NAME OF THE MEDICINE

_Auranofin_
Gold(+1) cation; 3,4,5-triacetyloxy-6-(acetyloxyethyl)oxane-2-thiolate; triethylphosphanium

CAS no: 34031-32-8
Chemical formula: C_{20}H_{35}AuO_{9}PS+
Molecular weight: 678.485 g/mol

DESCRIPTION

Auranofin is a synthetic gold co-ordination complex in which the oxidation state of the central atom of gold is stabilised by electron binding with two side groups or ligands: a phosphine ligand (triethylphosphine) and a sulphur (thiolate) ligand (tetraacetylthioglucopyranose).

Auranofin exists as a comparatively small monomeric species both in solid state and in solution. This size factor may contribute to the absorption of auranofin following oral administration.

Ridaura contains the following excipients: microcrystalline cellulose, ethanol, hypromellose, iron oxide yellow CI77492, lactose, magnesium stearate, propylene glycol, sodium starch glycollate, maize starch, titanium dioxide and purified water.
RIDURA® (Auranofin) Product Information

PHARMACOLOGY

Pharmacodynamics

It has been demonstrated by clinical and laboratory evaluations that prolonged treatment with Ridaura may modify the progress of active rheumatoid arthritis and so prevent or reduce subsequent damage to the joints.

Clinically, therapeutic response has been observed in three to four months; some patients require as long as six months to show a response. This response includes improvements in parameters such as joint swelling, tenderness, pain, morning stiffness and grip strength. Patients have been maintained on Ridaura for over 4 years with sustained improvement.

Ridaura reduces inflammation, lowers erythrocyte sedimentation rates, reduces rheumatoid factor levels and lowers elevated immunoglobulin levels. Radiographic evaluation of the joints after 12 months of therapy suggests that Ridaura may slow or suppress the progression of erosion. Ridaura’s efficacy was comparable to or slightly less than that of parenteral gold salts.

In standard animal models, Ridaura has exhibited significant anti-inflammatory properties. In vitro test systems have demonstrated immunoregulatory activity that further distinguishes it from other agents capable of producing disease modifying activity in RA patients.

Ridaura:

- Enhances cell mediated immunity
- Inhibits antibody dependent cellular cytotoxicity
- Inhibits release of lysosomal enzymes
- Suppresses the generation of superoxide radicals
- Inhibits platelet aggregation

In vitro, Ridaura has also been shown to inhibit chemotaxis, phagocytosis, and the inflammatory effects of prostaglandins.

Pharmacokinetics

Absorption

Following oral administration in man, approximately 25% of the auranofin gold is absorbed.

Distribution

In blood, approximately 40% of the gold from auranofin is associated with erythrocytes and 60% is associated with serum proteins. During long-term therapy with Ridaura, serum gold concentrations reach a plateau after about 12 weeks treatment and then remain stable, provided the dose is
unchanged. With Ridaura at 6 mg per day, mean blood gold levels of 0.63 µg/mL (0.30 - 1.20) have been observed. Serum concentrations are proportional to dose, but no correlation between blood gold levels and degree of efficacy or safety have been established.

**Excretion**

The principal route of elimination of Ridaura gold is via the faeces (84 - 92%), with the urine accounting for 9 - 17% of the administered dose (equivalent to about 60% of the absorbed gold).

Studies with radio-labelled auranofin in patients with rheumatoid arthritis demonstrated a plasma elimination half-life of 16.8 (range 11.0 - 23.1) days and 25.5 (range 20.7 - 31.3) days before and after 6 months treatment with non-labelled auranofin 6 mg per day. In the same patients mean terminal body half-life was 57.6 (range 30.0 - 78.3) and 81 (range 42.3 - 128.0) days respectively.

**INDICATIONS**

Adjunctive treatment of active classical or definite rheumatoid arthritis in adults who have an insufficient therapeutic response to, or are intolerant of, an adequate trial of a baseline therapeutic program, including among other measures, full doses of one or more nonsteroidal anti-inflammatory drugs. Ridaura is not indicated in non-rheumatoid arthropathies such as osteoarthritis. Ridaura should be added to a comprehensive baseline therapeutic program.

**CONTRAINDICATIONS**

- Previous serious toxicity to parenteral gold or to auranofin or to heavy metals other than gold
- Progressive renal disease
- Severe active hepatic disease
- History of bone marrow toxicity
- Severe chronic forms of dermatitis (severe urticaria or eczema, exfoliative dermatitis)
- History of gold-induced necrotising enterocolitis
- History of gold-induced pulmonary fibrosis
- Bone marrow aplasia
- Severe haematologic disorders
- History of hypersensitivity to gold compounds
PRECAUTIONS

Physicians should familiarise themselves thoroughly with this Product Information and discuss the potential adverse effects that may occur with patients on this therapy. Patients should be alerted to report promptly any unusual signs or symptoms suggesting toxicity.

