NDA

18-689

SBA

Orig
NDA

Summary Basis of Approval

REVISED 6-21-85

NDA 18-689

Applicant:
Smith Kline & French Laboratories
Philadelphia, PA 19101

Drug Generic Name:
Auranofin

Drug Trade Name:
Ridaura

I. Indications for Use:

'Ridaura' is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal antiinflammatory drugs. 'Ridaura' should be added to a comprehensive baseline program, including non-drug therapies.

Unlike antiinflammatory drugs, 'Ridaura' does not produce an immediate response. Therapeutic effects may be seen after three-four months of treatment, although improvement has not been seen in some patients before six months. When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.

In controlled clinical trials, 'Ridaura' was associated with fewer dropouts due to adverse reactions, while parenteral gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of 'Ridaura' in patients who are candidates for chrysotherapy.

II. Dosage form, route of administration and recommended dosage:

The usual adult dosage of 'Ridaura' 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, being associated with an increased incidence of diarrhea. If response 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.

Dosage recommendations and indications for use in children have not been established.

'Ridaura' is available in oral form as capsules containing 3 mg auranofin.

III. Manufacturing and Control:

A. Manufacturing and Controls

Satisfactory information is provided for manufacturing and controls of new drug substance and the drug product.

B. Stability

Data support expiration dating for a period of 36 months for the drug product.

C. Methods Validation

The proposed methods for the new drug substance and the drug product have been validated and are suitable for regulatory and controls purposes.

D. Labelling

The "How Supplied" section and "Description" section of the package insert are adequate from controls viewpoint.

E. Establishment Inspection

The firm is in compliance with the Current Good Manufacturing Practice Regulations. This conclusion is based on an inspection conducted September 4-20, 1984.

F. Environmental Impact Analysis Report

An EIAR has been submitted and judged to be satisfactory.

G. Bioavailability Requirement

The firm has provided data demonstrating that mean blood gold concentrations are proportional to dose and have met the bioavailability/bioequivalence requirements for this application.

IV. Pharmacology:

A. Auranofin is an orally administered gold compound which has anti-arthritic activity. Its mechanism of action is unknown. In several *in vivo* experimental animal models and *in vitro* tests of inflammatory cell function, auranofin reduced the inflammatory response. Various experimental studies have shown condition-dependent immunoregulatory effects of auranofin on humoral and cellular immunity.

B. The acute oral LD_{50} for auranofin is 310 mg/kg in adult mice and 265 mg/kg in adult rats.

C. In three month studies in rats (given oral auranofin doses of 3.6, 12 and 36 mg/kg/day) and in dogs (given oral auranofin doses of 1.8, 7.2 and 18 mg/kg/day), the main toxic effect was decreased body weight. Dose-related diarrhea and mild anemia also occurred in both species in the mid and high dose groups. Additionally, salivation and reduced serum alkaline phosphatase activity occurred in rats and emesis was observed in dogs.

In a 12-month study, rats treated with auranofin at 23 mg/kg/day (192 times the human dose) developed tumors of the renal tubular epithelium, whereas those treated with 3.6 mg/kg/day (30 times the human dose) did not.

In a 24-month carcinogenicity 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 (GST) at 2 or 6 mg/kg injected twice weekly (4 or 12 times the human dose) were compared to untreated control animals. Malignant renal epithelial carcinomas as well as renal adenomas, renal tubular cell karyomegaly and cytomegaly were significantly increased in animals receiving 1.0 or 2.5 mg/kg/day of auranofin. Similar findings were seen in animals receiving gold sodium thiomalate at 2 or 6 mg/kg twice weekly except for the carcinomas which were reported only at 6 mg/kg.

In an 18-month carcinogenicity study in mice given oral auranofin at doses of 1, 3 and 9 mg/kg/day (8, 24 and 72 times the human dose), there was an increase of benign hepatomas ($p = .02$) among high dose treated males. Applicant will submit an anlysis of mid-dose and low-dose liver tissues from the mouse carcinogenicity study.

In a one year study in dogs (given oral doses of up to 6 mg/kg/day), dose-related emesis, soft stools, salivation, subclinical anemia and hyperplasia of the thyroid glands occurred. The sponsor is conducting a seven-year carcinogenicity study in dogs.

In the mouse lymphoma forward mutation assay, auranofin at high concentrations (313 to 700 ng/ml) induced increases in the mutation frequencies in the presence of a rat liver microsomal preparation. 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.

D. In reproductive studies, pregnant rabbits given auranofin at doses of 0.5, 3 or 6 mg/kg/day (4.2 to 50 times the human dose) had impaired food intake, decreased maternal weights, decreased fetal weights and an increase above controls in the incidence of resorptions, abortions and congenital abnormalities, mainly abdominal defects such as gastrochisis and umbilical hernia.

Pregnant rats given 5 mg/kg/day (42 times the human dose) of auranofin 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.

E. Labelling is adequate from the standpoint of pharmacology.

V. Medical:

Auranofin is an oral form of gold for long-term therapy in rheumatoid arthritis patients. The gold in auranofin is coordinately bonded to a phosphorous from triethylphosphine and the sulfur of acetyl thioglucose. Although the native structure of auranofin may affect the absorption of gold and its partitioning among blood components (red cell vs. plasma protein binding), intact auranofin is not detected in the blood, and the presumed active moiety is the gold itself.

Auranofin has been investigated in 4,764 patients in 78 studies (22 studies, 2,474 patients in the U.S.; 56 studies, 2,310 patients in foreign studies). The studies are summarized in varying detail in the parts that follow. All studies have been done in patients with rheumatoid arthritis because the potential heavy metal toxicity of auranofin precluded the use of normal volunteers. In Section A, pharmacokinetic studies are described, as well as 2 dose ranging studies. The 2 dose ranging studies and the 3 studies providing the best data concerning effectiveness are presented in section B in more detail so that differences in results, i.e., % responders, dropouts for lack of efficacy, etc., can be put into some clinical perspective. The less definitive (supportive) studies are divided into US and foreign studies and are presented in tabular form in section C. Differences between the more definitive studies and the supportive studies are discussed in section B, rather than C.

All patients entered into auranofin clinical trials had to have active, classical or definite, adult-onset rheumatoid arthritis meeting the diagnostic criteria of the American Rheumatism Association. Patients were to be on an adequate therapeutic dose of salicylates and/or another nonsteroidal anti-inflammatory drug (NSAID) without having attained a completely satisfactory response.

This NSAID regimen was to be maintained throughout the double-blind comparative phases of auranofin clinical trials. The majority of protocols permitted concomitant use of maintenance dose steroids (up to 7.5 mg/day of prednisone or its equivalent for females and 10 mg/day for males). Patients who had previously exhibited heavy metal toxicities or had clinical or laboratory evidence of serious concomitant disease were excluded. Concomitant use of other second line therapies such as penicillamine, levamisole and hydroxychloroquine were prohibited. Where previous use of these agents, anti-neoplastic agents, or parenteral gold therapy was allowed, a washout period ranging from 3 to 6 months was required. Women of child bearing potential were required to practice a clinically accepted method of contraception. Pregnant or lactating women were excluded from these trials.

Although the choice of measurement instruments varied among protocols, rheumatoid activity evaluation generally included the following: Clinical: number of tender joints, number of swollen joints, severity of pain, duration of morning stiffness, time to onset of fatigue, grip strength and a global evaluation by the physician and/or patient; Laboratory: erythrocyte sedimentation rate or C-reaction protein, immunoglobulin levels (IgA, IgG, IgM) and rheumatoid factor.

For the purpose of evaluating effectiveness, the number of tender joints, number of swollen joints, severity of pain, the global assessment by the physician and/or patient, and withdrawal rates for insufficient therapeutic effect were considered to be the primary efficacy parameters.

Safety parameters (laboratory tests) and on-therapy events were recorded at each clinic visit and also evaluated by the investigators as to severity and probalility of being adverse drug reactions. For the purpose of evaluation of adverse effects, all on-therapy events were considered rather than limiting the analysis to those events considered drug related by the investigators.

A. Special Studies

Pharmacokinetics:

In rats and dogs, using ^{32}P, ^{35}S, and ^{195}Au labeled auranofin, no intact auranofin was found in blood. Gold was found mostly bound to red blood cells and plasma proteins. The phosphorous moiety was excreted in the urine as triethylphosphine oxide. The sulfur moiety is presumed to be acetyl thioglucose. The active moiety is presumed to be gold, and the possibility of pharmacological effects of the other two moieties has not been studied.

The pharmacokinetics of auranofin were examined in 6 rheumatoid arthritis patients. A single 6 mg (1.75 mg Au) dose of a solution of Au^{195} radiolabeled auranofin resulted in peak plasma gold concentrations of 0.039 to 0.11 mcg Au/ml in 1.5 to 2.5 hours. Approximately 25% of the gold was absorbed. By day 10 post-administration, 77% of the administered gold had been eliminated. At the end of six months, approximately 100% of the initially administered gold had been eliminated; approximately 60% of the absorbed gold (15% of the administered dose) was excreted in urine, the remainder was excreted in the feces. Total-body counting showed that only 0.4% was retained in the body at six months. The mean plasma terminal half-life was 17 days (range 11 to 23 days; N=5), while the mean total-body terminal half-life was 58 days (range 30 to 78 days; N=5).

When a second single 6 mg dose of a solution Au^{195} radiolabled auranofin was adminstered following six months of therapy with unlabeled auranofin, 3 mg b.i.d., the mean plasma terminal half-life was 26 days (range 21 to 31 days; N=5), while the mean total-body terminal half-life was 80 days (range 42 to 128 days; N=5).

The bioavailability of the auranofin tablet formulation was compared with that of a dilute alcohol solution of ^{195}Au-auranofin in 11 patients with rheumatoid arthritis. Based on the first seven day blood gold levels, the bioavailability of auranofin in tablet formulation was 81.5% of auranofin administered in solution. The bioavailability of auranofin in tablet formulation based on the area under the blood gold concentration curve was 82.3% of auranofin administered in solution. Urine and fecal recoveries of non-radioactive/radioactive gold in 96 hours after dosing were 0.843 and 1.043 respectively.

In clinical studies, steady-state blood gold levels were achieved in approximately 3 months, consistent with the serum half-life of about 3 weeks. On 6 mg/day at 3 months, mean blood gold levels were 0.62 ± 0.195 ug/ml (n = 91 patients); at 6 months they were 0.68 ± 0.452 ug/ml (n = 63 patients). Mean blood gold levels were proportional to dose; however, no correlation between blood gold levels and safety or efficacy has been established.

The results of the small pharmacokinetic studies (only 5 RA patients) suggested that elimination half-life may increase a bit above the single-dose level with continuing auranofin therapy. On the other hand, wider experience (in 60 - 90 RA patients) during clinical trials showed that the steady state blood gold levels achieved at about 3 months of auranofin therapy remained at essentially the same level after 6 months of continuing therapy, which is reassuring, suggesting that there is no time-dependent change in gold kinetics.

Dose Ranging Studies:

Auranofin protocols 14 and 15 were double-blind dose-range studies. In Protocol 14, auranofin doses of 1 mg/day and 9 mg/day were administered in an attempt to ascertain the lowest effective as well as the highest tolerated dose. One hundred thirty-eight patients entered the study with 71 patients being randomized to the 1 mg/day group and 67 patients to the 9 mg/day group. Protocol 15 was designed to compare auranofin at a dose of 2 mg/day to a dose of 6 mg/day. Two hundred seventy-three patients entered the study with 134 patients randomized to the 2 mg/day dose group and 139 to the 6 mg/day dose group. Patients entering these protocols were required to meet the general inclusion/exclusion criteria and were evaluated according to the efficacy criteria described above (pp. 4-5). If intolerable adverse events occurred, the drug could be discontinued temporarily or the dosage reduced. If, after at least three months of therapy, the investigator felt that there was an insufficient therapeutic response, the double-blind code could be broken and the low dose groups could be increased.

Table 1

Baseline Characteristics of Patients
Entered into Protocols 14 and 15

	Protocol 14 Auranofin		Protocol 15 Auranofin	
	1 mg/day	9 mg/day	2 mg/day	6 mg/day
Functional Class				
I	2	3	3	2
II	48	49	105	113
III	18	14	24	21
N.S.	3	1	2	3
Stage Class				
I	6	7	36	37
II	41	38	72	68
III	15	19	21	26
IV	0	0	0	1
N.S.	9	3	5	7
Baseline Averages of Primary Efficacy Parameters				
Number of Tender Joints	28.5	31.5	21.9	22.6
Number of Swollen Joints	17.5	15.3	18.8	19.5
Severity of Pain (10 cm line with 10 = severe pain)	5.7	5.8	4.3	4.6

N.S. = Not Stated

In protocol 14, patients in both dose groups of auranofin were similar with respect to sex distribution, age, duration of disease, number of patients on a maintenance dose of steroids and functional class and anatomical stage distributions. Both drug groups were also similar with respect to the baseline values of the primary efficacy parameters (Table 1).

More patients in the 1 mg/day group, 57% (32/56), broke their codes for insufficient therapeutic effect than in the 9 mg/day group, 33% (20/60). In contrast, more patients in the 9 mg/day group 28% (17/60) had their dosage altered due to adverse events than in the 1 mg/day group 7% (4/56). The major adverse events were diarrhea and rash. Diarrhea was dose-dependent. Thirty-six percent (20/56) of the patients on 1 mg/day of auranofin and 39% (23/60) of the patients on 9 mg/day of auranofin were able to complete a 6 month double-blind course of therapy. This study showed that neither 1 mg/day nor 9 mg/day appeared to be an optimum starting dose: 1 mg/day had an insufficient therapeutic effect and 9 mg/day had an excessive increase in incidence of diarrhea.

In protocol 15 patients in both dose groups of auranofin were similar with respect to sex distribution, age, duration of disease, number of patients on a maintenance dose of steroids and functional class and anatomical stage distributions. Both drug groups were also similar with respect to the baseline values of the primary efficacy parameters (Table 1).

In the 2 mg/day vs. 6 mg/day comparison study, the percentages of patients who broke their double-blind code after three months of therapy due to insufficient therapeutic effect were similar in the two dose groups: 28% (32/114) on 2 mg/day of auranofin and 22% (25/116) on 6 mg/day of auranofin. Both dose groups showed a statistically significant improvement from baseline in the number of tender joints, the number of swollen joints, the articular index, ESR and grip strength at both the three and six month intervals. This indicated response in both dosage groups. In addition, the 6 mg/day patients had a statistically significant change from baseline in duration of morning stiffness, onset of fatigue, severity of pain, IgA and IgM at both month 3 and month 6. The 2 mg/day patients had a statistically significant change in these parameters at month 6, but not month 3. Diarrhea and bowel problems were the most frequent adverse events and were more prevalent in the 6 mg/day group. (See table below for data on G.I. reactions to auranofin at all 4 doses.) However, the percent of patients who discontinued or reduced their initial dose of study medication due to any adverse reaction was similar in both groups: 12% (14/114) on 2 mg/day of auranofin (5/14 discontinued, 9/14 reduced) and 18% (21/116) on 6 mg/day of auranofin (3/21

discontinued, 18/21 reduced). Sixty percent (68/114) of the patients on 2 mg/day of auranofin and 60% (70/116) of the patients on 6 mg/day of auranofin completed 6 months of therapy on their initial dose of double-blind medication. This study showed that the 6 mg dose of auranofin was well-tolerated and was an appropriate dose at which to initiate therapy, giving a somewhat faster onset of effect than 2 mg/day.

Incidence of G.I. Reactions in Dose Ranging Studies

Daily Dosage	All Events		Reduced Dose or Discontinued	
	Diarrhea	Any G.I.	Diarrhea	Any G.I.
1 mg	15%	28%	1.8%	1.8%
2 mg	13%	25%	0	0
6 mg	37%	50%	7%	9%
9 mg	64%	76%	20%	23%

These dose ranging studies pose one difficulty: the 4 doses were studied in 2 separate populations rather than as a single study. This is somewhat problematic in that the second study population (2 and 6 mg/day) seemed to have less severe or less active disease (see Table 1) than the first, making a comparison between the 6 and 9 mg (or the 2 and 9 mg) groups open to some question. Although not ideal, the 2 studies provide sufficient information on dose-response to choose an initial dosage. It is particularly clear that diarrhea and G.I. complaints in general were dose-related.

After 6 months, when investigators in these two protocols were given the opportunity to adjust the dose over time, most patients were switched to higher doses (6 mg or 9 mg), with the majority of patients on 6 mg/day.

B. Double-Blind, Adequate and Well Controlled Studies

There were 4 US and 10 foreign trials that had placebo control groups. Two of these are reviewed in detail in this section. One (Protocol 20) had both placebo and positive contol groups (gold sodium thiomalate). In general the placebo control groups had more dropouts because of lack of effectiveness than the gold-treated groups; this was a more meaningful endpoint of effectiveness than evaluation of disease activity in patents completing the study, because the placebo completers probably represent a biased remnant of the initial placebo group (i.e., a subgroup that, by definition, does well on placebo). There were two placebo controlled US trials that did not show this trend (Protocol AU-104, section C and Protocol 20, this section). The results in Protocol 20 are consistent with the previously demonstrated ability of this group of investigators (Cooperative Clinics for Systematic Study of Rheumatic Diseases - John Ward,

Coordinator) to keep placebo patients in trials of 20 weeks duration. In Protocol AU-104 a concerted effort was also made to keep patients in the trial for 24 weeks and this was apparently successful. There were significant differences in effectiveness favoring auranofin over placebo in 3 out of 4 primary efficacy parameters (tender and swollen joint counts, pain assessment and patient global evaluation). In this study, quality of life assessments were a major focus. These also favored auranofin. They are of interest as effectiveness variables, but at the current level of knowledge they are more difficult to assess than more standard efficacy variables.

There were 3 U.S. trials comparing auranofin to traditional parenteral gold. One was a small pilot study (Protocol 21, section C), another was designed to study a regimen for transfering patients, for convenience, from an otherwise satisfactory stable maintenance parenteral gold regimen to auranofin (Protocol 29-M, section C), and the third study was Protocol 20 (this section).

There were 19 foreign studies comparing auranofin to parenteral gold preparations in patients who had not previously been treated with gold. One of these, the Schattenkirchner study, is reviewed in this section. The other foreign studies (all in section C) either had too few patients to develop sufficient power for a positive-controlled study, i.e., 30 or fewer per treatment group (7 studies), or were single blind (2 studies) or open label (9 studies). The results in these studies are consistent with those in the 2 positive-controlled studies described in this section, with a few exceptions where the numbers are so small that they are presumed to represent random variation.

For a study in rheumatoid arthritis with 60 patients per active treatment group, the power to detect a 2-fold difference in efficacy between groups would be 83%. Protocol 20 had sufficient completers in the active treatment groups to fall in this range. The Schattenkirchner study, with about 50 patients completing treatment on auranofin and 40 on sodium aurothiomalate, had less than 80% power to detect a 2-fold difference.

There were 3 additional foreign studies resembling Protocol 29-M (UK08/1, UK09/1 and UK12/1, section C) where the intent was to compare the results of transfering patients, for convenience, from satisfactory stable parenteral gold programs to auranofin. These studies, including Protocol 29-M, are reviewed in section C.

The patient populations in the 3 adequate studies were somewhat different in baseline characteristics relating to efficacy (Table 2). Note that the data on the Protocol 20 population includes completers only, whereas the other two study populations include all entrants.

1. Auranofin versus Placebo (Protocol 22)

A 6 month double-blind study was carried out in 18 centers in the United States. Three hundred and forty patients were randomized to either auranofin 3 mg b.i.d. (6 mg/day) or placebo. Of these, 18 in each group were entered in violation of the entry criteria, leaving 152 per group properly entered and randomized.

Patients in both groups were similar with respect to sex distribution, age, duration of disease, number of patients on a maintenance dose of steroids, functional class, and anatomical stage distributions. Both drug groups were also similar with respect to the baseline values of the primary efficacy parameters (Table 2).

The auranofin patients showed a greater decrease in the severity of pain, the number of tender joints and the number of swollen joints than those on placebo. These differences were statistically significant at 3 months (p less than 0.05). The reduction in the number of swollen joints was statistically significant at 6 months. At both 3 and 6 months, a significantly (p less than 0.05) greater proportion of patients on auranofin had "marked" or "moderate" improvement (physician global assessment) when compared to placebo.

After receiving at least 3 months of therapy, 8.5% (13/152) of the auranofin patients had the double-blind code broken and were withdrawn from the study due to insufficient therapeutic effect compared to 30.3% (46/152) of the placebo patients. This difference was statistically significant (p less than 0.05).

Table 2

Baseline Characteristics of Patients
Entered into Protocols 22 and the Shattenkirchner Study and Patients Completing Protocol 20

	Protocol 22		Schattenkirchner		Protocol 20		
	Auranofin (N=170)	Placebo (N=170)	Auranofin (N=60)	GST (N=62)	Auranofin (N=64)	GST (N=54)	Placebo (N=43)
Functional Class							
I	12	16	8	10	3	4	2
II	136	121	38	43	50	37	33
III	21	31	13	9	11	13	8
IV	1	0	1	0	0	0	0
N.S.	0	2	—	—	—	—	—
Anatomical Class							
I	35	31	17	21	8	12	12
II	89	102	30	26	29	27	17
III	40	34	13	15	23	13	12
IV	1	0	0	0	3	1	1
N.S.	5	3	—	—	1	1	1
Baseline Averages of Primary Efficacy Parameters							
Number of Tender Joints	23.3	22.4	20.9	19.7	31.7	30.3	29.0
Number of Swollen Joints	22.0	20.7	16.1	13.0	23.9	21.8	20.0
Severity of Pain (10 cm line with 10 = severe pain)	5.6	5.3	64.3	58.9	—	—	—
Patient Global Assessment*	—	—	43/100	38/100	2.9/5	2.8/5	3.1/5

N.S. = Not Stated

* The Shattenkirchner study used a 100 mm analog scale of "general health" with 100 representing poor health; Protocol 20 used a 5 point scale with 5 representing severe disease. Thus the values are expressed as mean/highest possible score.

