasia has been reported.

Occasional decreases in white blood counts have been reported during auranofin treatment. Rare cases of thrombocytopenia, leukopenia and aplastic anaemia have occurred in association with auranofin, some being marked and necessitating discontinuation. Most of these patients were also receiving drugs known to be associated with thrombocytopenia (see section Special Warnings and Special Precautions for Use). The occurrence of purpura, ecchymoses or petechia would suggest the presence of thrombocytopenia and may indicate a need for additional platelet count determinations.

Hepatic:

Occasional mild and transient abnormalities in tests of liver function (transaminases and alkaline phosphatase) have developed during treatment with auranofin.

Renal:

Transient proteinuria and abnormalities in tests of renal function (BUN, creatinine, uric acid) have developed in a few patients during treatment with auranofin; membranous glomerulonephritis and nephrotic syndrome have been reported. If significant proteinuria develops, quantification is recommended. If greater than 500 mg/day, treatment with auranofin should be stopped.

Ocular:

There have been some reports of gold deposits in the lens or corneas of patients treated with auranofin. 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.

Respiratory:

Reports of interstitial pneumonitis have been received.

Neurological:

Headache, dizziness and peripheral nerve lesions (peripheral neuropathies) have been reported rarely.

Overdose

The absence of experience with acute overdosage with auranofin precludes characterisation of sequelae and assessment of antidotal efficacy at this time. In case of accidental overdosage, immediate induction of emesis or gastric lavage is recommended. Chelating agents have been used in cases of severe toxicity induced by parenteral gold compounds and may be considered in auranofin overdosage. Gold from auranofin does not appear to be appreciably removed by haemodialysis.

Pharmacological Properties

Pharmacodynamic properties

Auranofin is a disease-modifying antirheumatic drug (DMARD) and has been shown to prevent or reduce damage to the joints, particularly if therapy is initiated in the early stages of the disease.

Therapeutic response is dependant on the individual and stage of disease but is generally seen between 3 and 6 months of treatment. Clinical benefit includes improvements in joint swelling, tenderness, pain, morning stiffness and grip strength. Auranofin also lowers erythrocyte sedimentation rate, level of rheumatoid factor and immunoglobulin level if elevated.

Although the mechanism of action has not been fully elucidated, auranofin exhibits a variety of antiinflammatory, antiarthritic and immunoregulatory activities, some of which are unique to auranofin and contribute to the orchestration of the therapeutic response. These properties include:

- stimulation of cell-mediated immunity
- suppression of immunoglobulin synthesis and antibody-dependent cytotoxicity
- suppression of the respiratory burst /superoxide radicals
- inhibition of neutrophil release of lysosomal enzymes and secretion of inflammatory eicosanoids
- inhibition of platelet aggregation, serotonin production and protein kinase C activity in vitro
- selective suppression of macrophage function
- inhibition of interleukin secretion by T-lymphocytes

- inhibition of neovascularisation - which may reduce inflammation by inhibiting mononuclear cell infiltration and synovial tissue proliferation

Pharmacokinetic properties

Auranofin is absorbed via the GI mucosa after binding and deacetylation. Inter-individual variation in absorption and metabolism of auranofin is high, which accounts for the wide ranges reported for pharmacokinetic indices.

Generally, 20 to 30% of dose is absorbed, but up to 60% absorption has been reported. Absorption is rapid, with peak concentrations occurring within 2 hours post-administration. The terminal half-life of the drug in plasma is between 10 and 30 days; plasma concentrations reach equilibrium after 4 to 8 weeks although longer periods may be necessary in some patients. Serum concentrations are proportional to dose but do not appear to be directly related to efficacy or safety.

In blood, approximately 40% of the gold from auranofin is associated with erythrocytes, and 60% is associated with serum proteins. Tissue gold concentrations with auranofin are lower than those seen with parenteral gold administration and are highest in the kidney. The principal route of elimination of auranofin gold is via the faeces, although much of this is unabsorbed gold. Urinary excretion accounts for 9-17% of the administered dose equivalent to about 60% of the absorbed gold, and biliary excretion is negligible.

Preclinical safety data

Studies in rats have shown that auranofin can cause dose-related renal lesions at very high doses, and an increased incidence of heavy metal nephropathies (renal tumours) was seen. The renal lesions in the auranofin-treated rats were histologically identical to those seen in both control and gold sodium thiomalate-treated rats. These tumours have not been seen in studies in mice. This heavy metal nephropathy is specific for rats and has no known counterpart in humans.

Pharmaceutical Particulars

Shelf Life

5 years

Special precautions for storage

Store below 30°C.

Medicine Classification

Prescription Medicine

Package Quantities

Bottles of 60 Tiltab tablets.

Name and Address

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