Other disease conditions
In conditions such as systemic lupus erythematosus, systemic sclerosis and Sjogren’s syndrome, Ridaura has not been evaluated and therefore its use cannot be recommended. Diabetes mellitus, congestive cardiac failure and hypertension should be under control before gold therapy is instituted.

Ridaura should be used with caution in patients with inflammatory bowel disease because of the possibility of inducing diarrhoea and further bowel irritation. Ulcerative enterocolitis is a rare serious gold reaction. Therefore, patients with gastrointestinal symptoms should be monitored for the appearance of gastrointestinal bleeding (see below).

Gastrointestinal effects
The incidence of diarrhoea appears to be related to the size of the dose, but not frequency of administration, and is apparently increased in patients of low body weight. The auranofin-induced diarrhoea may be controlled by a dose reduction, appropriate symptomatic treatment, use of variable dosage regimen or oral iron administration. If all the above fails, auranofin should be withdrawn.

Haematologic reactions
Ridaura should be used with caution in patients with a history of, or receiving therapy likely to result in, bone marrow suppression.

Blood dyscrasias including leucopenia, granulocytopenia and thrombocytopenia have all been reported as reactions to parenteral gold and Ridaura. These reactions may occur separately or in combination and may occur anytime during treatment. Regular monitoring for early diagnosis of blood dyscrasias is recommended.

It is recommended that whole blood count with differential cell count, haemoglobin, urinary protein, and renal and liver function tests be performed prior to Ridaura therapy to establish a baseline and to identify any pre-existing conditions.

Whole blood count with differential cell count, platelet count and urinary protein should then be monitored monthly; other parameters should be monitored as appropriate.

Danger signs of possible gold toxicity include: rapid fall in haemoglobin, leucopenia below 4000 WBC/mm³, granulocytes below 1,500/mm³, decrease in platelets below 150,000/mm³.
Thrombocytopenia has occurred in up to 1 - 3% of patients treated with Ridaura, some of whom developed bleeding. The thrombocytopenia appears to be peripheral in origin and is usually reversible upon withdrawal of Ridaura. Its onset bears no relationship to the duration of Ridaura therapy. Its course may be rapid. While patients’ platelet counts should normally be monitored monthly, the occurrence of signs and symptoms (e.g. purpura, ecchymoses or petechiae most commonly) 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 further studies show the signs, symptoms or thrombocytopenia to be caused by conditions other than gold toxicity.

Renal and hepatic effects
Ridaura should be used with caution in patients with renal impairment or hepatic dysfunction.

Gold compounds are well documented to be nephrotoxic. In order to detect early toxic effect complete urinalysis should be performed prior to therapy and at least monthly thereafter. If significant proteinuria (greater than 500 mg/day), or microscopic haematuria develops, treatment with auranofin and all other therapies with the potential to cause proteinuria or haematuria should be stopped. In view of known hepatotoxic effect of gold preparations (including auranofin) regular liver function monitoring is recommended.

Mucocutaneous effects
Gold induced dermatitis may be aggravated by exposure to sunlight and/or photosensitivity reactions may develop. Pruritus usually precedes dermatitis and early transient pruritus is considered a warning signal that the tolerance level has been exceeded. A metallic taste may precede oral mucous membrane reactions and may be considered as a warning signal of impending gold toxicity.

Moderately severe skin mucous membrane reactions may be relieved by symptomatic treatment (e.g. topical steroids, oral antihistamines and/or soothing anaesthetic lotion). Severe or generalised gold compound induced stomatitis or dermatitis may require systemic steroid therapy.

Ridaura should be used with caution in patients with a history of atopy because of the possibility of skin rashes occurring during treatment. Any eruption, especially if pruritic, that develops during treatment should be considered a gold reaction until proven otherwise.

Ocular effects
As gold preparations including auranofin cause ocular adverse effects, periodic ophthalmic examination is recommended in patients being treated with auranofin.
Use in pregnancy

Category B3
Adequate human data on use during pregnancy are not available, and animal studies have shown adverse effects on pregnancy and embryo-foetal development.

Auranofin has been shown to be teratogenic in some animal species. Auranofin induced abortion, increased resorption, decreased litter size and foetal weight when given in a dosage of 0.5 - 7.8 mg/kg/day to pregnant rabbits. The most prominent and constant foetal abnormalities were abdominal defects such as gastroschisis and umbilical hernia. Anomalies of the brain, heart, lung and skeleton were seen less frequently. Oedema was the only major defect noted in foetal offspring from pregnant rats administered auranofin from 0.5 to 80.0 mg/kg/day. The incidence of resorption was significantly greater than that of the control at higher doses (10 - 80 mg/kg/day).

Ridaura should not be used in pregnant women or those likely to become pregnant. 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 (see PHARMACOLOGY).