During the 6 month double-blind phase of this study, 5.4% (8/152) of the auranofin patients discontinued their coded medication due to adverse on-therapy effects compared to 2.6% (4/152) of the placebo patients. With the exception of gastrointestinal effects, adverse reactions were similar in both groups:

Adverse Events - Protocol 22

	Auranofin/NSAID (N=170)*				Placebo/NSAID (N=170)*			
	With Adverse Event		Discontinued		With Adverse Event		Discontinued	
	N	(%)	N	(%)	N	(%)	N	(%)
Diarrhea	52	(30.5%)	4	(2.4%)	9	(5.3%)	0	
Upper G.I.	27	(15.9%)	0		14	(8.2%)	1	(0.6%)
Skin	21	(12.4%)	4	(2.4%)	18	(10.6%)	0	
Mucous Membrane	11	(6.5%)	0		11	(6.5%)	1	(0.6%)
Proteinuria	5	(2.9%)	4	(2.4%)	4	(2.4%)	1	(0.6%)
Platelet Decrease	1	(0.6%)	1	(0.6%)	1	(0.6%)	0	
WBC Decrease	0		0		6	(3.5%)	1	(0.6%)
Insufficient Therapeutic Effect			16	(9.4%)			49	(28.8%)

* The numbers in this table reflect all 340 patients randomized to study medication. The results of the efficacy comparisons cited above are based upon the 304 patients (152 auranofin, 152 placebo) who met the entrance criteria specified in the protocol.

2. Comparison of Auranofin, Gold Sodium Thiomalate and Placebo (Protocol 20)

Protocol 20 was a 21 week double-blind study carried out in 11 U.S. centers. Two hundred and twenty-four patients were randomly assigned to 1) auranofin (3 mg b.i.d.) plus placebo injections, 2) placebo tablets plus gold sodium thiomalate (GST) injections (50 mg weekly) or 3) placebo tablets plus placebo injections. All patients were required to meet the general inclusion/exclusion criteria described above (p.4).

There was no statistically significant difference among treatment groups with respect to demographic parameters and baseline classifications. All three groups were also similar with respect to baseline values of the efficacy parameters (Table 2).

Among patients who remained on therapy for 21 weeks, both the auranofin and injectable gold regimens showed statistically significant improvement (p less than 0.05) in the number of tender and painful joints, physician assessment of disease activity and ESR when compared to placebo after 13 weeks of therapy and at the conclusion of the double-blind study (week 21). The mean reduction in the number of swollen joints, tender joint scores and duration of morning stiffness were greater for the GST group than auranofin (p less than 0.05). Eighty-two percent (64/78) of auranofin patients, 67% (54/81) of GST patients and 86% (43/50) of the placebo patients were able to complete a 21 week course of therapy.

Statistically significant improvements (p less than 0.05) from baseline were detected in both gold regimens in the number of tender joints, the number of swollen joints, physician assessment, patient assessment, duration of morning stiffness, grip strength and ESR. In the placebo group, only grip strength and patient assessment showed significant improvement from baseline (p less than 0.05).

Table 3

Adverse Events - Protocol 20

Treatment Groups

Adverse Events	Placebo (N=51)		Auranofin (N=85)		Gold Sodium Thiomalate (N=88)	
	# pts. with adverse event	# withdrawn	# pts. with adverse event	# withdrawn	# pts. with adverse event	# withdrawn
Flushing "nitritoid"	0	0	0	0	8	3
Rash	2	1	2	1	11	8*
Pruritus	1	0	0	0	1	0
Altered taste	0	0	3	0	2	0
Blurred vision	0	0	0	0	3	0
Stomatitis	0	0	1	1	6	4
Nausea	0	0	0	0	1	0
Abdominal bloating	0	0	1	0	1	0
"Soft stools"	0	0	3	0	1	0
Diarrhea	0	0	3	1	2	1
Other	0	0	3	2	16	9
Total	3 (6%)	1 (2%)	16 (19%)	5 (6%)	52 (59%)	25 (25%) 22 patients

*Three patients were withdrawn for more than one reason: 1 for rash and thrombocytopenia;
1 for rash and stomatitis; and
1 for rash and leukopenia.

An algorithm was developed to categorize the overall response (improvement from baseline) of each patient. The results of number of tender joints, swollen joints, physician's global, and patient's global assessment, were combined into a single score, with equal weight on each of the 4 variables. Using this algorithm, both the auranofin regimen and the GST regimen had a significantly greater proportion of patients (p less than 0.05) who showed some improvement than the placebo regimen did. The difference between the two gold regimens was not statistically significant.

Withdrawals due to adverse effects occurred four times more frequently with gold sodium thiomalate treatment (25%, 22/88) than with auranofin therapy (6%, 5/85). This difference was statistically significant (p less than 0.05). Two percent (1/51) of the placebo patients withdrew because of adverse reactions. (Table 3).

3. Schattenkirchner Study (Auranofin vs. Parenteral Gold

A one-year (48 week) double-blind comparison of auranofin and sodium aurothiomalate (Tauredon) in patients with active definite or classical adult rheumatoid arthritis was conducted by 5 participating centers: 4 in Germany and 1 in Austria.

Patients were randomly assigned to one of the following regimens:

1) auranofin tablets, 6 mg daily and placebo injections or

2) placebo tablets and sodium aurothiomalate injections given according to the following schedule:

Week 1	one injection	10 mg
Week 2	one injection	20 mg
Weeks 3-24	one injection	50 mg each week
Weeks 25-48	one injection	50 mg q 4 weeks.

A total of 122 patients received coded study medications: 60 patients were randomly allocated to the auranofin regimen and 62 patients to the sodium aurothiomalate regimen. The general inclusion/exclusion criteria described above (p. 4) also applied to this study, though use of corticosteroids was to be avoided.

Patients in both treatment groups were similar with respect to the distribution of sex, age, duration of disease, functional class and anatomical stage at entry (Table 2). The average baseline values of the primary efficacy parameters were somewhat higher (worse disease) in the

auranofin group than the sodium aurothiomalate group, though the differences were not statistically significant at the 5% level (Table 2).

One patient in the sodium aurothiomalate group was discontinued for insufficient therapeutic effect (ITE); no patient treated with auranofin was discontinued for ITE.

Two patients (1 auranofin, 1 sodium aurothiomalate) were withdrawn prior to completing one year of therapy because of sufficient therapeutic effect (STE), i.e., the signs and symptoms of their disease activity had disappeared.

At 12 months, both auranofin and sodium aurothiomalate showed significant improvement (p less than 0.05) from baseline in the parameters of disease activity.

Results of covariance analysis showed there were no statistically significant differences (p less than .05) between auranofin and sodium aurothiomalate in any of the parameters of disease activity, though mean improvement in the sodium aurothiomalate group was slightly greater. These analyses included only those patients who were able to complete one year of therapy, and the power to detect treatment differences was reduced compared to that of Protocol 20.

Defining the proportion of patients who were entered into this study and derived benefit from their study medication as those patients who improved at least 50% from baseline, the percents of patients who improved were as follows:

	Auranofin		Sodium Aurothiomalate	
Parameter	All Patients Entered (N=60)	Completers* (N=49)	All Patients Entered (N=62)	Completers* (N=41)
Number of Tender Joints	38%	47%	31%	46%
Number of Swollen Joints	53%	65%	44%	66%
Severity of Pain	22%	27%	19%	29%
General Health Rating (Patient Global Assessment)	23%	29%	16%	24%

* Completers include all patients who completed 12 months of therapy (48 auranofin, 39 sodium aurothiomalate), patients withdrawn for insufficient therapeutic effect (1 sodium aurothiomalate) and patients withdrawn for sufficient therapeutic effect (1 auranofin, 1 sodium aurothiomalate). Additionally, 11 auranofin patients (18%) and 21 sodium aurothiomalate patients (34%) were withdrawn for adverse effects (7 auranofin, 17 sodium aurothiomalate) or administrative reasons (4 auranofin, 4 sodium aurothiomalate).

Table 4

Adverse Reactions Resulting in Withdrawal
From Study Medication During One Year Treatment
(Schattenkirchner Study)

	Auranofin			Sodium Aurothiomalate		
	Week Withdrawn	No. of Patients (60)	Reason for Withdrawal	Week Withdrawn	No. of Patients (62)	Reason for Withdrawal
Skin and Mucocutaneous Disorders	7	1	pruritus, exanthema	9	1	rash, pruritus
	21	1	dermatitis	12	1	pruritus
	24	1	rash, aphthous stomatitis	14	1	stomatitis
	32	1	glossitis	28	1	stomatitis
				30	1	rash
	81	1	stomatitis	34	1	metal taste, pruritus, rash
				41	1	pruritus, rash
				42	1	stomatitis metal taste
				201	1	pruritus, rash and stomatitis
Gastrointestinal Events	35	1	flatulence, diarrhea			
Abnormal Laboratory Values				2	1	eosinophilia
				23	1	increased liver enzymes
				30	1	proteinuria

	Auranofin			Sodium Aurothiomalate		
	Week Withdrawn	No. of Patients (60)	Reason for Withdrawal	Week Withdrawn	No. of Patients (62)	Reason for Withdrawal
Other Adverse Reactions	11	1	herpes zoster	1	1	hot flushes, shivering diarrhea
				3	1	injection reaction
				4	1	"renal pain"2
				7	1	"osteomyelo-sclerosis"3
				16	1	fatigue, fever, chills sweating
Total Number of Patients	7 (12%)				17 (27%)	

[1]Adverse Reactions Resulting in Withdrawal of Therapy for greater than 2 weeks in the first 3 months or 4 weeks thereafter.

[2]Actual German term: Nierenschmerzen

[3]Actual German term: Osteomyelosklerose

Eighty-two percent (49/60) of the auranofin-treated patients and 65% (40/62) of sodium aurothiomalate-treated patients were able to complete one year of therapy or derive sufficient benefit to warrant discontinuation. This difference was due to the disproportionate number of patients withdrawn from sodium aurothiomalate due to adverse effects, 17/62 (27%) compared to auranofin, 7/60 (12%). (See Table 4.)

C. Supportive Studies for Rheumatoid Arthritis

There were 19 additional foreign studies comparing auranofin with parenteral gold. Sixteen were conducted in patients who had not previously received injectable gold. Study designs varied from double-blind, to single-blind and open trials of auranofin versus injectable gold. In all comparison studies, patients were randomly assigned to a regimen that included maintenance of baseline NSAID.

The data from these studies are consistent with those of the two double-blind, comparative trials of auranofin versus injectable gold described in the previous section. Both the auranofin and injectable gold groups showed significant improvement over baseline NSAID therapy. Auranofin was associated with fewer withdrawals for adverse events whereas injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect.

The incidence of reported adverse events and those events leading to withdrawal have been evaluated in all eighteen comparative trials of auranofin and injectable gold in patients who had not previously received gold therapy. After completion of the double-blind phase or evaluation period of efficacy, most studies permitted continuation of the study medication. Table 5 lists the incidence of all adverse on-therapy events (irrespective of investigator attribution) for patients who received auranofin or injectable gold for up to a maximum of two years. For the 18 comparative trials, the most prevalent adverse events leading to withdrawal over the two year period are listed in Table 5a. During this time interval, 16% of auranofin patients were withdrawn for adverse events vs. 34% of injectable gold-treated patients. Using life table methodology, the cumulative risk of being withdrawn for an adverse event was significantly greater for injectable gold when compared to auranofin (49% vs. 26%, p less than 0.05). During the two years, 12% of auranofin patients were withdrawn for insufficient therapeutic effect vs. 3% of injectable gold-treated patients. The cumulative risk of being withdrawn for insufficient therapeutic effect was significantly greater for auranofin when compared to injectable gold (26% vs. 9%, p less than 0.05).

Table 5

Incidence of All Adverse On-Therapy Events
for Specific Categories Over Two Year Period

Adverse Event	Auranofin (N=445)	Injectable Gold (N=445)	Statist. Signif.1 (p less than 0.05)
Diarrhea	42.5%	13%	+
Rash	25%	39%	+
Stomatitis	13%	18%	-
Anemia	3.1%	2.7%	-
Leukopenia	1.3%	2.2%	-
Thrombocytopenia	0.9%	2.2%	-
Proteinuria	0.9%	5.4%	+

Table 5a

Percent of Patients with Adverse Events Contributing
to Withdrawal[2] Over Two Year Period

Adverse Events	Auranofin (N=445)	Injectable Gold (N=445)	Statist. Signif.1 (p less than 0.05)
Diarrhea	4.9%	1.1%	+
Rash	5.1%	15.2%	+
Hematologic (anemia, leukopenia, thrombocytopenia)	1.1%	3.1%	+
Stomatitis	1.8%	5.1%	+
Proteinuria	0.7%	3.4%	+
All others	4%	10%	

1 + denotes statistically significant difference between groups by chi-square test.

2 These numbers are not additive as some patients reported more than one adverse event contributing to withdrawal.

The cumulative risk of being withdrawn from therapy during the first 2 years of treatment for all reasons was 57% for auranofin and 66% for injectable gold (favoring auranofin, p less than 0.05). Thus, the probability of remaining on therapy for at least 2 years was 43% for auranofin and 34% for injectable gold.

D. Transferring Patients from Injectable Gold to Auranofin (Protocols 29, UK08/1, UK09/1 and UK12/1)

The information from the UK series of studies is not available in the same detail as that from Protocol 29-M. Therefore Protocol 29-M is reviewed in more detail here than the other studies. It has been concluded that more detailed analysis and review of the UK studies need not be done prior to marketing in the US, but Smith Kline and French has agreed to expeditite the analysis and submission as a condition of approvasl.

A six month multi-center, double-blind study was carried out in six U.S. centers to determine 1) if rheumatoid arthritis patients controlled with injections of gold sodium thiomalate (GST) every 2 to 4 weeks could be transferred to auranofin and maintain control of disease activity and 2) if new or additive toxicity resulted from overlapping GST and auranofin therapy or from switching from parenteral gold to the oral gold compound.

Ninety-nine adult patients with rheumatoid arthritis, judged by physicians as having achieved a stable degree of control of rheumatoid disease with GST injections every 2 to 4 weeks, participated in this study. On Day 0, patients were randomly allocated, in a double-blind fashion, to auranofin tablets, 3 mg b.i.d. (50 patients) or a matching placebo (49 patients). All patients continued to receive open GST injections, according to their prior injection schedule, for approximately four weeks after coded tablets were initiated. At this time, open GST injections were replaced by coded injections, with those patients randomly assigned to auranofin tablets receiving placebo injections, and those patients taking placebo tablets receiving coded GST injections. Thus, those patients transferred to auranofin therapy had a 4 week period where they received open GST injections and coded auranofin tablets concurrently. Concomitant background medications for rheumatoid arthritis such as salicylates, nonsteroidal antiinflammatory drugs and low dose corticosteroids taken prior to the study were to be maintained during the study period.

The following parameters were assessed as measures of disease activity: number of tender joints, number of swollen joints, severity of pain, grip strength, duration of morning stiffness, time to onset of fatigue, ESR, gamma globulins and quantitative IgG and IgM.

At the conclusion of the study, 82% (28/34) of the patients transferred to auranofin and 88% (29/33) of the patients maintained on GST were judged to have maintained control of their disease activity as reflected by global efficacy ratings of "better" or "same".

There was no statistically significant difference between the two treatment groups with respect to changes (Month 6-Day 0) in the clinical and laboratory parameters of disease activity.

Comparisons with baseline values separately within each treatment group showed that both the patients transferred to auranofin and those maintained on GST had reductions in the median number of tender joints, swollen joints and pain scores though none of the differences were statistically significant. Both groups had statistically significant increases from baseline (one-tailed test, p less than 0.05) in ESR AND IgM.

Both treatment groups were comparable with respect to the number of patients withdrawn from study medication:

1) Two patients transferred to auranofin and 3 patients maintained on GST withdrew from the study because of insufficient therapeutic effect.

2) Three patients discontinued auranofin due to adverse effects (2 diarrhea and 1 rash) as compared to 2 patients who discontinued GST injections because of nitritoid reactions.

With the exception of diarrhea, the incidence of side effects of patients who tolerated injectable gold did not increase when these patients were transferred to auranofin. In addition, there was no additive toxicity when auranofin and GST were administered concurrently for a short period of time.

Two of the 3 UK studies from the data available on dropouts for lack of effectiveness and from adverse effects ostensibly show similar results as Protocol 29-M. The third study, however, had a relative increase in the number of dropouts for adverse effects. The explanation for the higher rate in this study is not clear but from looking at the adverse effects it is clear that they were not of a new or unusual nature (9 of 10 were G.I. disturbances, mostly diarrhea).

E. Summary of Worldwide Clinical Experience with Auranofin

Table 6 (immediately following the text) includes data on 4,784 patients who have received auranofin in worldwide clinical trials as reflected on the worldwide safety database of December, 1984. For each study listed, information is provided concerning study design, duration, study medication, number of centers and number of patients entered, completed and withdrawn. For controlled studies, withdrawals are listed for the blinded portion. "U.S. Clinical Trials" include a study done in Central America but monitored in the U.S. (Protocol 22LA).

In the U.S. studies, patients are listed according to their original protocols. Many of the patients continued to received auranofin in long-term open phase studies (A-99, AU-105) and/or special studies (A-28, A-98). In non-U.S. studies, most patients on auranofin were continued in an extension of the original protocol. Some patients treated with placebo or injectable gold were switched to auranofin after the controlled or comparative segment of the study or were entered in later protocols in which they received auranofin. These patients are listed under the "NOTES" section of the table.

F. Safety

The auranofin safety database included data from worldwide open label and controlled clinical trials as well as open label continuation of controlled studies. The incidence figures for adverse events listed in the product labelling are based on observations in 4,784 patients (2,474 U.S., 2,310 Foreign) treated with auranofin. Of these patients, 2,729 were treated for more than one year and 573 for more than three years. With rare exceptions, all patients were on concomitant nonsteroidal antiinflammatory drug therapy; some of them were also taking low doses of corticosteroids.

The highest incidence of adverse events occurred during the first six months of treatment. The most common reaction to auranofin was diarrhea/loose stools which was reported in approximately 50% of patients. It was generally manageable by a reduction in dose. Six percent of patients discontinued auranofin due to diarrhea. Rash occurred in 24% of patients and was the second most frequently reported reaction to auranofin. Most cases resolved with a reduction in dose or temporary cessation of therapy; in approximately 3% of patients, it was necessary to discontinue auranofin permanently. Proteinuria developed in 5% of patients with 1% of patients being withdrawn from therapy.

As with parenteral gold, proteinuria cleared over a few weeks to months on discontinuing auranofin with rare exception (2 patients took over 1 year). We conclude that with early recognition and discontinuation of treatment, renal effects are usually mild and subside completely. Therefore it is important to perform urinalyses regularly. This is reflected in the labelling by the inclusion of a urinalysis in the regular monitoring which should be performed at least monthly.

Thrombocytopenia occurred in approximately 1% of patients, some of whom developed bleeding. In addition, leukopenia and anemia were reported in some patients on auranofin (1.3% and 3.1% of patients respectively).

Among spontaneous reports from countries where auranofin has already been marketed are 5 cases of thrombocytopenia associated with fatal outcomes. Three of these cases occurred during the first 2 months of treatment. On reviewing these 3 cases, 2 had normal platelet counts in the week prior to their bleeding episode and the other had had a normal platelet count 9 days before signs or symptoms of thrombocytopenia developed. In addition to the value of monitoring the formed elements of the blood regularly throughout treatment which the NDA data base illustrates, these patients emphasize the importance of giving adequate instruction to patients as to signs or symptoms of thrombocytopenia which should cause them to immediately discontinue auranofin and consult their physician. Recommendations for patient instruction and at least monthly laboratory monitoring are reflected in the labelling.

Since a decision about whether or not to initiate gold therapy with oral or injectable gold involves a risk/benefit decision about products administered by the two routes of administration, the incidence of the major adverse effects observed in comparative trials are included in the package insert based on pooled data involving 890 patients equally divided between treatments by the 2 different routes of administration.

Other adverse events occurring with an incidence of greater than 1% but not considered to be as clinically important include abdominal pain, nausea with or without vomiting, constipation; anorexia, flatulence, dyspepsia, dysgeusia, pruritus, hair loss, urticaria, stomatitis, conjunctivitis, glossitis, eosinophilia, elevated liver enzymes and hematuria. These adverse effects are included in the ADVERSE EFFECTS section of the labelling with an indication of their incidence. In addition, rarer reactions occuring in between 1/100 and 1/1000 patients are identified in the ADVERSE REACTION section of the insert as well as rarer reactions, reactions for which a causal relation to auranofin was uncertain, and reactions observed with parenteral gold that have not yet been reported with auranofin.

The toxicity of oral (and parenteral) gold is clearly substantial and in rare cases the adverse reactions are life-threatening. Apart from identified toxicity, the consistent finding of rodent renal carcinogenicity with both forms suggests an additional concern. For these reasons, labeling for auranofin limits its use to persons unresponsive to NSAIDs and a comprehensive baseline prescription program and urges careful monitoring. Despite the known and potential risks, the benefits of this "second line" therapy outweigh its risks in properly selected and monitored patients. Alternative "second line" therapies such as azathioprine and penicillamine have comparable or more severe toxicity.

VI. Post-Marketing Surveillance:

The sponsor has agreed to conduct studies on 4 aspects of switching patients between the two routes, injectable and oral gold:

1. Switching patients successfully treated on injectable gold to oral gold;
2. Switching patients treated unsuccessfully on injectable gold (due to adverse reactions) to oral gold;
3. Switching patients treated unsuccessfully on oral gold (due to lack of efficacy) to injectable gold.
4. Initiating treatment (loading) with one route and then switching to the other route for maintenance therapy.

The sponsor will submit the results of the ongoing carcinogenicity study in dogs. Also, the data from the mouse carcinogenicity study mid and low dose groups on thymus tissue and liver will be submitted. If these data suggest tumorigenicity in the mouse, a repeat study with an injectable gold control group will be done in the mouse.

All questions raised by FDA's Division of Biopharmaceutics will be addressed by the sponsor.

VII. Approved Package Insert:

The labeling conforms to our guidelines for this class of product. A copy is attached.

0897B filed to 0178Q

Table 6

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
U.S. Clinical Trials											
Protocol 22	DB-R (Open - 6 mos.)	6 mos.	Auranofin Placebo	6 mg/day	18	170 170	143 (84%) 108 (63%)	13 49	8 4	6 9	18 placebo patients were placed on auranofin after DB phase.
Protocol 20	DB-R	21 wks.	Auranofin GST Placebo	6 mg/day 50 Lg/wk	11	85 88 51	44 (82%) 54 (67%) 43 (84%)	3 8 2	5 22 1	11 12 5	
Protocol 29-4	DB-R	6 mos.	Auranofin GST	6 mg/day 50 mg/wk	6	50 49	43 (86%) 41 (84%)	2 3	3 2	2 3	All pts. were previously stabilized on injectable gold.
Protocol 14	DB-R (Open - 18 mos.)	6 mos.	Auranofin	1 mg/day 9 mg/day	8	70 67	115 (84%)	2	8	12	
Protocol 15	DB-R (Open - 18 mos.)	6 mos.	Auranofin	2 mg/day 6 mg/day	14	134 139	239 (88%)	4	20	10	
Protocol AU-104	DB-R	6 mos.	Auranofin Placebo	6 mg/day	14	168 158	140 (83%) 142 (90%)	3 4	13 5	12 7	
Protocol 22LA	DB-R (Open - 6 mos.)	6 mos.	Auranofin Placebo	6 mg/day	5	52 53	41 (79%) 39 (74%)	2 8	4 0	5 6	46 placebo patients were placed on auranofin after DB phase.
Protocol 30	DB-R	24 wks.	Auranofin Auranofin Placebo	0.6 mg/day 6 mg/day	17	90 87 90	72 (80%) 71 (82%) 73 (81%)	7 5 11	5 7 1	6 4 5	
Protocol AU-101	DB-R	1 yr.	Auranofin Penicillamine	6 mg/day 250 mg- 750 mg/day	1	42 42	25 (60%) 29 (69%)	7 1	5 10	5 2	
Protocol AU-102	DB-R	1 yr.	Auranofin Penicillamine	6 mg/day 250 mg- 750 mg/day	1	70 58	50 (71%) 28 (48%)	8 5	9 23	3 2	

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
U.S. Clinical Trials (cont'd)											
Protocol A-28	DB-R	24 wks.	Auranofin	6 mg/day (once daily vs b.i.d.)	23	355	305 (86%)	13	23	14	Of the 355 pts., 227 were on placebo and 128 were on auranofin in a previous protocol.
Protocol 21	DB-R	6 mos.	Auranofin	6 mg/day	1	8	6 (75%)	0	1	1	
			OGT	30 mg/wk		8	6 (75%)	0	2	0	
Protocol 18	DB-R	6 mos.	Auranofin	6 mg/day	1	8	7 (88%)	0	0	1	
			Placebo			8	8 (100%)	0	0	0	
Protocol 20X	Open	1 yr.	Auranofin	6 mg/day	11	151	81 (54%)	34	17	19	Of the 151 pts., 59 were on auranofin, 51 were on OGT and 41 were on placebo in a previous protocol.
Protocol AU-100	Open	1 yr.	Auranofin	6 mg/day	51	553	354 (64%)	50	92	57	
Protocol AU-103	Open	1 yr.	Auranofin	6 mg/day	3	46	26 (57%)	4	6	10	
Protocols 2,3,4 & 6	Open	3 mos.	Auranofin	variable	4	13	2 (15%)	0	7	4	
Protocols 7,8,9, 9A,10,11 & 12	Open	6 mos.	Auranofin	1 mg-6 mg/day	7	101	83 (82%)	3	7	8	
Protocol AU-106	Open	Up to 2 yrs.	Auranofin	6 mg/day	14	136	88 (65%)	26	17	5	
Protocol A-98*	DB-R	6 mos.	Auranofin	3 mg-6 mg/day	16	112	96 (86%)	13	0	3	*U.S. Maintenance protocols and special studies; Patients on auranofin were entered into these studies after successful completion of a previous protocol.
Protocol A-99*	Open	Up to 6 yrs.	Auranofin	1 mg-9 mg/day	54	820	408 (68%)	140	77	115	
Protocol AU-105*	Open	Up to 2 yrs.	Auranofin	6 mg/day	68	490	328 (67%)	65	53	44	

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
Non-U.S. Clinical Trials											
AST1/1 (Champion)	DB-R	6 mos.	Auranofin	4 mg, 6 mg or 8 mg/day	1	46	35 (76%)	0	0	11	
AUSB/1,GERB/1-4 (Schattenkirchner)	DB-R	48 wks.	Auranofin OST	6 mg/day 50 mg/wk-m	5	60 62	51 (85%) 46 (45%)	0 1	6 16	3 5	13 OST patients were placed on auranofin after DB phase.
BEL02/1 (Boqueher)	DB-R	48 wks.	Auranofin Allechrysine Placebo	6 mg/day 100 mg/wk	1	20 20 4	15 (75%) 9 (45%) 2 (50%)	2 0 0	1 11 0	2 0 2	
DENA/2,3 (Jarner)	DB-R	48 wks	Auranofin OST	6 mg/day standard	2	32 30	16 (52%) 15 (50%)	1 3	11 12	4 0	
FRA/1-9 (Kahn)	DB-R	48 wks.	Auranofin Allechrysine	6 mg/day 50 mg- 100 mg/wk	7	37 36	13 (35%) 14 (39%)	2 5	17 12	5 5	
NZ02/1 (Palmer)	DB-R	6 mos.	Auranofin Placebo	6 mg/day	1	10 10	5 (50%) 5 (50%)	0 0	0 0	5 5	
SA02/1 (Botha)	DB-R	1 yr.	Auranofin Placebo	6 mg/day	1	24 12	15 (63%) 6 (50%)	1 6	5 0	3 0	
UK/04/1 (Davies)	DB-R	48 wks.	Auranofin Placebo OST	6 mg/day 50 mg/wk.	1	10 11 10	5 (50%) 3 (27%) 5 (50%)	1 7 2	3 1 3	1 0 0	Six placebo patients were placed on auranofin after DB phase.
UK07/1 (Lewis)	DB-R	48 wks.	Auranofin Placebo OST	6 mg/day 50 mg/wk	1	30 30 30	22 (73%) 1 (3%) 21 (70%)	2 27 0	5 2 9	1 0 0	Eighteen (17 placebo, 1 OST) patients were placed on auranofin after DB phase.
UK08/1 (Hughes)	DB-R	1 yr.	Auranofin OST	6 mg/day 50 mg/wk.	1 1	14 18	5 (36%) 12 (67%)	3 3	4 3	2 0	All patients were previously stabilized on OST.

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
Non-U.S. Clinical Trials (Cont'd)											
UK09/1 (Berry/ Panagi)	DB-R	48 wks.	Auranofin GST	6 mg/day 50 mg/wk-m	2	19 19	8 (42%) 16 (84%)	6 0	2 1	3 2	All patients were previously stabilized on GST.
UK09/2 (Panagi)	DB-R	1 yr.	Auranofin Placebo	6 mg/day	1	24 15	11 (42%) 0	9 12	5 2	1 1	
UK11/1 (Mathews)	DB-R	48 wks.	Auranofin Placebo GST	6 mg/day 50 mg/wk-m	1	17 16 17	7 (41%) 7 (43%) 7 (41%)	3 7 2	5 0 7	2 2 1	Four placebo patients were placed on auranofin after DB phase.
UK12/1 (Moran)	DB-R	1 yr.	Auranofin GST	6 mg/day 50 mg/wk-m	1	21 20	7 (33%) 14 (70%)	4 1	10 1	0 4	All patients were previously stabilized on GST.
UK13/1 (Bird/ Wright)	DB-R	48 wks	Auranofin Hydroxychloroquine	6 mg/day 400 mg/day	1	20 20	10 (50%) 13 (65%)	2 3	7 3	1 1	
UK15/1 (Roberts/ Buchanan)	DB-R	48 wks	Auranofin Placebo GST	6 mg/day 50 mg/wk-m	1	13 12 14	8 (62%) 4 (33%) 9 (64%)	2 6 1	2 2 5	1 0 0	Four (3 placebo, 1 GST) patients were placed on auranofin after DB phase.
AST2/1 (Barraclough)	SB-R	1 yr.	Auranofin GST Penicillamine	6 mg/day 50 mg/wk. 125 mg- 1500 mg/day	1	15 12 15	12 (80%) 4 (33%) 10 (67%)	0 0 0	0 0 5	3 8 5	
BEN01/1 (Manthorpe)	SB-R	1 yr.	Auranofin Penicillamine	6 mg/day 125 mg- 750 mg/day	1	23 24	15 (65%) 16 (67%)	1 2	5 6	2 0	
HOL02/1 (VanRiel)	SB-R	1 yr.	Auranofin GST	6 mg/day 50 mg/wk-m	1	24 26	11 (42%) 11 (42%)	12 2	3 12	0 1	
UK06/1 (F[illegible] Davies)	SB-R	48 wks.	Auranofin Penicillamine	6 mg/day 500 mg/day	1	19 24	15 (79%) 16 (67%)	0 0	3 7	1 1	

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
Non-U.S. Clinical Trials (Cont'd)											
UK10/1 (Muki)	SB-R	1 yr.	Auranofin Hydroxychloroquine	6 mg/day 400 mg/day	1	20 19	12 (60%) 8 (42%)	4 2	3 4	1 5	
ARAC (Menard)	Open-R	48 wks.	Auranofin GST	6 mg/day 50 mg/wk.	3	44 42	28 (37%) 35 (57%)	11 5	0 14	7 6	
BELG2/1 (Franchimont)	Open-R	1 yr.	Auranofin Penicillamine	6 mg/day 500 mg/day	1	24 26	18 (47%) 13 (25%)	1 6	2 5	3 2	
DENM/1 (Tvede)	Open-R	48 wks.	Auranofin GST	6 mg/day 50 mg/wk	1	13 15	10 (47%) 8 (53%)	2 1	1 5	2 1	
FIN02/1 (Hissila)	Open-R	48 wks.	Auranofin GST	6 mg/day 50 mg/wk-m	1	30 29	23 (90%) 20 (69%)	1 0	5 8	0 1	
IT061 (Marcolongo)	Open-R	1 yr.	Auranofin Levamisole	6 mg/day 150 mg/wk.	1	20 20	20 (100%) 5 (25%)	0 0	0 0	0 15	
ITA (1-7)	Open-R	1 yr.	Auranofin Penicillamine	6 mg/day 150 mg - 600 mg/day	7	73 54	53 (63%) 25 (46%)	7 4	14 17	4 8	
NOR1/1	Open-R	up to 2 yrs.	Auranofin GST	6 mg/day 50 mg/wk	1	5 5	5 (100%) 3 (60%)	0 0	0 1	0 1	
SW01/2 (Smith)	Open-R	6-24 mos.	Auranofin GST	6 mg/day standard	1	30 30	26 (87%) 15 (50%)	1 1	1 9	2 5	
SWE02/2 (Hafstrom)	Open-R	1 yr.	Auranofin GST	6 mg/day 50 mg/wk-m	1	7 7	5 (71%) 1 (14%)	1 1	1 5	0 0	
UK02/1 (Prouse)	Open-R	1 yr.	Auranofin Placebo GST	6 mg/wk. 50 mg/wk.	1	11 10 10	4 (36%) 0 (0%) 3 (30%)	2 10 1	3 0 5	2 0 1	Nine patients (6 placebo, 3 GST) were placed on auranofin after the evaluation period.

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
Non-U.S. Clinical Trials (Cont'd)											
UK85/1 (Keegan)	Open-R	48 wks.	Auranofin GST	6 mg/day 30 mg/wk-m	1	25 25	20 (80%) 16 (64%)	0 0	3 4	2 5	
AST1/2 (Champion)	Open	up to 5 yrs.	Auranofin	6 mg/day	1	16	3 (19%)	0	0	13	
AU882/1	Open	up to 3 yrs.	Auranofin	6 mg/day	1	8	2 (25%)	0	3	3	
FIN81/1	Open	up to 2 yrs.	Auranofin	6 mg/day	1	5	2 (40%)	1	2	0	
FIN82/2 Nissila	Open	up to 2 yrs.	Auranofin	6 mg/day	1	37	27 (73%)	5	5	0	
FRB/1-9	Open	up to 4 yrs.	Auranofin	6 mg/day	10	113	33 (29%)	23	34	23	
IT81/1 (Carese)	Open	up to 4 yrs.	Auranofin	6 mg/day	1	33	20 (61%)	7	1	5	
IT82/1 (Pasero)	Open	up to 3 yrs.	Auranofin	6 mg/day	1	9	1 (11%)	1	5	2	
IT83/1 (Colombo)	Open	up to 3 yrs.	Auranofin	6 mg/day	1	10	4 (40%)	1	2	3	
IT851 (Portioli)	Open	up to 3 yrs.	Auranofin	3 mg/day 6 mg/day	1	13	8 (62%)	2	3	0	
IT871 (Lippi/ Mathieu)	Open	up to 3 yrs.	Auranofin	6 mg/day	1	32	26 (81%)	0	3	3	

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Completed^	Dropouts LE	Dropouts AR	Dropouts Other	Notes
Non-U.S. Clinical Trials (Cont'd)											
KOR1/1 (Moon)	Open	1 yr.	Auranofin OGT	6 mg/day 20 mg - 50 mg/wk.	1	15 9	10 (67%) 6 (67%)	0 0	0 0	5 3	
MCT-86	Open	up to 4 yrs.	Auranofin	6 mg/day	75	766	400 (52%)	100	139	127	
MUA	Open	up to 5 yrs.	Auranofin	6 mg/day	10	156	51 (33%)	32	30	43	
PHI1/1 (Amante)	Open	up to 3 yrs.	Auranofin	4 mg/day 6 mg/day	1	48	23 (48%)	0	0	25	
SN03/1 (Schorn)	Open	up to 5 yrs.	Auranofin	6 mg/day	1	31	13 (42%)	7	3	8	
SPAA 1-2 (Vallado/ Beltran)	Open	up to 4 yrs.	Auranofin	6 mg/day	2	17	4 (24%)	2	5	6	
SPAB 1-2 (Raig, Gijon, Larrea)	Open	up to 4 yrs.	Auranofin	6 mg/day	3	33	22 (67%)	2	8	1	
SU101/1	Open	3 mos.	Auranofin	3 mg, 6 mg or 9 mg/day	1	4	0 (0%)	0	0	4	
SWE02/1	Open	up to 2 yrs.	Auranofin	6 mg/day	1	18	9 (50%)	5	4	0	
SWE03/1	Open	up to 2 yrs.	Auranofin OGT	6 mg/day 20 mg - 50 mg/wk-bimonthly	1	9 8	4 (44%) 2 (25%)	0 1	5 4	0 1	
SWE05/1 (Szanto)	Open	1 yr.	Auranofin	6 mg/day	1	8	3 (38%)	5	0	0	

^For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

Table 6 (continued)

Summary of Patient Experience in Clinical Trials of Auranofin

Study/Investigator	Design	Duration	Drugs	Doses	No. Centers	No. Pts. Entered	No. Pts. (%) Complete*	Dropouts LE	AR	Other	Notes
Non-U.S. Clinical Trials (Cont'd)											
SWEA1	Open	up to 3 yrs.	Auranofin	6 mg/day	1	20	10 (50%)	2	6	2	
SWEA3	Open	up to 2 yrs.	Auranofin	6 mg/day	1	5	1 (20%)	0	4	0	
UK91/1 (Huskisson)	Open	18 mos.	Auranofin Penicillamine	6 mg/day 500 mg/day	1	12 12	3 (25%) 9 (75%)	6 1	0 2	1 0	
UK93/1 (Holt)	Open	up to 4 yrs.	Auranofin	4 mg-8 mg/day	1	31	6 (19%)	5	18	2	

*For pts. in long-term maintenance protocols, defined as no. of pts. still on study or were on-going at termination of the study.

Abbreviations
DB-R - double-blind, randomized
SB-R - single-blind, randomized (evaluator was blinded)
LE - lack of therapeutic effect
AR - adverse reaction
Other - intercurrent illness or administrative

P' '20

PRESCRIBING INFORMATION

RI:L20

Ridaura®

brand of **auranofin**

Capsules

Ridaura (auranofin, SK&F) contains gold and, like other gold-containing drugs, can cause gold toxicity, signs of which include: fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work (See PRECAUTIONS) 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:

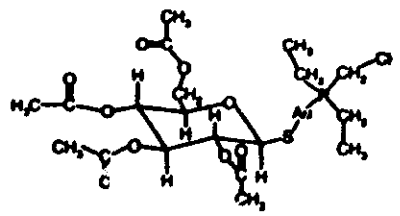
1. The possibility of adverse reactions should be explained to patients before starting therapy.

2. Patients should be advised to report promptly any symptoms suggesting toxicity (See PRECAUTIONS – Information for Patients.)

DESCRIPTION

Ridaura (auranofin, SK&F) is (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S-) (triethylphosphine) gold and is available in oral form as capsules containing 3 mg. auranofin.

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



1

CLINICAL PHARMACOLOGY

The mechanism of action of Ridaura (auranofin, SK&F) 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-containing compounds induce remission of rheumatoid arthritis.

Pharmacokinetics: Pharmacokinetic studies were performed in rheumatoid arthritis patients, not in normal volunteers. Auranofin is rapidly metabolized and intact auranofin has never been detected in the blood. Thus, studies of the pharmacokinetics of auranofin have involved measurement of gold concentrations. Approximately 25% of the gold in auranofin is absorbed.

The mean terminal plasma half-life of auranofin gold at steady state was 26 days (range 21 to 31 days, n=5). The mean terminal body half-life was 80 days (range 42 to 128; n=5). Approximately 60% of the absorbed gold (15% of the administered dose) from a single dose of auranofin is excreted in urine; the remainder is excreted in the feces.

In clinical studies, steady state blood-gold concentrations are achieved in about three months. In patients on 6 mg. auranofin/day, mean steady state blood-gold concentrations were 0.68 ± 0.45 mcg./ml. (n=63 patients). In blood, approximately 40% of auranofin gold is associated with red cells, and 60% associated with serum proteins. In contrast, 99% of injectable gold is associated with serum proteins.

Mean blood-gold concentrations are proportional to dose; however, no correlation between blood-gold concentrations and safety or efficacy has been established.

INDICATIONS AND USAGE

Ridaura (auranofin, SK&F) is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs. 'Ridaura' should be added to a comprehensive baseline program, including non-drug therapies.

Unlike anti-inflammatory drugs, 'Ridaura' does not produce an immediate response. Therapeutic effects may be seen after three to four months of treatment, although improvement has not been seen in some patients before six months.

When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.

2

In controlled clinical trials comparing 'Ridaura' with injectable gold, 'Ridaura' was associated with fewer dropouts due to adverse reactions, while injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of 'Ridaura' in patients who are candidates for chrysotherapy.

CONTRAINDICATIONS

Ridaura (auranofin, SK&F) is contraindicated in patients with a history of any of the following gold-induced disorders: necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe hematologic disorders.

WARNINGS

Danger signs of possible gold toxicity include fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea.

Thrombocytopenia has occurred in 1-3% of patients (See ADVERSE REACTIONS) treated with Ridaura (auranofin, SK&F), some of whom developed bleeding. The thrombocytopenia usually 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 and its course may be rapid. While patients' platelet counts should normally be monitored at least monthly (See PRECAUTIONS – Laboratory Tests), the occurrence of a precipitous decline in platelets or a platelet count less than 100,000/cu mm or signs and symptoms (e.g., purpura, ecchymoses or petechiae) suggestive of thrombocytopenia indicates a need to immediately withdraw 'Ridaura' and 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 has developed in 3-9% of patients (See ADVERSE REACTIONS) treated with 'Ridaura'. If clinically significant proteinuria or microscopic hematuria is found (See PRECAUTIONS – Laboratory Tests), 'Ridaura' and other therapies with the potential to cause proteinuria or microscopic hematuria should be stopped immediately.

PRECAUTIONS

General: The safety of concomitant use of Ridaura (auranofin, SK&F) with injectable gold, hydroxychloroquine, penicillamine, immunosuppressive agents (e.g., cyclophosphamide, azathioprine, or methotrexate) or high doses of corticosteroids has not been established.

3

Medical problems that might affect the signs or symptoms used to detect 'Ridaura' toxicity should be under control before starting Ridaura (auranofin, SK&F).

The potential benefits of using 'Ridaura' in patients with progressive renal disease, significant hepatocellular disease, 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: 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 50% of the patients. This is generally manageable by reducing the dosage (e.g., from 6 mg. daily to 3 mg.) and in only 6% of the patients is it 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.

Cutaneous Reactions: Dermatitis is the most common reaction to injectable 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 or an actinic rash may develop. The most serious form of cutaneous reaction reported with injectable gold is generalized exfoliative dermatitis.

Mucous Membrane Reactions: 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.

4

Renal Reactions: Gold 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 urinalyses regularly* and to discontinue treatment promptly if proteinuria or hematuria develops.

Hematologic Reactions: 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 anytime 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; gold bronchitis and interstitial pneumonitis and fibrosis; peripheral neuropathy; partial or complete hair loss; fever.

Information for 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 PRECAUTIONS – Pregnancy).

Laboratory Tests: CBC with differential, platelet count, urinalysis, and renal and liver function tests should be performed prior to Ridaura (auranofin, SK&F) 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.

5

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) developed tumors of the renal tubular epithelium, whereas those treated with 3.6 mg./kg./day (30 times the human dose) did not.

In an 18-month study in mice given oral auranofin at doses of 1, 3 and 9 mg./kg./day (8, 24 and 72 times the human dose), there was no statistically significant increase above controls in the instances of tumors.

In the mouse lymphoma forward mutation assay, auranofin at high concentrations (313 to 700 ng./ml.) induced increases in the mutation frequencies in the presence of a rat liver microsomal preparation. 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.

Pregnancy: Teratogenic Effects – Pregnancy Category C. Use of Ridaura (auranofin, SK&F) by pregnant women is not recommended. Furthermore, women of childbearing potential should be warned of the potential risks of 'Ridaura' therapy during pregnancy (see below).