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

Gold has been demonstrated in the milk of lactating mothers following the administration of parenteral gold. Trace amounts of the medicine appeared in the serum and red blood cells of the nursing offspring. It has been postulated that this may be the cause of unexplained rashes, nephritis, hepatitis and haematological aberrations in the nursing infants of mothers treated with parenteral gold.

Because of potential serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue medicine therapy, taking into account the importance of the medicine to the mother. The slow excretion of gold and its persistence in the mother after discontinuation of treatment should be kept in mind.

Paediatric use
Ridaura has not been evaluated in juvenile rheumatoid arthritis and, consequently, its use in children below 16 years cannot be recommended.

Genotoxicity
Ridaura has shown weak mutagenic potential in the mouse lymphoma cell assay. Auranofin produced no mutation effects in the Ames Test (Salmonella), in the in vitro assay (Forward and Reverse Mutation Inducement Assay with Saccharomyces), in the in vitro transformation of BALB/T3 cell mouse assay or in the Dominant Lethal Assay.
Carcinogenicity
As with other gold preparations, karyomegaly, cytomegaly and cystic development leading to development of adenoma and adenocarcinoma of the renal tubular epithelium has been observed in rats.

INTERACTION WITH OTHER MEDICINES

The safety of concomitant administration with penicillamine, antimalarials, immunosuppressants, cytotoxic agents, phenylbutazone, oxyphenbutazone, levamisole, chloroquine/hydroxychloroquine, high dose corticosteroids (in view of potential of these medicines to cause blood dyscrasias or other additive toxicity) has not been established. Therefore, concomitant use of Ridaura with these agents cannot be recommended.

Animal toxicology studies demonstrated an increase in toxicity of Ridaura when it was administered with warfarin, dextropropoxyphene and clonidine. Although the clinical significance of this is not clear it should be borne in mind when these medicines are used concomitantly.

ADVERSE EFFECTS

The incidences of adverse reactions listed below are based on post-marketing experience and on observations of 4,784 patients. Of these, 2,729 were treated for more than one year and 573 for more than three years. The highest incidence is during the first 6 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 doses of corticosteroids.

More common (>1%)
Gastrointestinal: loose stools or diarrhoea (47%), abdominal pain/cramps (14%), nausea with or without vomiting (10%), constipation (1 - 3%), anorexia (3 - 9%), flatulence (3 - 9%), dyspepsia (3 - 9%), dysgeusia (1 - 3%)
Dermatological: rash (24%), pruritus (17%), hair loss (1 - 3%)
Mucous membrane: stomatitis (13%), conjunctivitis (3 - 9%), glossitis (1 - 3%)
Haematological: anaemia, leucopenia, eosinophilia, thrombocytopenia (1 - 3%)
Renal: proteinuria (3 - 9 %), haematuria (1 - 3%), increase in blood urea and serum creatinine (1 - 3%)
Hepatic: elevated liver enzymes (1 -3 %)

Less common (<1%)
Gastrointestinal: positive stool for occult blood, ulcerative enterocolitis (<0.1%), peptic ulcer, metallic taste, dysphagia, (<0.1%), gastrointestinal bleeding, melaena
Dermatological: angioedema (<0.1%)
**RIDAURA® (Auranofin) Product Information**

*Mucous membrane:* dry mucous membrane, gingivitis
*Haematological:* neutropenia, agranulocytosis (<0.1%), aplastic anaemia and pancytopenia
*Renal:* membranous glomerulonephritis (<0.1%), nephrotic syndrome (<0.1%)
*Respiratory:* interstitial pneumonitis (<0.1%)
*Hepatic:* jaundice (<0.1%)
*Neurologic:* peripheral neuropathy (<0.1%), headache and dizziness

The following have been reported on occasion in clinical trials but no definite relationship to Ridaura therapy has been established:
Bell’s palsy, ototoxicity, progression of pre-existing pulmonary disease, corneal lesion and chrysiasis.
Three cases of pure red cell aplasia have been reported.

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.

**DOSAGE AND ADMINISTRATION**

The usual adult dosage is 6 mg per day with food.

Ridaura may be co-prescribed with anti-inflammatory medicine/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 10 mg) corticosteroid therapy.

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

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.

**OVERDOSAGE**

**Symptoms**
The absence of experience with acute overdosage with Ridaura precludes characterisation of sequelae and assessment of antidotal efficacy at this time.
A 50 year old female, previously on Ridaura 6 mg daily, took 27 mg daily for 10 days and developed encephalopathy and peripheral neuropathy. Ridaura was discontinued and she eventually recovered.

Treatment
In the case of accidental overdosage, immediate induction of emesis or gastric lavage is recommended.

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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Square, bevel-edged, pale yellow, film-coated tablets having raised domes on both faces, containing auranofin 3 mg in bottles of 60.

Store below 30°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Amdipharm Mercury (Australia) Pty Ltd
Level 1, 134 Willoughby Road
Crows Nest NSW 2065

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 August 1991
DATE OF MOST RECENT AMENDMENT

09 February 2016

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