Pregnant rabbits given auranofin at doses of 0.5, 3 or 6 mg./kg./day (4.2 to 50 times the human dose) had impaired food intake, decreased maternal weights, decreased fetal weights and an increase above controls in the incidence of resorptions, abortions and congenital abnormalities, mainly abdominal defects such as gastroschisis and umbilical hernia.

Pregnant rats given auranofin at a dose of 5 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 and mice, 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, SK&F) is not recommended for use in children because its safety and effectiveness have not been established.

ADVERSE REACTIONS

The adverse reactions incidences listed below are based on observations of 4,784 'Ridaura'-treated patients (2,474 U.S., 2,310 foreign), of whom 2,729 were treated more than one year and 573 for more than three years. 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 (47%), 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 3.9% of the patients. The other reactions listed occurred in 1.3%.

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: neutropenia†; agranulocytosis.

Hepatic: jaundice.

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

Respiratory: interstitial pneumonitis.

Neurological: peripheral neuropathy.

Reactions reported with injectable gold preparations, but not with Ridaura (auranofin, SK&F) (based on 4,784 patients in clinical trials and on postmarketing experience)

Cutaneous Reactions: generalized exfoliative dermatitis.

Hematologic Reactions: pancytopenia, aplastic anemia.

Nitritoid, Anaphylactoid and Anaphylactic Reactions: Reactions of the "nitritoid type" which may resemble anaphylactic reactions.

Incidence of Adverse Reactions for Specific Categories – 18 Comparative Trials

	Ridaura (445 patients)	Injectable Gold (445 patients)
Proteinuria	0.9%	5.4%
Rash	25%	39%
Diarrhea	47.5%	13%
Stomatitis	13%	18%
Anemia	3.1%	2.7%
Leukopenia	1.3%	2.7%
Thrombocytopenia	0.9%	2.7%
Elevated liver function tests	1.9%	1.7%
Pulmonary	0.2%	0.7%

OVERDOSAGE

The acute oral LD_{50} for auranofin is 310 mg./kg. in adult mice and 265 mg./kg. in adult rats. The minimum lethal dose in rats is 30 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 6 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.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage: The usual adult dosage of Ridaura (auranofin, SK&F) 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. If response 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 on injectable gold have been transferred to 'Ridaura' 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 PRECAUTIONS – Information for Patients.) At six months, control of disease activity of patients transferred to Ridaura and those maintained on the injectable agent was not different. Data beyond six months are not available.

HOW SUPPLIED

Ridaura (auranofin, SK&F) is supplied as tan and brown opaque capsules containing 3 mg. auranofin, in bottles of 60.

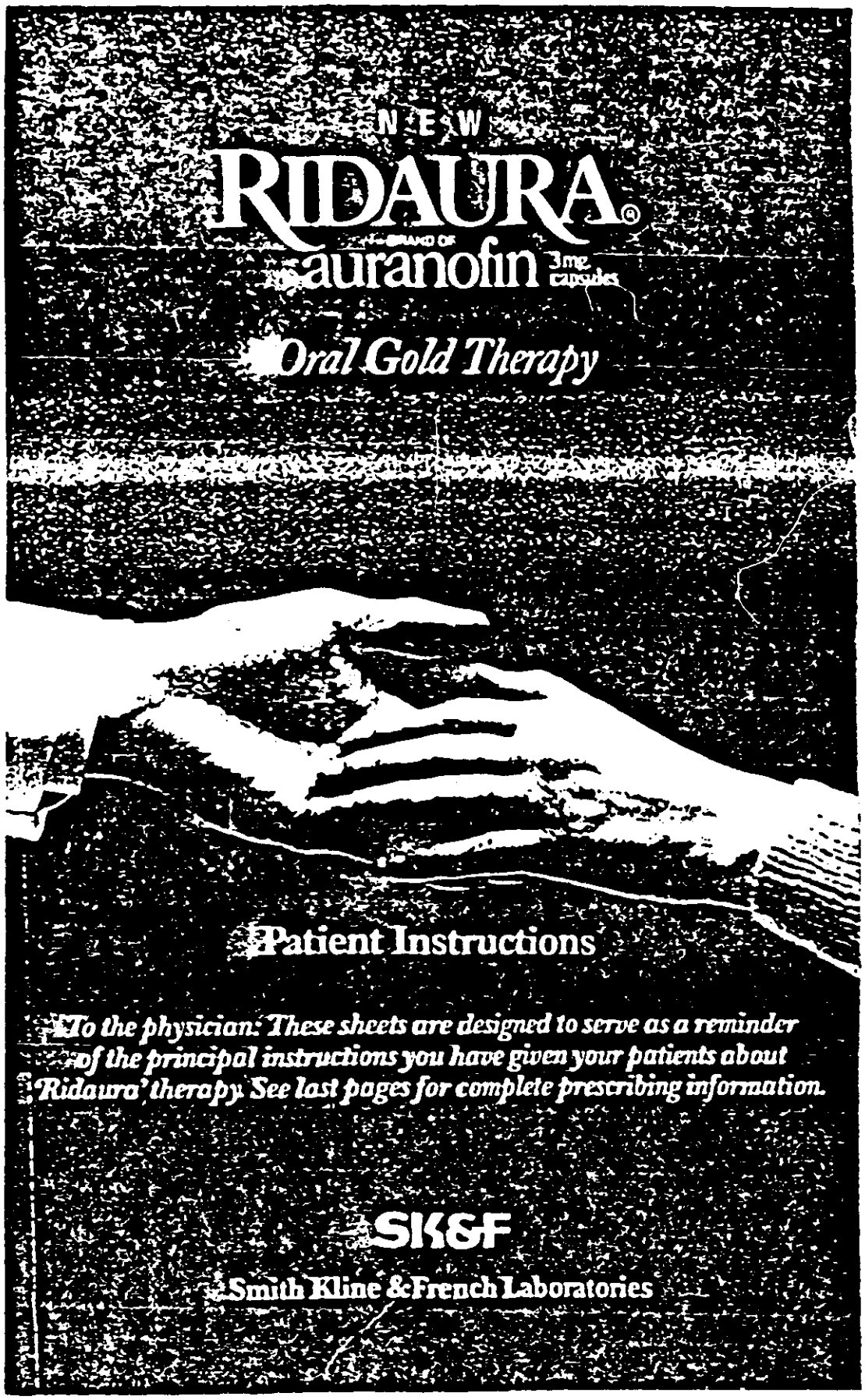
STORAGE AND HANDLING

Store at controlled room temperature.

DATE OF ISSUANCE MAY 1985

SmithKline & French Laboratories
Division of
SmithKline Beckman Corporation
Philadelphia, PA 19101

RI L 20 Printed in U.S.



Complete Prescribing Information will be included with this piece.

3

Important Instructions About Your Prescription

1. I have given you a prescription for 'Ridaura'. This medication contains gold and is only for the treatment of rheumatoid arthritis in adults.

2. It may be three to six months or longer before you begin to feel the effects of 'Ridaura'. It's very important that you take 'Ridaura' every day, just the way I told you, to give it time to help you. Don't take more or less 'Ridaura' than I asked you to, and don't skip doses.*

3. You should continue to take any other medication I have prescribed for you.

4. As I have discussed with you, this medication can cause serious problems. To help me detect as early as possible any problems due to your medications, you must have blood and urine tests regularly, at least monthly.

5. If you experience any unusual bruising or unusual or prolonged bleeding, for example, bleeding gums, let me know immediately.

6. Some people on 'Ridaura' experience changes in bowel habits, such as more frequent, soft, or loose stools, and occasionally diarrhea, that usually disappear after a few days. If you get diarrhea that lasts for more than three or four days, or diarrhea that interferes with your normal daily routine, get in touch with me promptly.

7. Also, some people taking 'Ridaura' develop a rash, itchiness, or mouth sores. These conditions usually don't require stopping the drug, but they could be early warning signs of more serious problems. If these or any other unusual things occur, I want you to let me know right away.

8. A reminder to my female patients: Do not become pregnant while on this medication. If you want to become pregnant or think you are pregnant, let me know so we can review all the medication you're taking and make any necessary changes.

9. Keep this and all other medicine out of the reach of children.

*See other side.

3

Next Appointment: _____

Instructions: _____

_____

_____

_____

_____

Help yourself remember when you've taken your medication: each time you take 'Ridaura', put a check mark in the appropriate box.

	WEEK #1		WEEK #2		WEEK #3		WEEK #4	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Sun.								
Mon.								
Tues.								
Wed.								
Thurs.								
Fri.								
Sat.								

Approval

Letter +

FPL

NDA 18-689

MAY 24 1985

Smith Kline and French Laboratories
1500 Spring Garden Street
P.O. Box 7929
Philadelphia, Pennsylvania 19101

Attention: Bruce A. Wallin, M.D.
Director
Rheumatology/Immunology Group
Regulatory Affairs

Dear Dr. Wallin:

Please refer to your new drug application (NDA) dated September 30, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Ridaura (auranofin) capsules.

We also refer to your communications of April 22, 1982; April 13 and October 12, 1983 and May 14, 1985; our letters of May 10, 1982; February 28 and November 18, 1983; and numerous other submissions and meetings.

This application was filed on May 15, 1985.

We have completed our review of your application and have concluded the drug product is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

This approval is, however, contingent upon the following Phase IV commitments which were made in your letter of May 14, 1985:

CLINICAL

The additional clinical requirements may be met by studies already underway or by new studies yet to be done. If there are unresolved differences of opinion about the results of studies or the design of protocols, such differences will be presented to the Arthritis Advisory Committee.

1. Additional studies of patients successfully treated with injectable gold then switched to auranofin are needed to show that there is no long-term difference in effectiveness between auranofin and injectable gold. These should be of at least 1 year duration and involve sufficient patients to detect a 25% or greater reduction in efficacy using a one-sided test with alpha =.05 (q of .75).

2. A study is needed of unsuccessfully treated auranofin patients due to lack of efficacy to determine if lack of response at six months represents a slow response to auranofin, an auranofin failure, or a gold therapy failure.

3. A study is needed in which some patients unsuccessfully treated with injectable gold because of adverse reactions are switched to auranofin. We agree that it would be more ethical and efficient if this were an unblinded pilot study rather than a controlled clinical trial. The goal would be to see whether significant adverse reactions occur in such patients so that appropriate warnings or precautions should be added to the labeling. If it appears that auranofin is well-tolerated in such patients, and therefore might be specifically indicated in them, then a more formal study will be performed.

4. Pilot studies will be conducted to ascertain if combination therapy with injectable gold and auranofin poses special risks or provides special benefits such as faster onset of activity. If it appears that there are special benefits with this treatment, then more formal studies will be performed.

5. A registry will be established by SKF to follow children exposed to auranofin in utero during IND studies. Followup will be at two years and then at five year intervals indefinitely or until terminated by mutual agreement by SKF and FDA.

PHARMACOLOGY

1. SKF will submit the final report of the seven-year dog study in October 1985. Myochrysine treated dogs are still under treatment and due to be sacrificed in August 1985. The tissue examinations on these latter dogs will be submitted in May 1986.

2. SKF will submit the histopathological and statistical analyses of mid-dose and low-dose mouse liver and thymus tissues. If these analyses suggest tumorigenicity in the mouse, the mouse study will be repeated with a positive control, using a mutually agreed upon protocol.

BIOPHARMACEUTICS

1. SKF will address the remaining 12 biopharmaceutics concerns conveyed at the meeting of March 4, 1985 and will make subsequent labeling revisions which FDA feels are appropriate.

We note that copies of the introductory promotional material for this product have been received by both the Acting Director, Division of Oncology and Radiopharmaceutical Drug Products (HFN-150) and the Director, Division of Drug Advertising and Labeling (HFN-240).

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc: FBI-DO
ORIG. NDA 18-688
HFM-150/DIV. FILE
HFM-83
HFM-100
HFM-20
HFM-140/EPappas
HFM-150/EJohnson
HFM-150/CChen
HFM-150/DWPease/4-18-85
R/D dwp 4/18/85 DRAFT #1 init. by EPappas 5/9/85
JLeak 5/9/85
rev. dwp 5/9/85 DRAFT #2 init. by EGScully 5/9/85
rev. dwp 5/14/85 DRAFT #3 revised by JGHarter 5/15/85
rev. dwp 5/15/85 DRAFT #4 revised by JGHarter/meeting
rev. dwp 5/15/85 DRAFT #5 init. by JGHarter 5/15/85
EJohnson 5/15/85
CChen 5/15/85
DJRichman 5/15/85
RAJerussi/5/15/85

F/T by P. Amoss/5/15/85
Revised by JFPalmer/5/16/85
F/T by EBarnes/5/16/85
rev. and F/T dwp 5/23/85

Wang #08088

APPROVAL

5/23/85
D w/ comm
5/24/85
5/24/85
24-85
5/24/85

RI:

PRESCRIBING INFORMATION

RI:L20

Ridaura®

brand of **auranofin**

Capsules

Ridaura (auranofin, SK&F) contains gold and, like other gold-containing drugs, can cause gold toxicity, signs of which include fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work (See PRECAUTIONS) 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:

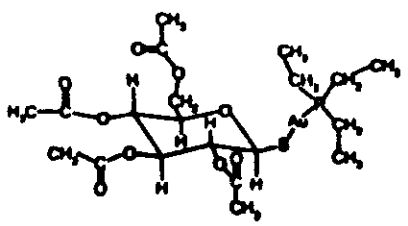
1. The possibility of adverse reactions should be explained to patients before starting therapy.

2. Patients should be advised to report promptly any symptoms suggesting toxicity (See PRECAUTIONS – Information for Patients.)

DESCRIPTION

'Ridaura' (auranofin, SK&F) is (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S-) (triethylphosphine) gold and is available in oral form as capsules containing 3 mg auranofin.

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



CLINICAL PHARMACOLOGY

The mechanism of action of 'Ridaura' (auranofin, SK&F) is not understood. In patients with adult rheumatoid arthritis, 'Ridaura' may modify disease activity as manifested by synovitis and associated symptoms, and reduce oral by laboratory parameters such as ESR. There is no substantial evidence, however, that gold containing compounds induce remission of rheumatoid arthritis.

Pharmacokinetics: Pharmacokinetic studies were performed in rheumatoid arthritis patients, not in normal volunteers. Auranofin is rapidly metabolized and intact auranofin has never been detected in the blood. Thus, studies of the pharmacokinetics of auranofin have involved measurement of gold concentrations. Approximately 25% of the gold in auranofin is absorbed.

The mean terminal plasma half-life of auranofin gold at steady state was 26 days (range 21 to 31 days, n=5). The mean terminal body half-life was 80 days (range 42 to 128, n=5). Approximately 60% of the absorbed gold (15% of the administered dose) from a single dose of auranofin is excreted in urine, the remainder is excreted in the feces.

In clinical studies, steady state blood-gold concentrations are achieved in about three months. In patients on 6 mg auranofin/day, mean steady state blood-gold concentrations were 0.68 ± 0.45 mcg /ml (n=63 patients). In blood, approximately 40% of auranofin gold is associated with red cells, and 60% associated with serum proteins. In contrast, 99% of injectable gold is associated with serum proteins.

Mean blood gold concentrations are proportional to dose, however, no correlation between blood gold concentrations and safety or efficacy has been established.

INDICATIONS AND USAGE

'Ridaura' (auranofin, SK&F) is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs. 'Ridaura' should be added to a comprehensive baseline program, including non-drug therapies.

Unlike anti-inflammatory drugs, 'Ridaura' does not produce an immediate response. Therapeutic effects may be seen after three to four months of treatment, although improvement has not been seen in some patients before six months.

When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.

In controlled clinical trials comparing 'Ridaura' with injectable gold, 'Ridaura' was associated with fewer dropouts due to adverse reactions, while injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of 'Ridaura' in patients who are candidates for chrysotherapy.

CONTRAINDICATIONS

'Ridaura' (auranofin, SK&F) is contraindicated in patients with a history of any of the following gold-induced disorders: necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe hematologic disorders.

WARNINGS

Danger signs of possible gold toxicity include fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea.

Thrombocytopenia has occurred in 1-3% of patients (See ADVERSE REACTIONS) treated with 'Ridaura', some of whom developed bleeding. The thrombocytopenia usually 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 and its course may be rapid. While patients' platelet counts should normally be monitored at least monthly (See PRECAUTIONS – Laboratory Tests), the occurrence of a precipitous decline in platelets or a platelet count less than 100,000/cu mm or signs and symptoms (e.g., purpura, ecchymoses or petechiae) suggestive of thrombocytopenia indicates a need to immediately withdraw 'Ridaura' and 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 has developed in 3-9% of patients (See ADVERSE REACTIONS) treated with 'Ridaura'. If clinically significant proteinuria or microscopic hematuria is found (See PRECAUTIONS – Laboratory Tests), 'Ridaura' and other therapies with the potential to cause proteinuria or microscopic hematuria **should be stopped immediately.**

PRECAUTIONS

General: The safety of concomitant use of 'Ridaura' (auranofin, SK&F) with injectable gold, hydroxychloroquine, penicillamine, immunosuppressive agents (e.g., cyclophosphamide, azathioprine, or methotrexate) or high doses of corticosteroids has not been established.

Medical problems that might affect the signs or symptoms used to detect 'Ridaura' toxicity should be under control before starting 'Ridaura' (auranofin, SK&F).

The potential benefits of using 'Ridaura' in patients with progressive renal disease, significant hepatocellular disease, 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: 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 50% of the patients. This is generally manageable by reducing the dosage (e.g., from 6 mg. daily to 3 mg.) and in only 6% of the patients is it 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.

Cutaneous Reactions: Dermatitis is the most common reaction to injectable 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 or an actinic rash may develop. The most serious form of cutaneous reaction reported with injectable gold is generalized exfoliative dermatitis.

Mucous Membrane Reactions: 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.

Renal Reactions: Gold 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 urinalyses regularly* and to discontinue treatment promptly if proteinuria or hematuria develops.

Hematologic Reactions: 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 anytime 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; gold bronchitis and interstitial pneumonitis and fibrosis; peripheral neuropathy; partial or complete hair loss; fever.

Information for 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 PRECAUTIONS – Pregnancy).

Laboratory Tests: CBC with differential, platelet count, urinalysis, and renal and liver function tests should be performed prior to Ridaura (auranofin, SK&F) 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) developed tumors of the renal tubular epithelium, whereas those treated with 3.6 mg / kg /day (30 times the human dose) did not.

In an 18 month study in mice given oral auranofin at doses of 1, 3 and 9 mg /kg /day (8, 24 and 72 times the human dose), there was no statistically significant increase above controls in the instances of tumors.

In the mouse lymphoma forward mutation assay, auranofin at high concentrations (313 to 700 ng /ml) induced increases in the mutation frequencies in the presence of a rat liver microsomal preparation. 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/3 cell mouse assay or in the Dominant Lethal Assay.

Pregnancy: Teratogenic Effects - Pregnancy Category C. Use of Ridaura (auranofin SK&F) by pregnant women is not recommended. Furthermore, women of childbearing potential should be warned of the potential risks of Ridaura therapy during pregnancy. (See below.)

Pregnant rabbits given auranofin at doses of 0.5, 3 or 6 mg /kg /day (4.2 to 50 times the human dose) had impaired food intake, decreased maternal weights, decreased fetal weights and an increase above controls in the incidence of resorptions, abortions and congenital abnormalities, mainly abdominal defects such as gastroschisis and umbilical hernia.

Pregnant rats given auranofin at a dose of 5 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 and mice, 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, SK&F) is not recommended for use in children because its safety and effectiveness have not been established.

ADVERSE REACTIONS

The adverse reactions and clinical laboratory abnormalities listed below are based on observations of 4,784 Ridaura-treated patients (2,474 U.S., 2,310 foreign), of whom 2,729 were treated more than one year and 573 for more than three years. 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 (47%), 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.

*These items, marked with an asterisk, occurred in 1-3% of the patients. The other reactions listed occurred in 1-3%.

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

Gastrointestinal: dysphagia, gastrointestinal bleeding†, melena†, positive stool for occult blood†, ulcerative colitis, colitis.

Dermatological: angioedema.

Mucous Membrane: gingivitis†.

Hematological: neutropenia†, agranulocytosis†.

Hepatic: jaundice.

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

Respiratory: interstitial pneumonitis.

Neurological: peripheral neuropathy.

Reactions reported with injectable gold preparations, but not with Ridaura (auranofin, SK&F) (based on 4,784 patients in clinical trials and on postmarketing experience)

Cutaneous Reactions: generalized exfoliative dermatitis.

Hematologic Reactions: pancytopenia, aplastic anemia.

Nitritoid, Anaphylactoid and Anaphylactic Reactions: Reactions of the "nitritoid type" which may resemble anaphylactic reactions.

Incidence of Adverse Reactions for Specific Categories— 18 Comparative Trials

	Ridaura (447 patients)	Injectable Gold (445 patients)
Proteinuria	8.9%	5.4%
Rash	26%	39%
Diarrhea	42.5%	13%
Stomatitis	13%	18%
Anemia	3.1%	7.7%
Leukopenia	1.3%	7.7%
Thrombocytopenia	0.9%	2.2%
Elevated liver function tests	1.9%	1.7%
Pulmonary	0.7%	0.7%

OVERDOSAGE

The acute oral LD_{50} for auranofin is 310 mg /kg in adult mice and 265 mg /kg in adult rats. The minimum lethal dose in rats is 30 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 6 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.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage: The usual adult dosage of Ridaura (auranofin, SK&F) 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. If response 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 on myochrysine gold have been transferred to Ridaura 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 PRECAUTIONS - Information for Patients.) At six months, control of disease activity of patients transferred to Ridaura and those maintained on the injectable agent was not different. Data beyond six months are not available.

HOW SUPPLIED

Ridaura (auranofin, SK&F) is supplied as tan and brown opaque capsules containing 3 mg auranofin, in bottles of 60.

STORAGE AND HANDLING

Store at controlled room temperature.

DATE OF ISSUANCE MAY 1985

Smith Kline & French Laboratories
Division of
SmithKline Beckman Corporation
Philadelphia, PA 19101

RI L20 Printed in U

Pharm.

NDA 18-689
Div. File

MAY 24 1985

REVIEW AND EVALUATION OF PHARMACOLOGY

AND TOXICOLOGY DATA

Date of submission 8/3/83 & 2/8/83

Date of review April 12, 1985

NDA: 18-689

SPONSOR: Smith, Kline & French Laboratories
Philadelphia, PA 19101

DRUG: Ridaura (auranofin)

CATEGORY: Non-steroidal gold containing agent for treatment of rheumatoid arthritis.

CHEMICAL NAME: (2,3,4,6-tetra-O-acetyl-1-thio-B-D gluco-pyranosato-S-)(triethylphosphine)gold

OTHER NAME: SKF D-39162

RELATED TO:

BACKGROUND: NDA 18-689 was originally reviewed by Dr. A M. Guarino on March 22, 1982 (stamped April 12, 1982). Subsequently, Dr. Guarino wrote another review on July 8 1982 to an NDA amendment dated June 22, 1982. Dr. Guarino felt that the sponsor has adequately defined the expected toxicities for this drug and it has the basic pharmacodynamic activities for the therapeutic indication intended. He also stated that in addressing the potential carcinogenicity of this drug "the sponsor appears willing to concede that it causes renal tumors in rats and attributes this to a species specific effect".

Dr. Guarino thought NDA 18-689 is approvable if the package insert adequately addresses: 1). the potential for chronic renal toxicity, 2). the potential carcinogenicity (renal adenoma) suggested from rodent positive bioassay results, and 3). bioavailability and metabolism studies which adequately identify major metabolites of this drug. He also pointed out in his original review that the possible effects of auranofin on drug metabolizing enzymes and the possible interactions of auranofin with a number of commonly used drugs should also be addressed in the labeling.

PRECLINICAL STUDY:

In this supplement to NDA dated August 1, 1983 (stamped August 3, 1983), the sponsor submitted the reports of the two-year chronic toxicity study on SK&F D-39162 in rats and the 18-month chronic toxicity study on SK&F D-39162 in mice.

In the cover letter to this submission, the sponsor stated that on July 23, 1983, the Committee on the Safety of Medicine (CSM) in the United Kingdom informed SK&F that during their ongoing review of Ridaura submission they have concerns regarding the results of the rodent studies. The sponsor stated that SK&F will be meeting with the CSM on this in the near future in order to resolve those problems raised by CSM.

1. Two-year chronic toxicity study in rats, conducted at

   from October 1, 1979 to October 6, 1981.

   75/sex/group Charles River CD rats, dose: SK&F D-39162 at 0.4, 1.0, or 2.5 mg/Kg/day by oral intubation, Myochrisine at 2, or 6 mg/Kg/2x/week by intramuscular injection. Two other groups were given vehicle orally (0.5% tragacanth) to serve as controls. Salivation was considered as auranofin-related effect. No drug effect on mortality was observed up to 17th or 18th month. During 18th month and thereafter, mortality was higher in the auranofin treated groups. The mortality rate in the male was: combined control 48.0%; auranofin 42.7%, 45.3% 37.3%; and myochrysine 41.3%, 46.7%. The mortality rate in the female was: combined control 42.7%; auranofin 58.7%, 49.3% 57.3%; myochrysine 32.0% 44.0%.

   At several time points, the body weights of high-dose auranofin and high-dose myochrisine groups were lower than controls. The food consumptions were not significantly different among the groups.

   Most organs from the the following animals were examined microscopically: 1). all rats found dead or killed in extremis, 2). all rats in group I, II and V killed terminally, 3). 20 males and 20 females in group VII. In addition, both kidneys from rats in group III, IV, and VII killed terminally, the thyroid gland and the testes/epididymis of all rats were also examined histologically.

   The incidence of neoplasia (adenoma and carcinoma) of the renal tubular epithelial cells was 2/150 3/150, 1/150, 8/150, 34/150 and 55/150, respectively for group I, II, III, IV, V, and VII Group VI rats that survived to the end were examined only for gross lesions hence they were not included. The incidence and degree of enlargement of the renal tubular epithelial cells, especially the nucleus (karyomegaly) were increased in a dose-related fashion. A

drug-related increased incidence of eosinophilic hyaline droplets in the renal tubular epithelium was also found. The incidence was 5/150 7/150, 13/150, 13/150, 20/150, and 36/150, respectively for group I, II, III, IV, V, and VII.

In the statistical analysis of tumor incidences, animals found dead and animals killed terminally were compared together. Sometimes the killed terminally groups were compared alone in order to explore the possible masking effect of the found dead group on the treatment effects. The results showed that testicular adenoma, mammary gland neoplastic lesions, pancreas neoplastic lesions, mandibular lymph node (plasma cells prominent) nonneoplastic lesions, and nonneoplastic lesions in the extremities and in the mesenteric lymph nodes could be treatment related. In some cases the Myochrysine group showed higher incidences than the auranofin group, or vice versa.

The sponsor, by quoting SK&F historical control incidences (Crl: COBS CD rat) of testicular interstitial cell tumors (9% and 15%), claimed that the testicular adenoma in this study was non-drug related. A focal lesion of "neuronal-type" cells in thyroids was found in treated females only but was called in lack of knowledge of their biological meanings.

2. 18-month chronic toxicity study in mice, conducted at

from May 7, 1980 to November 16, 1981. 110/sex/group Charles River CD-1 mice, dose: 0, 0 1, 3, 6, (increased to 9 on day 294) mg/Kg/day by oral intubation in 0.5% gum tragacanth. Necropsies were done on all mice. Histological examinations were done on all mice found dead or killed in extremis, and killed terminally in groups I, II, and V.

Salivation was the only treatment-related clinical effect. The mortality incidence at the end of study is 27%, 21.8%, 29.1%, 25.5% and 29.1%, respectively for five male gruops and 26.4%, 30%, 22.7%, 20.9%, and 32.7%, respectively for five female groups. No drug related effect on mortality is apparent. However, it is noted that mortalities were higher in low-dose males during months 11 to 15, in high-dose males during months 12 to 15, and in high-dose females during months 13 to 14.

The malignant lymphoma of thymus was found to be higher in high-dose females killed terminally (29.9%) than in two control females (9.7% and 21.1%). The incidences of

malignant lymphoma of thymus on all mice (males and females in "found dead" and "killed terminally" added together) were 16/156 (10.3%), 27/168 (16.1%), and 27/157 (17.2%) for group I, II, and V respectively. The statistical analysis of these tumor incidences showed that in the high-dose females killed terminally it was significantly increased. However, the tumor was not statistically significantly increased when all mice were included in the comparison.

The incidence of neoplasia of the uterine muscles (leiomyoma, leiomyosarcoma) was 1/81 (1.2%), 2/77 (2.6%), and 4/74 (5.4%) for groups I, II, and V killed terminally, respectively.

When all mice were taken into account, the incidence was 2/110 (1.8%), 2/110 (1.8%), and 4/110 (3.6%) for groups I, II, and V respectively. The sponsor stated that this was not drug-related. The incidence of neoplasia of the liver (neoplastic nodule, hepatocellular carcinoma and hepatoma) was statistically higher in the high-dose group males killed terminally [18/78 or 23.1% vs. 8/80 or 10% (group I) and 12/86 or 14.0% (group II)]. The incidence of chronic hepatitis of high-dose males killed terminally was also higher than the control groups statistically.

The incidence of acute myocarditis was higher in the high-dose females "found dead". However, the incidence of all myocarditis (acute, subacute, and chronic) in group I, II, and V for all mice was 12/220 (5.5%), 9/220 (4.1%), and 14/219 (6.4%) respectively. The difference between the groups is not statistically significant. The incidence of inflammation of parotid salivary gland was statistically higher in the high-dose males killed terminally. Brown degeneration of the adrenal gland occurred in an incidence of 2/29, 1/33, 7/24, 2/23, and 6/36 in groups I, II, III, IV and V females, respectively. The difference between this treated group and the control group is statistically significant.

3. Primary report of 7-year toxicity study in dogs (February 8, 1983 IND submission) 7/sex/group, dose: 0, 1.8, 3.6, and 7.2 mg/Kg/day, but dosings were reduced later to 0 0.9, 1.8, and 2.4 mg/Kg/day and animals were off the drug at certain times. According to the brief report, postmortem examination did not reveal any drug effects in animals. Postmortem examination did not reveal any drug effects in animals. The completion of the whole study is estimated as 4th quarter in 1985.

4. A table listing all toxicity studies completed or in progress was attached to February 8,1983 IND annual progress report.

EVALUATION AND COMMENT:

In previous pharmacology reviews completed in 1982, it was commented that auranofin was approvable if certain animal toxicity findings which were acknowledged by the sponsor to be adequately addressed in the labeling. The toxicities being mentioned were chronic renal toxicity, renal adenoma, and possible interaction with other drugs. It is assumed that some of those findings were from a previously conducted 12-month study on Charles River CD rats.

In this NDA supplement dated August 3, 1983, the complete reports of 2-year rat study and 18 month mouse study were submitted. In the 2-year rat study it was found that renal neoplasia (adenoma and carcinoma), karyomegaly, and eosinophilic hyaline droplets (red pigments in tubular epithelium) were significantly increased in the treated groups. Other toxicity findings which were significantly increased in treated groups but were claimed to be non-drug-related by applicant included: testicular adenoma, mammary gland neoplastic lesions, pancreas neoplastic lesions, mandibular lymph node nonneoplastic lesions, and nonneoplastic lesions in extremities and in mesenteric lymph nodes. Those were all statistically significant increases by applicant's analysis. In the 18-month mouse study, the applicant stated that there was no drug-related effect on incidence of neoplasms. However, it appeared that malignant lymphoma of thymus was increased in high-dose females killed terminally. The incidence of neoplasia of the uterine muscles (leiomyoma, leiomyosarcoma) in females killed terminally was 1/81, 2/77, and 4/74 for control I, control II, and high-dose group, respectively. The incidence for all females (killed terminally and found dead) in the same three groups was 2/110, 2/110, and 4/110, respectively. This is considered not to be drug-related by the sponsor. The incidences of neoplasia of liver and chronic hepatitis were increased in the high-dose males killed terminally, however, these increases were considered as chance occurrance and non-drug-related (by adding incidence of acute, subacute, and chronic hepatitis together) by the applicant. The higher incidence of acute myocarditis in high-dose females "found dead" was judged as non-drug-related by the sponsor by the similar method (by adding acute, subacute, and chronic myocarditis together). Other increase in incidence in treated groups included inflammation of parotid salivary gland in high-dose males killed terminally and brown degeneration of adrenal gland in treated females. The sponsor considered these changes as a non-drug-related effect. However, they were all statistically significant by the analytical method adopted by the applicants (namely, Chi-square).

A conference telephone call was made tetween this reviewer and Drs. B. Wallin and E. Saunders of SK&F on March 27, 1985 (see memos of conversation written by me and SK&F of that date). It became clear that the safety concern of auranofin by the Committee on the Safety of Medicine (CSM) of the United Kingdom, as mentioned in NDA cover letter dated August 1, 1983, pertained to incidences of renal adenoma and testicular tumor in 2-year rat study and hepatic tumor and thymic lymphoma in 18-month mouse study. CSM was unsatisfied with the terminalogy and analytical method by the company. The problems have not been resolved yet between CSM and SK&F.

RECOMMENDATION:

It appeared that there were treatment-related incidences of neoplasms and organ toxicities in carcinogenicity studies in addition to renal neoplasms and renal toxicity than admitted to by the applicant. The applicant interpreted these data by "chance occurrence" or "within historical control" or "of unknown (biological) significance" and claimed they were not drug-related without satisfactory explanation. These issues need to be resolved. It is felt that the data of neoplastic and non-neoplastic lesions in 2-year rat and 18-month mouse studies should be examined by our biostatistician.

NDA 18-689 is non-approvable at this time.
See Dr. Richman's Addendum which is attached to this review.

Conrad H. Chen

Conrad H. Chen, Ph.D.
April 17, 1985

cc:
Orig NDA 18 689
HFN-150/Div File
HFN-150/CSO
HFN-150/CHChen/4-17-85
HFN-342
F/T:dl:4-24-85
Wang #0874B

NDA 18-689
D. F. File

MAY 2 4 1985

NDA 18-689

REVIEW AND EVALUATION OF PHARMACOLOGY
AND TOXICOLOGY DATA
Date of Submission: April 26, 1985
Date of Review: May 3,1985

SPONSOR: Smith Kline & French Laborotories
Philadelphia, Pennsylvania 19101
DRUG: Ridaura (auranofin) Capsules (3&6mg) and Tablets (1,3&6 mg)
CATEGORY: Non-steroidal gold containing agent for treatment of rheumatoid arthritis.
OTHER NAME: SKF D-39162
RELATED TO:
BACKGROUND: The pharmacologist's review of 2-year rat and 18-month mouse studies (submitted Aug. 3,1983) has been completed, dated April 12, 1985. The supervisory pharmacologist's addendum to the pharmacologist's review was written on April 15, 1985. In essence, NDA 18-689 was recommended as non-approvable because of the possibility of the wider range of tumorgenenesis than the previously reported ra renal neoplasms. Subsequent to an in-house meeting, a telecon between Dr. Harter and representatives of SKF was held on April 24, 1985 (see telecon memo of that date). The applicant was asked to submit several informations to help resolve the pending problems. On April 26, a 9-page submission by the applicant was received by FDA. The review of that submission follows:

REVIEW AND COMMENT:

1. 2-year rat study:

   A. Testicular adenoma: The applicant used the same data which were submitted previously in doing further statistical analysis. It appeared that the originally detected statistically significant difference in tumor incidence between the treated and the control groups was no longer existing. The trend analysis performed by the applicant also showed a negative result. It is felt that the statistical analysis of the data should be examined by our statistician.

   B. Mammary gland neoplastic Lesions:
   According to the applicant's statistical analysis, the incidence of adenocarcinoma did not show any treatment related increase. However, the incidences of adenoma amd all tumors (adenoma, fibroadenoma, and adenocarcinoma) of high dose group killed terminally showed significant increase when compared with Control I but showed no increase when compared with Control II. No data from low-and mid-dose groups were available in the submission.

C. The applicant failed to submit the data from low- and mid-dose groups and failed to explain further if pancreas neoplastic lesions, mandibular lymph node nonneoplastic lesions and nonneoplastic lesions in the extremities and in the mesenteric lymph nodes were treatment related.

2. 18-month mouse study:

A. Hepatocellular tumors:

The applicant stated that "in the animals which were killed after 18 months of drug administration, malignant tumors of hepatic origin were encountered only in the controls" (3/161, 0/163, and 0/152 for Control I, Control II, and high-dose group, respectively). However, the statement is misleading because of livers from low- and mid-dose groups killed terminally were not examined histologically. In that context, the incidences of hepatocellular carcinoma quoted for animals treated for a shorter period (animals found dead), 0/59 Control I, 2/57 Control II, 2/57 low dose, 2/51 mid dose, and 1/68 high dose, had little meaning because the total incidences (found dead plus killed terminally) for all groups were not available.

The applicant has classified hepatoma as equal to adenoma and termed them as benign tumor. The incidences were 7/161 Control I, 13/163 Control II, and 18/152 high dose group. No data from the low- and mid-dose group was available. The incidences of neoplastic nodule in animals found dead were 0/59, 0/57, 1/57, 0/51, and 1/68 for Control I, Control II, low-, mid-, and high-dose groups, respectively. Although no neoplastic nodule was found in controls and high-dose groups killed terminally, the incidences of neoplastic nodule in low- and mid-dose groups killed terminally, were not available. The liver tumors have been broken down to carcinoma, hepatoma, and neoplastic nodule by the applicant. However, no statistical analysis of the data was given in this submission. It should be reminded that the incidence of neoplasia of liver (neoplastic nodule, hepatocellular carcinoma and hepatoma) was statistically significantly higher in high-dose males killed terminally (23.1% vs 10% Control I or 14.0% Control II).

B. Malignant lymphoma of thymus: No data from low- and mid-dose groups or trend analysis could be found in this submission. It was previously shown that the malignant lymphoma of thymus was significantly increased in high-dose females killed terminally (29.9% vs 9.7% Control I or 21.1% Control II).

C. The treatment effects on neoplasia of uterine muscle, chronic hepatitis, and acute myocarditis have been suspected. Inflammation of parotid salivary gland and brown degeneration of adrenal gland were also increased in the treated groups.
These findings were not discussed in this submission.

NDA 18-689

RECOMMENDATION:

1. The statistical analysis submitted by the applicant should be evaluated by our statistician as to its properness and accurateness.

2. It is found that many organs/tissues from the low- and mid-dose group animals in 2-year rat (mammary gland, pancreas, mandibular lymph node, etc.) and 18-month mouse (liver, thymus, uterine muscle, etc.) studies were not histologically examined (especially from those animals killed terminally). In the absence of these data, meaningful analysis would not be possible. The applicant should examine these organs/tissues and make the data available.

3. The applicant should respond to other questions raised in pharmacologist reviews regarding carcinogenicity studies. Better description and interpretation of the following findings are needed: mandibular lymph node neoplastic lesions and nonneoplastic lesions in extremities and in mesenteric lymph nodes (in rat study), inflammation of parotic salivary gland and brown degeneration of adrenal gland (in mouse study).

4. Ridaura is highly tumorigenic in rat kidney and possibly in other rat and mouse organs/tissues. The approval of NDA 18-689, therefore, should be based on careful evaluation of clinical benefit versus possible risk factors.

Conrad H. Chen

Conrad H. Chen, Ph.D.

Orig NDA 18-689
HFN-150/Div File
HFN-150 CSO DPease
HFN-150/Originators CHChen 4/26/85
R/D endorsed by:
F/T by S.Anceleitz 5/9/85
Wang # 1121B

See attached addendum.

NDA 18,689(Ridaura. FINISHED REVIEW Review # 2 7/27/82 37 7-20-82

Sponsor: SKF, Philadelphia,Pa 19101 Date of review 6Jul82

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA AMENDMENT dtd 22Jun82

Submission information: Spondot cover ltd dtd 22Jun82; no BD stamp; HFD-150 stamped 24 Jun82; AMG recd 8Jul82.

This amendment was in response to our ltr of 10May82.

Review & evaluation:

1. The comment raised in the pharmacology portion of the letter to the sponsor has been adequately answered. The comment was re: the reported Au levels in control dogs and the response was that there may have been a mix-up of samples in the laboratory. The results of this single experiment are not pivotal to the preclinical studies since other studies of this nature have been done.

2. In my original review of this NDA dtd 12Mar82, I pointed out that the sponsor had adequately defined the expected toxicities for this drug and that it appeared to have the basic pharmacodynamic activities for the therapeutic indication intended. Other possible problems in this area, I felt could be handled with adequate labeling. As is still the case as of this date I have yet to see a copy of the currently proposed label. If the following three major area are properly addressed in the label, I see no major problems in the limited use of this drug for refractory rheumatoid arthritis: 1) the potential for chronic renal toxicity; 2) the potential carcinogenicity suggested from rodent positive bioassay results, and 3) bioavailability and metabolism studies which adequately identify major metabolites of this drug.

Comments for sponsor:

Items 1 and 2 above may be conveyed to sponsor.

2. Studies may proceed with cautious lookout particulary for symptoms of nephrotoxicity in advanced clinical trials.

3. NDA is approvable pending review of package insert.

R/D initialed DJRichman 7/27/82

A. M. Guarino,Ph.D. 8Jul82

cc: Orig. NDA 18-689
HFD-150, HFD-180
HFD-150/AGuarino:7/8/82
HFD-150/CSO/DMoore
R/D endorsed by DJRichman:7/12/82

7/27/82

FINISHED REVIEW APR 12 1982 5/31/82

NDA 18,689 Review #1

Sponsor SKF, Philadelphia, PA 19101 Date of review 12Mar82

Submission information: Sponsor cover letter dtd 30Sep81;
ED stamped 50ct81; HFD 150 stamped 150ct81; AMG recd 290ct81

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

Original Summary

DRUG

Auranofin, SKF D-39162, Ridaura, s-triethylphosphine gold 2,3,4,6,-tetra-O-acetyl-1-thio-beta-D-glucopyranoside

CATEGORY Non-steroidal Au containing for active rheumatoid arthritis at a dose of 6 mg/d.(ca 3 mg/sq.m.). Forms: capsules(3 & 6mg), tablets(1,3 & 6mg).

RELATED SUBMISSIONS

PRECLINICAL TEST FACILITIES

Unless otherwise stipulated, studies were done at sponsor's facilities in Philadelphia, PA.

PHARMACOLOGY

1. Primary pharmacological studies

These have been summarized in the review of by Dr. Lee-Ham dtd 27Jan77. Basically, these studies such as the adjuvant-induced arthritic rat, showed the drug to be active orally at doses of 10-20 mg/kg/d.

2. Biochemical pharmacologic studies

Four(4) studies of this type are summarized in Table I. Two of these focused on the role of SH groups in the inflammatory process and showed either slight or negative effects from the drug. The third study was concerned with the inhibition of lysosomal enzymes since their release is thought to play a role in inflammatory diseases such as arthritis. Auranofin significantly decreased the extracellular release of lysosomal enzyme markers(lysozyme & beta-glucuronidase) from zymosan-stimulated rat leucocytes. in comparison with two other clinically available related compounds, Au Na thiomalate and Au thioglucose, auranofin was more potent in this test system. The [illegible]-th test on galactosyltransferase was negative for this drug.

PHARMACOLOGIC DISPOSITION & METABOLISM

In Table 2 are summarized 18 reports regarding this aspect of auranofin. Three different labeled forms of the drug were prepared with either Au195,S35 or P32. Both in vivo and in vitro studies were done in rats,dogs and humans with the following major conclusions:

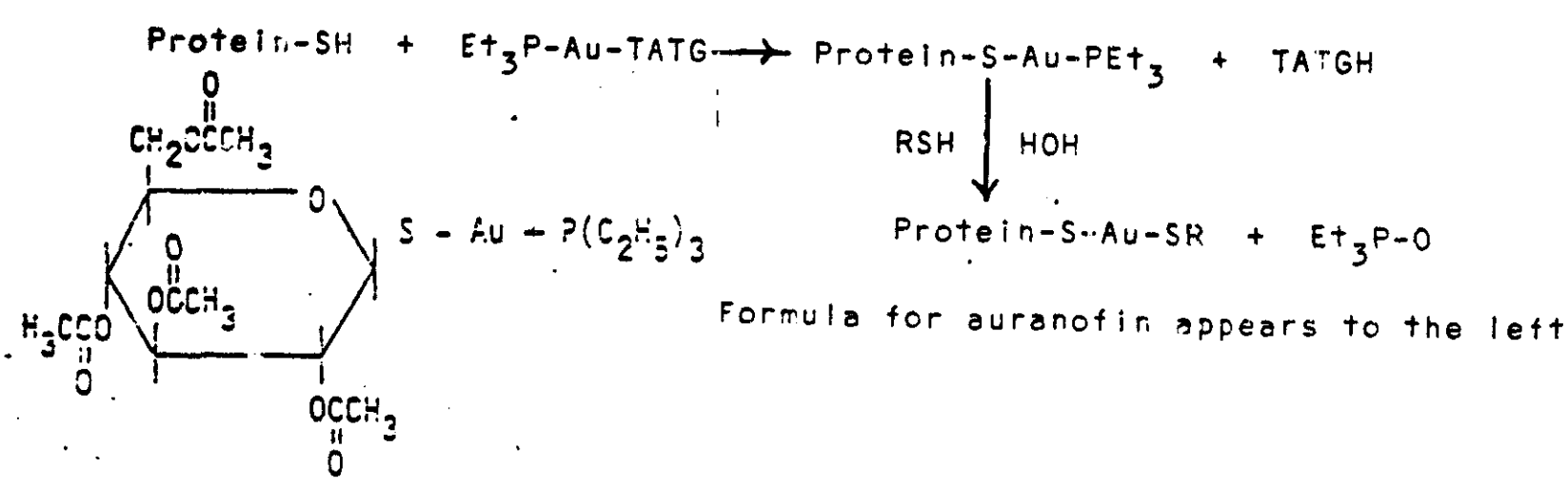
1. Both in vivo and in vitro, the Au portion is rapidly & extensively bound to plasma proteins and RBCs in all three species. While the Au-195 labeled drug can be extracted with chloroform from water or urine, it is unextractable from whole blood. About equal amounts of bound drug(50-50%) are found in plasma and RBCs.

2. The use of the S-35 form of the drug in vitro with human blood showed that about 1% binds to RBCs, 37% to plasma proteins and 62% is free in plasma water. Since about the same pattern appeared following the use of P32 labeled drug, it can be concluded that both the Au-S and Au-P bonds are readily broken even in vitro.

3. Rats treated with Au-195 drug excrete up to 7% in urine and 62% in feces in 24 hrs. P-32 drug is excreted primarily in urine (55%) in 24 hrs and was idetified in the form of triethylphosphine oxide.

4. In dogs, Au-195 drug given either PO or IV doses, yielded terminal half lives of about one week. Either P-32 or S-35 drug gave $t_{1/2}$ in the range of 6-16 hours, providing futher data on major differences in distribution patterns from the various labels. About 60% drug was excreted in urine in 24 hr for these isotopes.

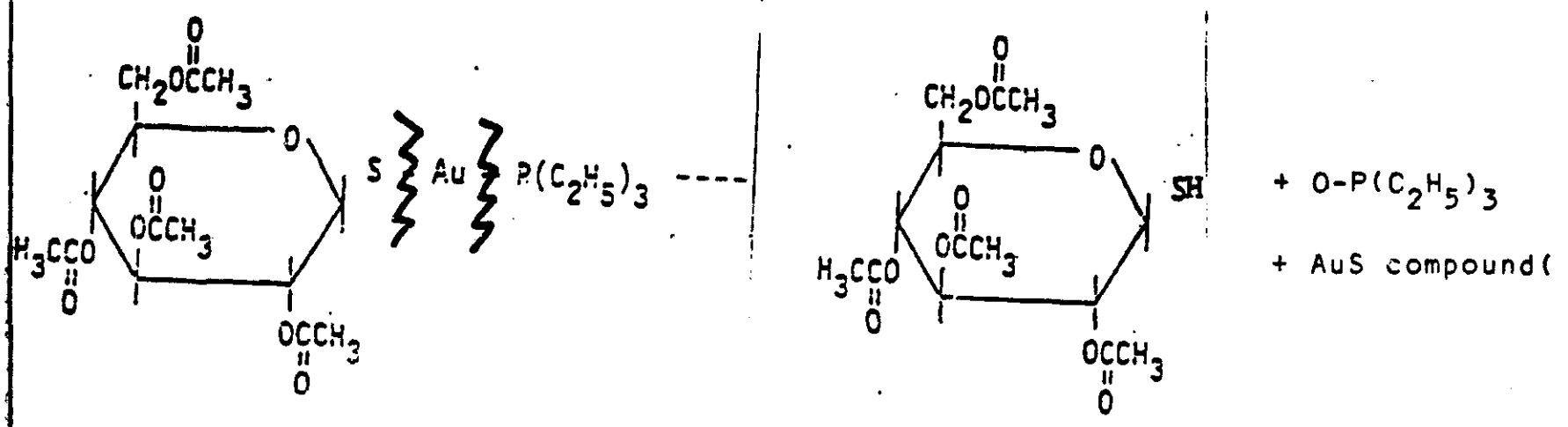
5. In all 3 species the drug seems to involve three major products: a protein-Au complex, triethylphosphine oxide and tetraacetylthioglucose(TATG) according to the following type scheme where where RSH could be something like glutatione or cysteine:



Formula for auranofin appears to the left

6. By both direct counting of tissue samples and autoradiographic methods, the Au-195 drug cleared from rat blood with a half life of ca 2 days and showed significant accumulation in the kidneys. When drug was given PO or into either of 4 segments of the GI tract, some absorption did occur. In comparing IV vs PO treatment the bioavailability was ca 30%. After PO dosing of 1 mg/kg one time, the urine continue to contain some label with about 1, 6 & 10% appearing at days k,5 & 21 respectively. On these same days the feces contained 62,78 and 79% of the label. By day 21 the carcass still retained 3% of the singly administered dose(see item 12 of Table 2). Biliary, mammary and placental transport of Au-195 drug was also studied in rats. For this drug these routes proved to be of little significance for the orally administered drug. For example, 6 days after treatment of rats with 10 mg/kg of PO drug only 3% appeared in the bile. On the other hand up to 25% was excreted via this route in 7 d if given IV. Fetal and milk levels of Au-195 were considerably less than maternal blood levels and even where milk did contain significant radioactivity, it was in a form which was not absorbed by the pups. See items 1,2,10,11,12, 14 & 16 of Table 2.

7. Metabolism and or degredation of auranofin seems to occur either in vivo or in vitro, as noted in items 9 & 13. Both Au-S and Au-P bonds are broken as evidenced by products in dog & rat urines. The following reactions seem to occur but the form in whtch the Au appears is uncertain but in thought to involve binding to SH groups from either small or macromolecular species such as proteins and/or glutatione:



8. Rat liver drug metabolizing capacity was tested after treatment with 10 mg/kg of the drug and certain pathways were inhibited by auranofin(Table 3, item 17)..

9. In studies were urinary excretion was used as an assessment of bioavailabity in dogs or rats treated IV and orally, one could infer that 25-33% of the PO drug was absorbed(Table 2, items

ACUTE TOXICOLOGY

These studies in mice, rats & dogs are summarized in Table 3. Because of a wide range of observation times, it is difficult to compare strain and species. There were some of these studies which were range finding, wi th little detailed observations. In mice treated PO with a number of strains and both sexes, the LD_{50}'s ranged from 139 to 345 mg/kg with most of the deaths occurring within the 1st 24 hrs after treatment. General observations provided no clues as to the cause of death. In rats treated IM vs PO, the drug was more toxic by the IM route; LD_{50}' s were ca 30 vs 300. Dog studies showed that at doses of 6.9 mg/kg, PO emesis consistantly occurred within 1 hr. Lower doses cause no obvous effects.

SUBCHRONIC TOXICOLOGY

Mice treated x5 PO with 96 mg/kg/d showed 3/10 dead within 3 d while at 48 mg/kg there were just sl dec in bw gains. The 2 month study in mice yielded an LD_5 = 10 mg/kg with an LD_{70} = 160 mg/kg. Another mouse LD_{50} on a x 5 PO schedule was 116 mg/kg. Rats on this same schedule & route at their highest dose of 69 mg/kg/d showed diarrhea & dec bw gains. Rats treated for 3 mos at 3.6 mg/kg had sl dec in bw gains while at higher doses of 12 - 35 mg/kg/d there were signs of toxicity to the following systems:BM,kidney liver, and GI tract. The dog HNTD on a x5 Rx was 0.85 mg/kg/d, bid. When extended to 3 mos the dog HNTD was iess than 1.8 mg/kg/d, with higher doses causing BM, GI, and hepatic effects

CHRONIC TOXICOLOGY

12 Month Rat Studies

These have been review by Dr. Lee-Ham appear as Refs 70 & 71, Vol 1.16 of the NDA. Doses of 3.6, 12 & 23 mg/kg/d were given to "Charles River" unspecified strain, rats PO, 7 days/week for 12 months. Animals were sacrificed at 4.5,6,9 & 12 months The highest mortaility occurred between

9 and 12 months with an overall incidence of 60%. As early as 4.5 months renal lesions consisting of karyomegaly which by 12 mos progressed to cytomegaly and neoplasia of the renal cortical tubular epithelia. A second target organ was the GI tract with brown spots on the gastric mucosa at early sacrific times with later focus on ileocecocolic ulcers, gastric erosions and bile duct absceses. By one year the renal lesions had progressed to include high incidences of cytomegaly, karyomegaly and renal adenomas

12 Month Dog Studies

Beagle dogs were given 0.6, 1.2 or 2.4 mg/kg tid orally with the latter dose escalated to 6.0 m/kg in 4 increments between d 225 & 330. Major early toxicities were GI, such as emesis and watery stools. There were decreases in the following parameters: TP, alb, Ca and SGPT. There were increases in BUN, urinary bilirubin. There was also evidence of hematologic toxicity which might have been due to secondary causes such as the GI toxicity. Histopathologic evaluations revealed lesions of the following types: marrow hyperplasia and hyperplasia of follicular cells of thyroid gland. Increased pigmentation(? Fe) was seen in spleen, and liver of dogs. Hypothrombinemia was also reported.

REPRODUCTION STUDIES

Some of these are summarized in Table 5 of this review and others appear in the Lee-Ham review of

Segment I - General Reproductive and Fertility Studies.

Male rats were treated with 1,2 or 4 mg/kg/d of PO drug for 63 days prior to mating with untreated females. No significant adverse effects were reported

Female rats were treated with 0.25, .75 or 3 mg/kg/d for 14 d prior to mating, throughout pregnancy and lactation with no adverse effects noted.

Segment II - Teratology Studies

Mice-pregnant animals were treated on d 6-15 with PO drug, 0.5 - 40 mg/kg/d. Some parameter were altered only at the highest dose(40 mg/kg) eg, sig. dec in ave number of corproa lutea and implants. The ave no. of fetuses and ave litter size was normal only up to 5 mg/kg. While there seemed to be fetotoxicity, no sig malformations were reported in the pup which went to term. No embryotoxicity or teratogenicity occurred in mice treated with up to 5 mg/kg

Rats-pregnant animals were treated on d 6 - 15 with PO drug, 0.5,2.5 or 5 mg/kg/d. While a slight inc in number of resorptions occurred at the highest dose, the incidence and types of abnormalities seen in the fetuses were within the same incidence as in control rats.

Rabbits-pregnant animals were treated on d 6 - 18 with PO drug, 0.5, 3.0, or 6.0 mg/kg/d. There was maternal toxicity as evidence as dec bw, especially at the hi dose; this same dose caused an increase in the number of resorptions. The incidence of malformations for these three respective doses were 15.5,4.7 & 1.9%. Typical malformations such as the following were reported in drug treated groups: protrusion of intestines, hydrocephalus, hypoplastic sternal centers, enlarged lateral ventricles of brain.

Segment III - Perinatal & Postnatal Studies

Rats- animals were treated from d 15 of pregnancy to d 20 of lactation with 0.5, 2 or 8 mg/kg/d. Most of the adverse effects were noted only at the highest dose and included the following: inc number of resorptions, dec in litter size and dec in birth weight. During the lactation interval, the bw gains in all pups from drug treated mothers, were somewhat less than in controls.

SPECIAL TOXICOLOGIC STUDIES

In standard(Draize) tests of rabbit eyes and skin, ocular reactions were quite serious progressing to corneal opacities. Prompt irrigation did attenuate but did not eliminate these effects. Some rabbits were resistant to the dermal effects of auranofin but others became inflammed and scabs forms at the site of application of both abraided and unabraided ares of skin.

In another type of special tests, the sponsor examined the potential for additive and/or synergistic toxicities of auranofin with a number of commonly used drugs. On the 3rd page of Table 6 is a summary of the results and there was some evidence of potentiation toxicity for the following drugs in experiments with rats: acetaminophen,allopurinol, aspirin,chlorpropamine,cimethidine, clonidine,diphenoxylate,furosemide, phenylpropanolamine,propoxyphene, quinidine,sulindac, thoridazine, tolmetin andespecially warfarin which showed the greatest potentiation values.

MUTAGENICITY TESTS

It would appear that due to the positive carcinogenicity test resulting from the 1 year rat study, the sponsor did extensive mutagenicity testing; nine of these are summarized in Table 7. Four in vitro tests were done and one in vivo(mouse dominant lethal) was reported. In the Ames test using Salmonella typhimurium of the strains TA 98,100,1535,1537 & 1538, results were negative either with or without S9 fraction. Both positive and negative controls were done. The second in vitro test was with the yeast Saccharomyces cervisiae S288ca with both forward and reverse systems studies, with and without S9 and including + and - controls. All results were negative. A malignant transformation assay using the mouse BALB/3T3 line gave the expected results with + and - controls, but was negative with auranofin. The 4th in vitro assay was the L5178Y TK +/- mouse lymphoma and employed both + a - controls. Results were negative for auranofin in uninduced systems, but positive in the presence of S9; values were about 4-fold greater number of mutant colonies than in control in this forward mutation assay. Myochrysine was a weak mutagen both with and without S9. In a standard in vivo test of dominant lethality in mice, auranofin was negative.

SUMMARY & EVALUATION

Auranofin is an Au containing compound to be used in patients with rheumatoid arthritis. There are other related compounds on the market but this one is proposed for oral use; others commonly are given IM with the obvious disadvanges. It my understanding that the daily patient dose will be 6 mg/d.

The spectrum of pharmacologic activities seen preclinically is what would be expected for an antiinflammatory agent. Rather complete preclinical toxicologic studies have been submitted by the sponsor. These are adequate to establish both acute and chronic toxicities expected for this drug. In addition to the GI and renal target organ effects common to other NSAIAs, there is the addition liability of heavy metal toxicities due to the Au portion of the molecule. The heavy metal nephropathy becomes most obvious on chronic dosing and in rats renal adenomas are found. Distribution and metabolism studies of this drug are inconclusive since it is unlikely that the intact molecule appears in the blood. In a variety of pharmacokinetic studies using three different labels, S, P and Au, different patterns of distribution emerge in all animals and human studies. Even in vitro, intact drug is not found 20 min after incubation with blood. Very elegant whole body autoradiograph studies with these same three radiolabels, confirm the extensive degradation of the auranofin molecule. These same studies show the obvious and persistant localization of the Au portion of the molecule in the kidneys. In addressing the potential carcinogenicity of this drug, the sponsor appears willing to conceed that it causes renal tumors in rats and attributes this to a species specific effect. No other carcinogenicity are provided but in most mutagenicity assays, the drug is negative. In this latter area there is one notable exception in that with S9 the L5178Y line, which is defficient in thymidine kinase(TK) activity, there is a positive response.

This reviewer feels that the sponsor has adequately defined the expected toxicities for this drug and that it has the basic pharmacodynamic activities for the therapeutic indication intended. Since I have yet to see the sponsor's intended labeling and clinical brochure, I can not render a final recommendation on this drug. There are three areas I would like to see addressed in these documents by the sponsor: 1) chronic renal problems; 2) potential carcinogenicity; and, 3) metabolism of the drug, including identification of most of the metabolites.especially as these relate to bioavailability.

If the sponsor adequately addresses these three major issues and the few specific question below, this is an approvable NDA in my opinion.

SPECIFIC COMMENTS TO THE SPONSOR.

1. Repeat 2nd para from p. 8 above.

2. Ref A-23, Vol 1.22, May 1979. In testing the possible effects of auranofin on drug metabolizing enzymes, the sponsor concluded that the drug"may have slight inhibitory effects on some of the enzyme systems in rats". In this report the activity of the acetanilide pathway was 2 to 4.6-fold decreased compare to control. This is not a slight effect and thus the sponsor may wish to restate this section and in the labeling include a statement that like many heavy metals this drug may inhibit drug metabolizing enzymes.

3. Ref 62, Vol 1.15, Dec 1970. Dogs were treated with oral drug and blood was analized for Au by AAS methods. The sponsor should explain how none of the auranofin treated dogs had detectable levels of Au in their blood but the two "controls" , # P-1142 and P604 had 0.5 ug.ml Au detected in their serum.

4. Refs 116 & 117, Vol 1. 15, Mar 1981. The sponsor has identified a number of commonly used drugs which are likely to cause interations resulting in increased toxicities; how are these to be addressed in the labeling?

R/D initialed DJRichman djr 3/26/82

A. M. Guarino, Ph.D.
A. M. Guarino
22 Mar 82

Reviewer completed
typed draft 22Mar82

workyste
3/29/82

Addendum to Pharmacology Review

NDA 18-689

April 15, 1985

Addendum: In the interest of expediting resolution of questions on the two carcinogenicity studies, so that regulatory action may be taken, I wish to summarize several important questions regarding intrepretation of the results of these studies:

.) Applicant appears to have analysed all data employing chi-square. As this type of analysis does not take into account any trend analysis and does not correct for early deaths among treated animals, I question whether the analysis is appropriate.

2) Applicant appears to have examined all tissues from only the controls and high dose animals. Thus according to Dr. Chen, in several organs at risk (eg. mouse - thymus, uterus, liver; rat - pancreas, mammary) the tissues from most low and mid-dose animals were not examined histopathologically.

3) Dr. Chen noted that applicant in some cases called statistically significant findings (by chi-square) not biologically significant and did not explore findings in all animals (eg. thymic lymphomas in female mice).

Given the question as to whether proper analysis was made of tumors found in the rodent studies and the possibility that the range of tumorigenesis caused by Ridura is much wider than the previously reported rat renal neoplasms, we should have our biostatistitions examine both studies. The benefit-risk analysis of Ridura may have to be re-examined in light of these studies, especially if the carcinogenic spectrum of the oral product is found to differ from the parentral gold employed as a positive control. It is recommended the application be considered non-approvable until these questions can be better resolved.

It should be noted from Dr. Chen's memorandum of telephone conversation of March 27, 1985 with representatives of SKF (see memorandum of memo between Dr. Chen (FDA) and Dr. Harry Saunders and Dr. Bruce Wallin (SKF) attached) that the Committee of the Safety of Medicine (CSM) was concerned with many of the same questions raised here; methods of analysis were criticized by the CSM as well as their expressing concerns about renal adenomas and testicular tumors in rats and hepatic neoplastic nodules and thymic lymphomas in mice.

We have already alerted and met with D.s. Harter and Fairweather regarding the above concerns.

David J. Rubman

David J. Rubman, Ph.D.

cc: Orig NDA 18-689
HFN-150/Div File
HFN-150/Pease
HFN-150/Harter
HFN-150/Palmer
HFN-100/Temple
HFN-102/Glocklin
HFN-715/Fairweather
F/T by P. Amoss/4/19/85
Wang #0837B

J Palmer 5-15-85

Pharmacology Addendum

NDA 18-689

Addendum: Following discussions with our medical and statistical staffs (see memorandum of meetings of April 24, 1985, May 2, 1985 and May 15, 1985) and review of the SKF submission of April 26, 1985, the following amendment of my April 15, 1985 addendum may be made, regarding the carcinogenicity studies submitted to support approval of auranofin.

Rat Carcinogenicity Study:

Auranofin causes malignant renal epithelial carcinomas as well as renal adenomas, renal tubular cell karyomegaly and cytomegaly. These findings occurred in animals receiving 1.0 or 2.5 mg/kg/day orally (8 or 21 times the human dose). The testicular tumors seen did not reach levels of statistical significance (see memorandum from biostatisticians). There did not appear to be drug-related findings of carcinogenicity in other tissues. The types of lesions found in this study appeared similar for both gold sodium thiomalate treated animals and auranofin treated animals.

Mouse Carcinogenicity Study:

There was a slight numerical increase in thymic lymphomas observed in female mice (12/87 control 1; 22/92 control 2; 23/85 high dose) which was not considered significant by our statisticians.

There was an increase, p= .0[illegible] for control 1 vs. treated and for combined controls vs. treated, of hepatomas in male mice (5/80; 12/86; 18/78). Historically, male mice have a high incidence of this tumor.

At the conference of May 2, 1985 our clinical staff noted that the impact of increases of these murine tumors on approvability was nil, in light of the unequivacol renal carcinogenicity in the rat. It was agreed, however, that applicant must commit to examining slides from low- and mid-dose animals for both tissues.

No other tissues appeared to have drug-related findings of carcinogenicity.

There appeared to be an increase in chronic hepatitis among high-dose treated male mice, but concurrently, a decrease in chronic hepatitis among high-dose treated female mice. There was a finding of increased acute nyocarditis among female high-dosed mice found dead during the study (0/29; 2/33; 7/36). There is also a possible increase in salivary gland inflammation and in nonneoplastic lesions of the kidney. Dr. Chen's review also notes several possible nonneoplastic lesions which might be elevated in treated animals. It was recommended at the May 2, 1985 meeting by the clinicians that these findings need not to be placed in the package insert, since enough clinical data has accumulated regarding the potential human chronic toxicity of gold compounds.

Dog Carcinogenicity Study:

Applicant completed a 7 year study in the dog during the last quarter of 1984. Gross pathologic examination has been completed and applicant has informed us that no alarming findings were found (we have not seen the raw data).

Applicant has stated that histopathic reports will be available to the Agency by the end of 1985. Since only 56 animals were involved in the study, it would seem feasible that, given a priority at SKF, the slides could be examined and the reports finalized at an earlier time. A commitment for early submission of this data to the Agency should be obtained from the applicant.

CONCLUSION:

The documented carcinogenicity of auranofin in the rat kidney as well as other findings in the carcinogenicity and chronic toxicity studies have been reported and discussed with our medical and statistical staffs. The studies appear adequate to have demonstrated the toxicological profile of the drug in animals. With suggested revisions in the package insert and commitments regarding completion of histopathology reports of the mouse and dog bioassays, we would not object to approval of the auranofin NDA from the standpoint of pharmacology, provided in the judgment of our clinical staff the benefits anticipated outweigh the potential risks observed.

David J. Richman, Ph.D.
Supervisory Pharmacologist

cc: Orig NDA 18-689
HFN-150/Div File
HFN-150/Pease
HFN-150/Harter
HFN-150/Palmer
HFN-100/Temple
HFN-102/Glocklin
HFN-715/Fairweather
F/T by D. Pease
Revised by DJRichman/5/15/85
F/T by P. Amoss/5/15/85
Wang #1047B

5-15-85

Chem.

DPM

Division of Oncology and Radiopharmaceutical Drug Products

Chemist's Review # 1

NDA: 18-689 November 12, 1981

Applicant: Smith Kline French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

Product Name(s)

Proprietary: Ridaura
Non-proprietary: Auranofin
USAN: Auranofin
Compendium: -
Code name and/or number: SKF,D-29162

Dosage Form(s) and Route(s) of Administration:

Capsules (3 and 6 mg) Tablets (1, 3 and 6 mg) orally

Rx or OTC: Rx

Pharmacological Category and/or Principal Indication:

Antirheumatic

(2,3,4-6-Tetra-o-acetyl-1-thio-β-D-Glucopyranosato-s) (Triethylphosphine) Gold, $C_{20}H_{34}AuO_9PS$ M.P. 110-112°C

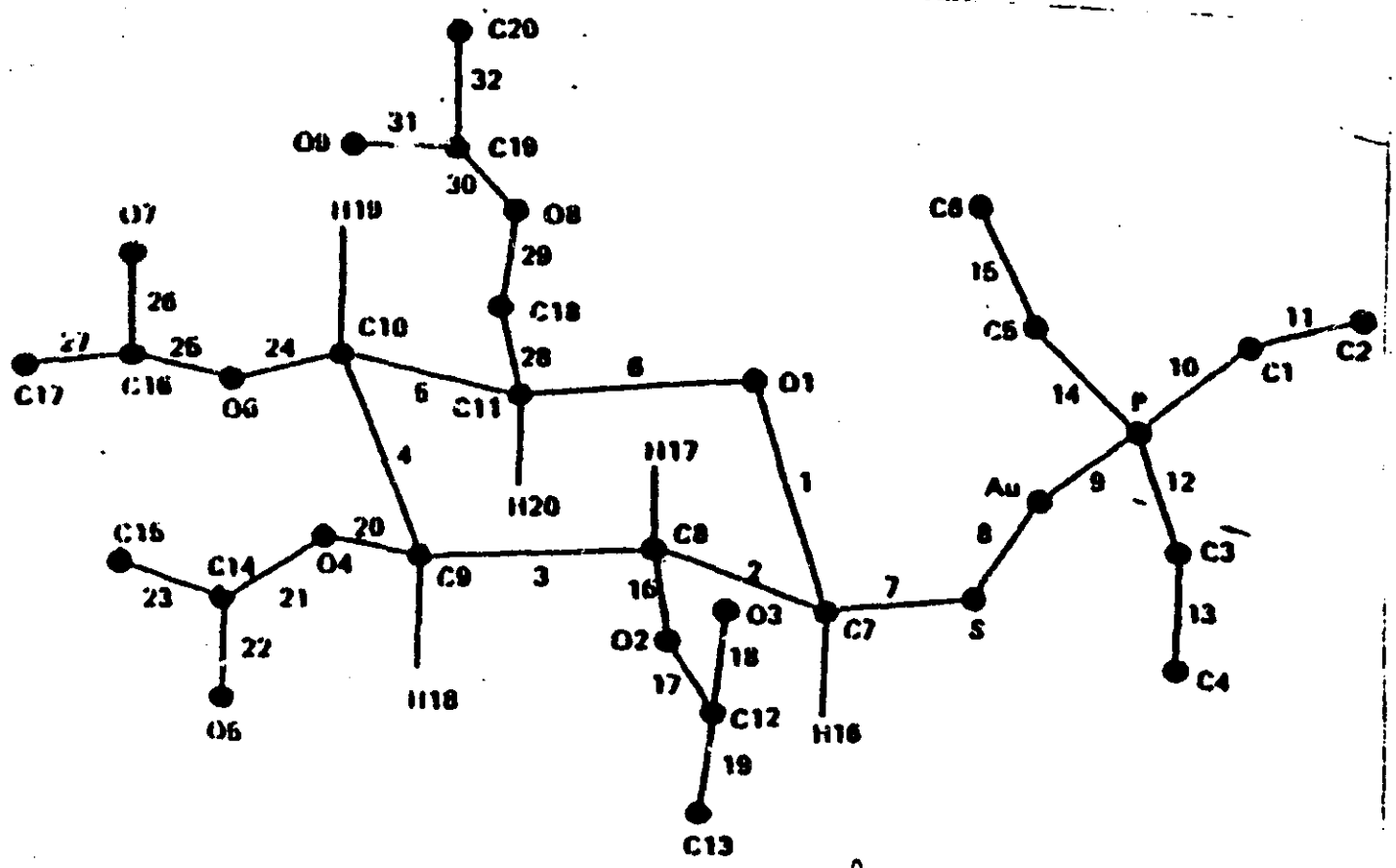


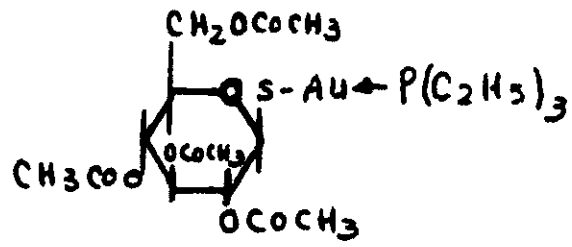
FIGURE 1 Auranofin

Ref: D. T. Hill and B. M. Sutton*, Cryst. Struct. Comm. (1980) 9, 679.
Also, Vol. 1.481, article #65

*SKF

- Chair confirmation
- All groups are in an equatorial position
- -configuration of the anomeric C-S bond confirmed

Structural Formula and Chemical Name(s):



$C_{20}H_{34}AuO_9PS$, An alkylphosphine gold coordinated complex.

Gold (2,3,4,6-tetra-O-acetyl-1-thio- -D-glucopyranosato-S)-(triethyl-phosphine)-.

(1-Thio- -D-glucopyranosato)-(triethylphosphine) gold 2,3,4,6-tetra acetate

Initial Submission

Dated September 30, 1981
In BD October 5, 1981
In HFD-150 October 21, 1981
Assigned October 22, 1981

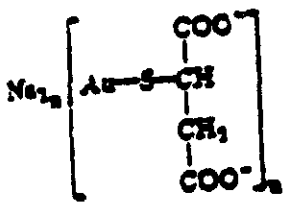
Amendments

Supporting IND, NDA, MF and Letters of Authorization:

Related Documents (IND's, NDA's, etc.)

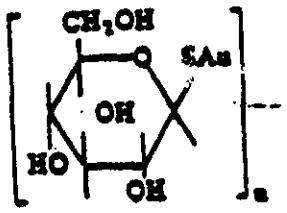
1) Myochrisin (MSD) - Grandfather clause drug. Available as Rx item. See the attached page for similar drugs.
2) Solganol (Schering) - Rx in the U.S.

1



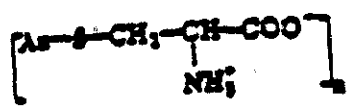
Gold sodium thiomalate
$Na_2[AuTM]$ (Myochrysin)

2



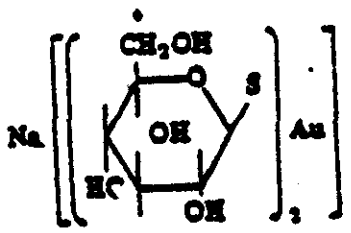
Gold thioglucose
AuTG (Solganol)

3



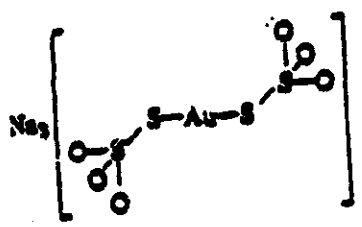
(L-Cysteinato) gold(I)
[AuSCy]

4



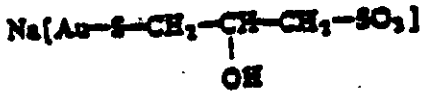
Gold sodium thioglucose
$Na[Au(TG)_2]$

5



Gold sodium thiosulfate
$Na_3[Au(S_2O_3)_2]$ (Sanochrysin)

6

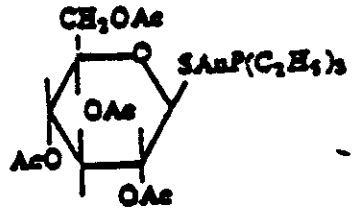


Gold sodium thiopropanolsulfonate
Na[AuTPS] (Allochrysine)

7 $ClAuP(C_2H_5)_3$

Chloro(triethylphosphine) gold(I)
Et_3PAuCl

8



S-2,3,4,5-Tetraacetyl-1-β-D-thioglucose
(triethylphosphine) gold(I)
$Et_3PAupATG$ (Auranofin)

Fig. 1. Gold(I) thiolates. Abbreviations used in this review are given below the chemical name. Trade names are in parentheses.

Ref: Inorganic Perspective in Biology and Medicine 2 (1979) 287-355 by C.F. Shaw III (see Vol. 1.481, article #62)

Remarks

1. On 10-22-1981 the group leader (Dr. J. Harter) was informed that this NDA contains both capsule and tablet dosage forms, and possibly based on HFD-100 memo dated 1-9-75 SKF should have submitted separate NDAs for these dosage form. Then, the group leader briefed Dr. Jerussi about this observation, and it was understood from the conversation that the Deputy Director will call SKF (Tel. con dated 10-21 and 22-1981).

2) NDA Vol. 1.1 Form 356H, table of contents
Vol. ? Item 12q cannot be located
1.10 Labeling, Item No. 4
1.11 Composition, Item No. 7
1.11 Components, Item No. 6
1.11 Mfg & Controls Item No. 8
1.11 Samples Item No. 9
1.481 E.I.A.R. Item #15
1.3, 1.22, 1.24 to 1.27 } ADME

3) Bio-review was requested on 10/26/81. These volumes have been shipped to Dr. Alice Lee by HFD-520. It was understood from the conversation (HFD-520 representative Dr. Viswanathan and HFD-150 representatives) during the meeting held in HFD-150 (11-4-81, 8:30 AM, in-house) that since there are still gross deficiencies for bio-studies, it would not be approved by Dr. Alice Lee. Therefore, further input from chemist was not necessary until SKF provides all data requested by HFD-520 during IND stages, in their NDA, and then, found to be acceptable (e.g., computer printout, etc.).

4) Methods (sections 8d, 8n and 9) are not suitable for requesting M.V., unless either corrected or suitable explanations are provided by SK&F.

Conclusions and/or Recommendations:

The NDA is not approvable under section 505 (b) (4) (5) and (6) of the Act.

The division should inform SK&F by telephone to correct chemistry-related deficiences as soon as possible because this drug has been classified as "1B" type. Many deficiencies can be corrected by SKF within 2-3 months, if SKF is notified promptly.

R. M. Patel Ph.D. 3/1/82
R. M. Patel, Ph.D.

cc:
Orig. NDA 18-689
HFD-150, HFD-102/Kumkumian
HFD-150/RPatel:11/12/81
HFD-150/DMoore
R/D endorsed by RHWood:11/17/81
F/T dog:2/25/82 2552W

RHWood 3/2/82

RPatel 4/3/82

FINISHED REVIEW kaf 7/26/82 DPM

Division of Oncology and Radiopharmaceutical Drug Products
Chemist's Review #2
Date Completed: June 26, 1982
Classification: 1E

pg 31
7-27-82
deg

NDA 18-689

Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

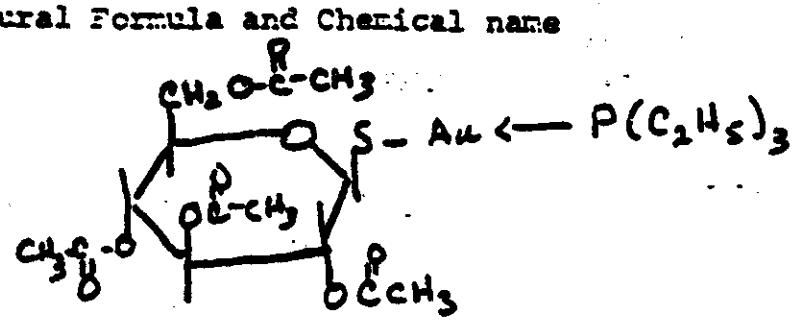
2 Product Names

Proprietary:	Ridaura
Non-proprietary	Auranofin
USAN	Auranofin
Code Number:	SKF-D-29162

3 Dosage Form and Route of Administration:
Oral, tablets and capsules

4 Pharmacological Category and/or Principal Indication.
Antirheumatic

5. Structural Formula and Chemical name



(2,3,4-6-Tetra-o-acetyl-1-thio- -D-Glucopyranosato-S) (Triethylphosphine) Gold

B.1 Initial Submission:

Dated: September 30, 1981
Received: October 5, 1981

2. Resubmission:

Dated: April 22, 1982
Received: April 22, 1982
Assigned: June 15, 1982

3. Supporting Documents: See Chemist's Review #1

4 Related Documents: See Chemist's Review #1

I. Remarks:

This submission dated April 22, 1982 represents a response to the reviewing chemist's questions pertaining to the New Drug Substance (NDS) communicated by telephone.

The requested information pertaining to this NDS was also submitted to the amendment on April 1, 1982.

On May 10, 1982 an FDA letter issued to the firm describing the complete chemical deficiencies conveyed to the firm by telephone on November 20, 1981.

Again note, this submission only addresses the NDS. Additional information as requested in the letter of May 10, 1982 has not been included. The following notes and comments refer to the attached copy of the deficiency letter and the firms responses.

Firm responded 6/22/82. RAW

NOTE 1.

Gold triethylphosphine chloride may be purchased commercially from:
Johnson Matthey
1401 King Road
Westchester, PA 19380

Alternately it may be manufactured by SMITHKLINE BECKMAN CORPORATION

The [redacted] has been amended to incorporate make or buy information for the gold triethyl phosphine chloride.

The manufacturing process is described as follows

$$HAuCl_4 \cdot 3H_2O + S(CH_2CH_2OH)_2 \xrightarrow[IPA]{N_2} [ClAuS(CH_2CH_2OH)_2]$$

Chloroauric acid; 2,2'-Thiodiethanol

$$[ClAuS(CH_2CH_2OH)_2 + P(C_2H_5)_3 \xrightarrow{IPA} (C_2H_5)_3P \cdot AuCl$$

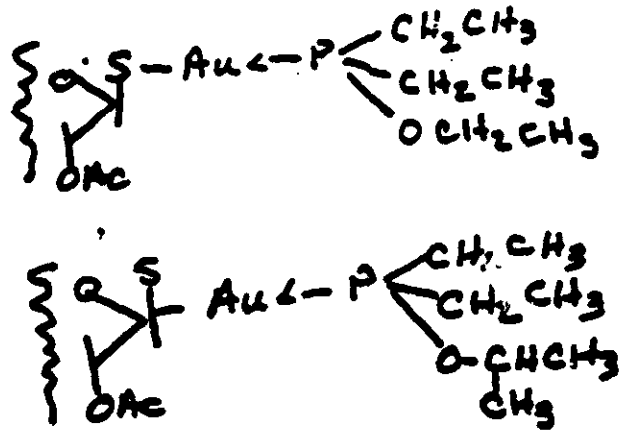
triethylphosphine; gold triethyl phosphine

An aqueous solution of chloroauric acid is reacted with a cooled solution of 2,2'-thidiethanol in iscpropyl alcohol, under nitrogen. Triethylphosphine in isopropyl alcohol is added with agitation. The resultant gold triethylphosphine chloride is collected, washed with water and dried.

A batch record has been included for lot XL 1 ACD, 16.2 kg. The manufacturing instructions and in process controls are described in complete detail Assay is by Atomic Absorption Method or a gravimetric method. Identification is by IR.

Comments:

1. The information presented is adequate to describe the manufacturing and in-process controls for this substance. However, since the batch record notes that TLC can enchance with less noble metals (see Manufacture of Auranofin) and TLC of Auranofin indicated the presence of Ethoxy and Isopropoxy products



The firm is requested to submit a quantitative impurities profile for this compound. (TLC)

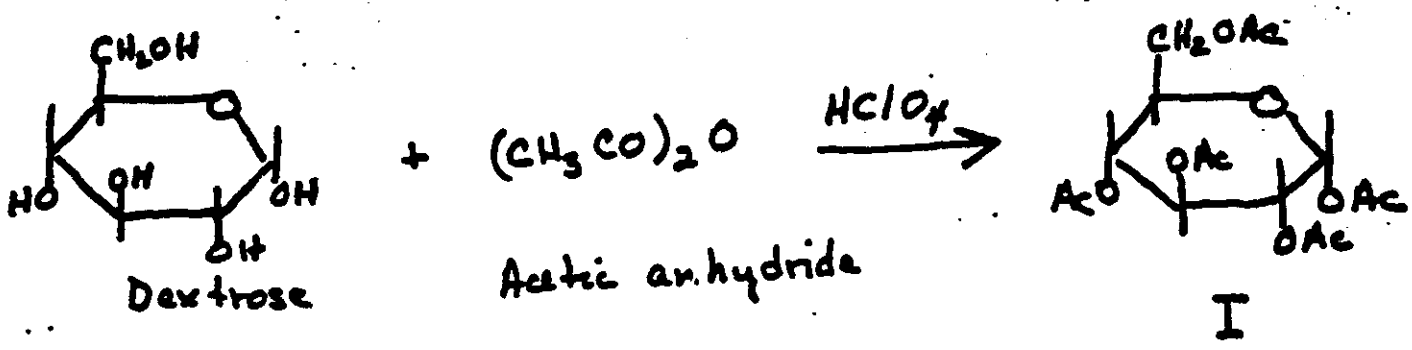
2. The firm indicates that this material is regarded as a raw material since it is commercially available, not as a key intermediate or a drug substance, and therefore there is no requirement that our supplier(s) have Drug Master File coverage for this item.

We will not debate this point with the firm if they provide impurities profiles and eventually an impurities specification and procedure to their gold triethylphosphine acceptance procedures.

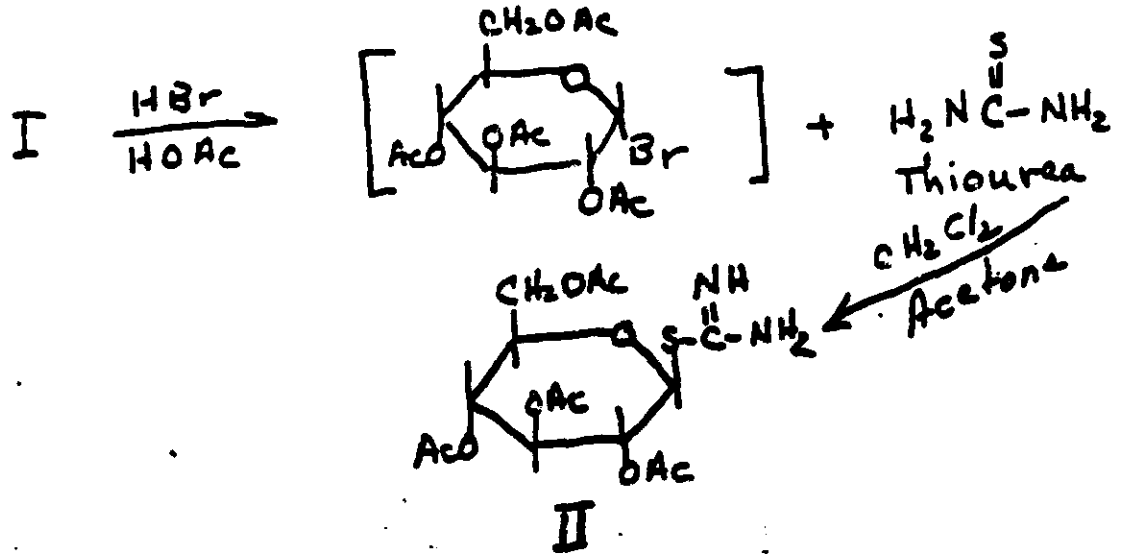
NOTE 2.

The firm has provided partial information in their resubmission to NDA 18-689 of April 22, 1982 or in their addendum to of April 1, 1982. on the manufacture and control of the auranofin processes. Batch records are included for each of the manufacturing operations. The reaction sequence is as follows:

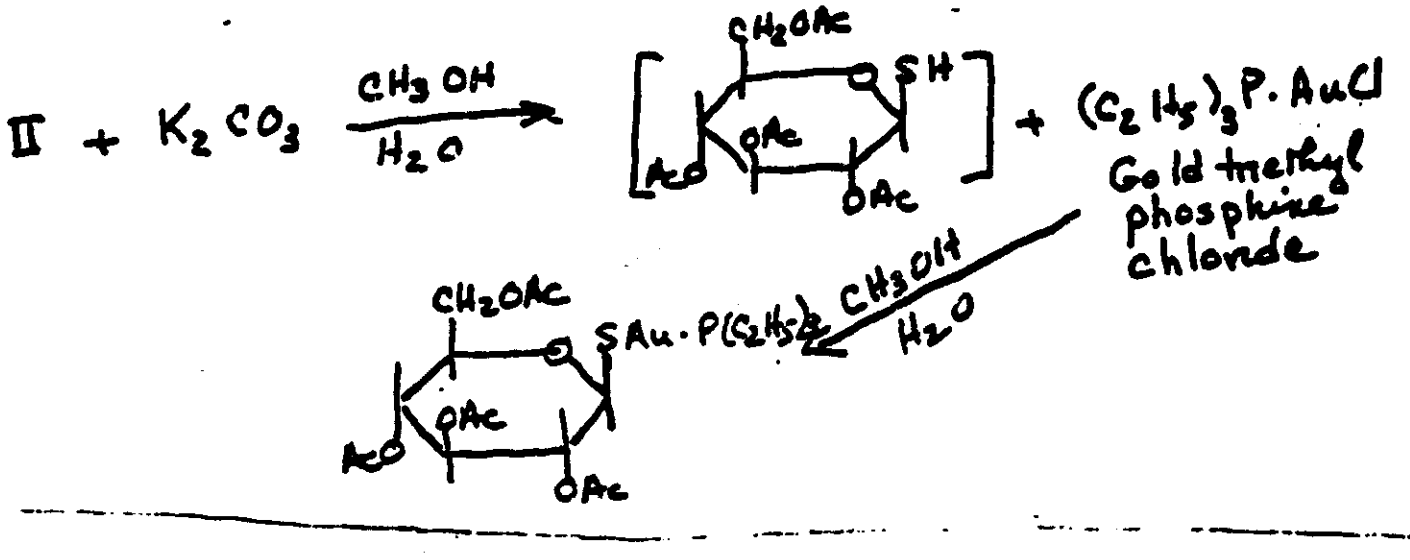
Step I - Preparation of D-Glucopyranose Pentaacetate (I)



Step II - Preparation of 2 3 4 6 Tetra-O-acetyl-beta-D-Glucopyranosyl Carbamidothioate Monohydrobromide (II)



Step III - Preparation of Auranofin (III)



An interesting reaction precaution appears in the pilot directions for the final reaction. (see also previous comments under gold triethyl phosphine).

"AURANOFIN contains GOLD, which could exchange with less noble metals. This is more likely to occur with the CHLORO(TRIETHYL PHOSPHINE) GOLD starting material, since this is essentially a complex of GOLD CHLORIDE with TRIETHYL PHOSPHINE. The extent of possible exchange has not been determined in either case

For this reason, contact of the reaction mixture and the product with any metal should be kept to a minimum. Glass lined reactors and plastic or teflon line equipment are recommended if possible."

Comment: It will be necessary for the firm to determine the metal exchange properties of these corponds and relate this information to all subsequent manufacturing oerations involving AURANOFIN

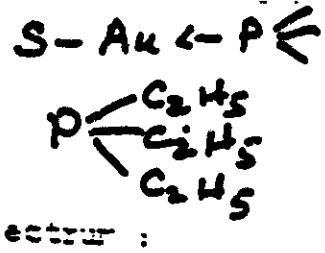
Item 8.

Information has been provided for the reference standard. The firm indicates that a portion of a batch of auranofin prepared by the commercial process which assayed 99+% purity was selected as Reference Standard Code SF-330, and completely characterized. Analytical data were submitted to the DMF as follows:

a) Name, Molecular formula, Molecular weight.
b) Description
c) IR
d) NMR - proton
e) Optical Rotation
f) Mass Spectrum
g) Elemental analysis
h) Melting point
i) Loss on drying
j) TLC
k) HPLC

Comments:

1. IR assignments were included for acetate groups but not



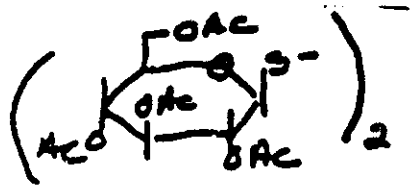
2. The mass spectrum :
   a) charged with the probe temperature which indicated a slow thermal decomposition
   b) provided no fragments for sulfur containing groups
   c) included an additioanal designation X20 which was not explained

3. Elemental analysis was not included for sulfur or oxygen

4. The TLC procedure using detection with Iodine vapor (but not with UV at 254 nm) noted the following quantities of materials.

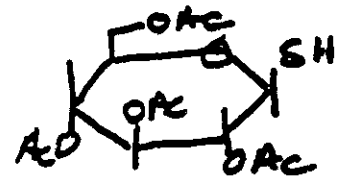
Rf	Amount	Substance
0.00	very small	Inorganic gold
0.02	trace	
0.06	trace	Various deacetylated products
0.09	trace	Not specifically identified
0.17	trace	
0.18	—— not given	Cl–Au<–P(CH2CH3)3 SKF 36914

0.27 —— not given



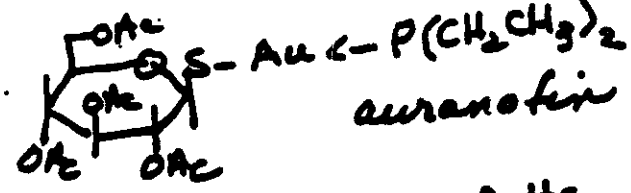
disulfide

0.35 —— not given



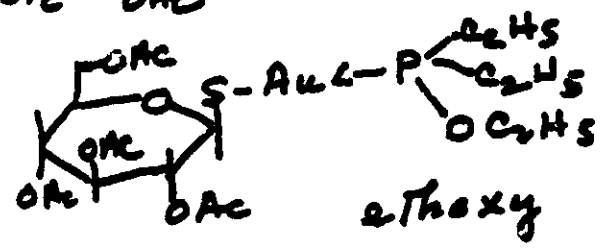
Thiol

0.40 major



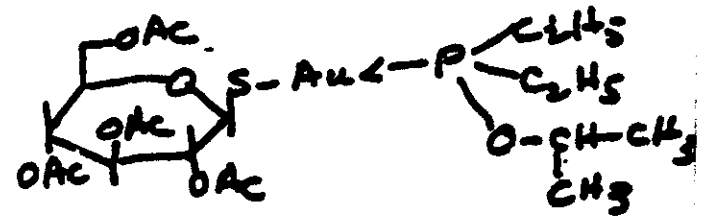
auranofin

0.49 trace



ethoxy

0.52 trace



isopropoxy.

The TLC procedure is referred to Figure 4 which is a comparison of lot BP-330 with various commercial lots. Note: The ethoxy , isopropoxy compounds and elemental gold are detected in all lots.

It will be necessary for the firm to include a quantitative impurities profile for the reference standard and for a typical commercial lot

5. Thermal Behavior of the compound is to be provided, i.e.
   a) Differential Scanning Calorimetry (DSC)
   b) Thermal Gravimetric Analysis (TGA)

NOTE 4.

The firm has provided data, as requested for intermediates in the synthesis. Note their response to the questions concerning alpha and beta isomers of D-glucopyranose pentacetate:
   a) with hydrogen bromide in glacial acetic acid: always results only in the formation of the alpha anomer of tetra-O-acetyl alph-D-glycopyrancsyl bromide which is the more thermodynamically stable isomer (1)
   b) the subsequent reaction with thiourea is likewise specific to yield the beta-anomer of compound II (2)

(1) Methods in Carbohydrate Chemistry - Whistler and Wolfram (Volume II (55), page 221, 1963)

(2) Methods in Carbohydrate Chemistry - Whistler and Wolfram (Volume II (108), page 433, 1963)

NOTE 5.

The firm has not addressed the questions relating to the bulk drug substance.

Comments:

1. The firm is to provide information, as previously requested on the bulk drug substance.

2. Additionaly melting point determinations and impurities tests are to be added. and the firm is to clarify the rationale for controling particle size.

An additional Comment:

It is to be suggested to the firm that they compile an Analytical Profile for the Drug Substance (akin to those published by Florey) for inclusion in their drug master file. This would include data compiled for the NDA; published information (e.g. crystal structure) ; Solubility information (particularly for those solvents used in synthesis and analytical procedures) ; Stability information; ...

D. Conclusion and Recommendations:

It is recommended that a letter issue to the applicant reaffirming the unanswered issues raised in the FDA letter of May 10, 1982 and noting the additional points covered in Remarks.

Mary Ann Jarski
Chemist, HFD-150

RAtwood 7/16/82
7/12/82

RaJenssen 7/26/82

cc:
Orig. NDA 18-689
HFD-150
HFD-150/MAJARSKI:6/26/82
HFD-150/CSO/DMOORE

FINISHED REVIEW Rajan 1/11/83

OPMOR

Division of Oncology and
Radiopharmaceutical Drug Products
Chemist's Review #3
Date Completed: December 9, 1982
Classification: 1B

A. 1. NDA 18-689

Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

2. Product Names:

Proprietary: Ridaura
Non-proprietary: Auranofin
USAN: Auranofin
Code Number: SK&F D-39162

3. Dosage Form and Route of Administration:

Capsules: 3 mg. and 6 mg.

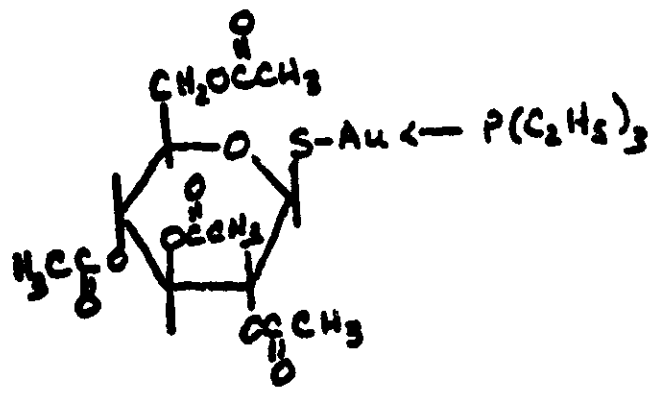
Tablets: 1 mg., 3 mg. and 6 mg.

Oral, Rx

4. Pharmacological Category and/or Principal Indication:

Antirheumatic
(Disease Modifying Antirheumatic
Drug - DMARD)

5. Structural Formula and Chemical Name(s):



(1) Gold, (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)-(triethylphosphine).

(2) (1-Thio- -D-glucopyranosato)-(triethylphosphine)gold 2,3,4,6-tetraacetate

Molecular Formula: C H AuO SP

Molecular Weight: 678.488

B 1. **Initial Submission:** September 30, 1981
Received: October 5, 1981

2. **Resubmissions:**

Dated:	April 21, 1982	
Received:	April 22, 1982	Package insert
Dated:	April 22, 1982	
Received:	April 22, 1982	Relating to NDS
Assigned:	June 15, 1982	
Dated:	June 22, 1982	
Received:	June 24, 1982	Manufacturing and Control information
Received by Chemist:		
Dated:	October 19, 1982	
Received:	October 29, 1982	Relating to NDS
Received by Chemist:	November 8, 1982	

3. **Supporting Documents:** See Chemist's Reviews #1 & #2 and Notes

4. **Related Documents:** See Chemist's Reviews #1 & #2 and Notes

C. Remarks:

The applicant chose to answer deficiencies in manufacturing and controls information noted in Chemist's Review #1 in two parts, i.e.
Those relating to synthesis were answered 4-22-82. These were reviewed on 6-26-82 - and the additional deficiencies were conveyed to the applicant by Dr. R.H. Wood, Supervisory Chemist, HFD-150. They were answered in a submission dated October 19, 198[illegible]

Those relating to other manufacturing and control deficiencies were answered in a submission dated June 22, 1982.

After reviewing current submissions to the application - as well as previously submitted material, the application remains deficient and/or ambiguous in major areas.

1. Formulations:
   a) The application proposes 5 dosage forms: 1, 3, 6 mg. tan colored, film coated, tablets and 3 and 6 mg. hard shell gelatin capsules.

      Note: Only the 3.0 mg. core formulation was used in clinical trials. However, 0.34 mg. and 1.0 mg. formulations used in trials are essentially equivalent to the 3.0 mg. cores.

      1.0 and 3.0 mg. capsules were of different formulations than proposed in the NDA.

   b) The applicant proposes to initially market a 3 mg. capsule.

   c) It is unclear why the applicant has chosen to color their tablets with iron oxide (cosmetic ochre) when manufacturing instructions and current literature cite metal exchange as a possibility for Gold(I) compounds.

2. Synthesis information is deficient as follows:
   a) molar quantities have not been cited.
   b) yields have not been given.
   c) the firm proposes to buy gold triethylphosphine chloride-used in the last step of the synthesis reaction - but does not consider synthesis at other sources as necessary to the application.

3. Proof of structure is deficient. The basic information relied on for proof of structure is NMR. (Mass Spec reveals no sulfur fragments, Au-S vibration frequencies are not identified in IR and X-ray crystallographic data has not been submitted (though requested)) However, NMR interpretations are not consistent between submissions nor are they consistent with data for the intermediate, 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl carbamimidothioate monobromide.

4. Impurities/Degradates:
The applicant does not see a problem with impurities or degradates. and HPLC procedures used for control do not identify them any. However, TLC pictorials all show 'impurities/degradation' profiles and hypothetical materials have been identified by the applicant (without proof).

5. Stability of the NDS:
The only instabilities noted are those formed on exposure to light or in basic solution — (They are not identified except for $(C_2H_5)_3-P=S$ (unproved)) .. and These have been dismissed as of academic interest only - or as controllable.

6. Controls for the NDS and dosage forms are inadequate or not described in sufficient detail to permit duplication in our laboratories.

7. Packaging configurations are cited which are not included in the HOW SUPPLIED Section of the package insert and for which no stability data has been submitted.

D. Recommendations/Conclusions:

1. The application is inadequate under 505(b)(2)(3) and (4) of the Act

See Chemist's Review Notes and "Draft of Chemistry Part, Letter to the Applicant."

2. The Division is to consider the appropriateness of dosage forms in the application which have no basis in IND submissions or which the applicant does not currently plan to market/manufacture

3. The CSO is to be aware that final container labels should correlate with those in the HOW SUPPLIED Section of the Package Insert

cc: Orig NDA
HFN-150
HFN-100/Tomek
HFN-150/Moore

R.A. Wood
12/10/82

Mary Ann Jarski
Chemist HFD-150
12/9/82

R.A. Jenner
1/11/83

FINISHED REVIEW
RA Jenkins 5/24/83

Division of Oncology and Radiopharmaceutical Drug Products
Chemist's Review: # 4
Date Completed: May 6, 1983
Classification: 1B

DPM
pg 56
PJ 5/24/83
dlg

A 1 NDA 18-689

Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

2. Product Names:

Proprietary: Ridaura
Non-proprietary: Auranofin
USAN: Auranofin
Code Number: SK+F D-39162

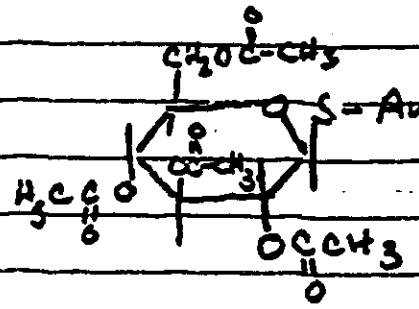
3. Dosage Form and Route of Administration:

Capsules: 3 and 6 mg. Rx
Tablets: 1, 3 and 6 mg. Rx

4. Pharmacological Category and/or Principal Indication:

Anti-rheumatic
(Disease Modifying Anti-rheumatic Drug - DMARD)

5. Structural Formula and Chemical Name(s):



$C_{20}H_{34}AuO_9SP$
M.W: 678.488

(1) Gold, (2,3,4,6-tetra-O-acetyl-1-Thio-β-D-glucopyranosato-S)(triethylphosphine)

(2) (1-Thio-β-D-glucopyranosato)-(triethylphosphine)gold 2,3,4,6-tetraacetate.

B. 1. Initial Submission: 9-30-81

2. Resubmissions / Amendments: See prior chemist's reviews and
Dated: April 13, 1983
Received BD: April 13, 1983
Received by Chemist: Apnl 13, 1983

3. Supporting Documents: See prior chemists reviews

4. Related Documents: See prior chemists reviews and.

a) Tetrahedron Letters, Vol. 23 No. 32, pp 3245-3248, 198
Synthesis of Chloro (Diethylalkoxyphosphine) Gold (I) Salts and their subsequent conversion to S-Diethylalkoxyphosphine Gold 2,3,4,6-Tetra-O-Acetyl-1-Thio-β-D-Glucopyranosides. - F. Ouwrigh et al.

b) ACS Symposium Series # 209, American Chemical Society 1983, Ligand Exchange Reactions of Gold Drugs in Model Systems and in Red Cells - M. Tahir Razi, et. al.

(Facsimilies contained in Attachment J. of 4-13-83 submission)

NDA 3-689 Page 3

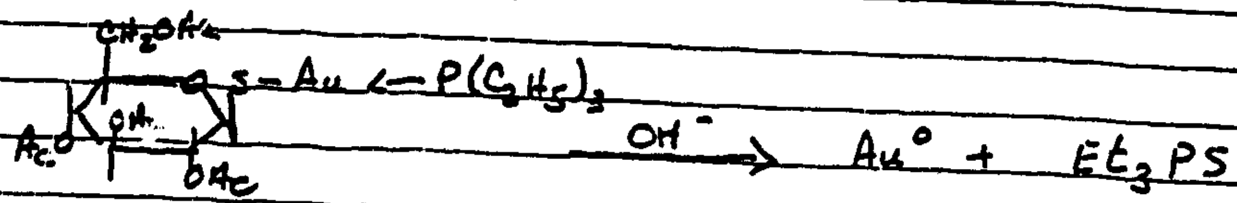
Remarks:

Pending methods validation and a satisfactory inspection report, the manufacturing and controls portion of the application is basically adequate.

However, there are some issues relating to the 'Chemistry' of auranofin that require clarification. These are mainly:

- The existance of two polymorphs, A and B as noted in ACS Symposium Series # 209, 1983 paper pages 376 and 378

- The proposed degradation of auranofin particularly in basic solution, i.e



See chemist's review notes (pg. 3+4)

Additional deficiencies relate to controls applied to auranofin and stability protocols; stability commitments; proposed expiration dating. See chemist's review notes

Insert

Conclusions and/or Recommendations:

The application is inadequate under 505(b)(4) of the Act.
See Chemist's Review Notes and draft of Chemist's letter to the Applicant.

Also, refer to Recommendations/conclusions 2., 3. in Chemist's Review #3.

Mary Ann Jarski
Chemist, HFN-150

Orig NDA 18-689
HFD-150 / M. Jarski
HFN-150 CSO / Mock

Errors & deficiencies as [illegible]
5/15/83 = [illegible]

PH Wood 5/18/83

APR 5 - 1984

Chemist's Review

Divisions Name: DORDP
Chemist's Review: 5
Date Completed: 12/13/83

A. 1. NDA 18-689
Applicant: Smith, Kline and French Laboratories
Address: Philadelphia, PA 19101

2. Product Name(s):

Proprietary: Ridaura
Non proprietary (generic): Auranofin
Code name and/or number: SKF D 39162

3. Dosage Forms(s), potencies and Route(s) of Administration:

Rx: 3 and 6 mo capsules, 1, 3, and 6 mo tablets oral

4. Pharmacological Category and/or Principal Indication:

Anti-rheumatic

B. Amendments: Resubmission 10/12/83; received HFN-150, 10/13/83; reassigned to this reviewing chemist 10/19/83; received from CSO 10/31/83.

C. This NDA was originally submitted 9/30/81 and the first chemists review (4/12/81) considered it not approvable. Subsequent chemist's review (6/26/82, 12/9/82, 5/6/83) found substantial deficiencies. A non-approval letter was issued 2/28/83. The current submission was orginally classified as an amendment and then reclassified as WD/RS 10/19/83. This is a 1 B drug and per memo from the supervisory chemist, the review should be given priority.

A methods validation report was received 11/16/83, but details from the two district labs containing specific comments were not included.

D. A non-approvable letter should be sent to the applicant containing the material contained in the draft chemist's part.

John C Leak

John C. Leak, Ph.D.
Chemist

cc: Orig NDA 18-689
HFN-150/Div File
HFN-150/JCLeak
HFN-150/Pease
R/D endorsed by: RHWood/12/15/84
F/T by P. Amoss and S. Hill/2/23/84
Wang #1394P

RHWood 2/28/84

RA Dennis 3/26/84

NDA 18-689

MAR 19 [illegible]

Division Name: DORDP
Chemist's Review: 6
Date Completed: 2/12/85

A. 1. NDA 18-689
Applicant: Smith, Kline and French Laboratories
Address: Philadelphia, PA, 19101

2. Product Name(s):

Proprietary: Ridaura
Non proprietary (generic): Auranofin
Code name and/or number: SKF D 39162

3. Dosage Forms(s), potencies and Route(s) of Administration:

Rx: 3 and 6 mg. capsules, i, 3, and 6 mg. tablets oral

4. Pharmacological Category and/or Principal Indication:

Anti-rheumatic

B. Amendments: Resubmission 10/12/83; received HFN-150 10/13/83; reassigned to this reviewing chemist 10/19/83; received from CSO 10/31/83.
Resubmission 6/6/84; Received Bureau 6/6/84; received 11/19/84 by chemist.

C. Remarks:

The applicant amended their New Drug application on 6/6/84 with additional information on manufacturing and controls as requested on March 27, 1984. This information was reviewed and found to comply; however, an additional correction to the raw materials controls should be made via telecon (see "Draft"). Methods Validation from District Laboratories were found suitable for regulatory purposes (see memo 11/10/83 from HFO-620). Establishment Inspection Report from the Office of Compliance for EIR of 5/6/83 is still pending; however, celecon with Compliance indicated the firm is approved. (see memo of telecon dated 2/11/85).

D. Conclusion and/or Recommendations:

From a manufacturing and controls standpoint, the NDA is approvable pending FPL. The firm should be notified by telecon of additional revisions in the controls which should be made (see "Draft").

Ernest G. Pappas 3/13/85
Ernest G. Pappas

Orig. NDA 18-689
HFN-102
HFN-150/Div File
HFN-150/CSO Please
HFN-140/EPappas
R/D endorsed by:RHWood 2-21-85
F/T by SA 3-6-85 ;rev.by dwp 3-12-85

RHWood 3/13/85
Wang # 0226B

R.A. Jewett 3/18/85

MAR 1 . 1 ::

Division of Oncology and Radiopharmaceutical Drug Products

Chemist's Review #7

A. 1. NDA 18-689

Applicant: Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

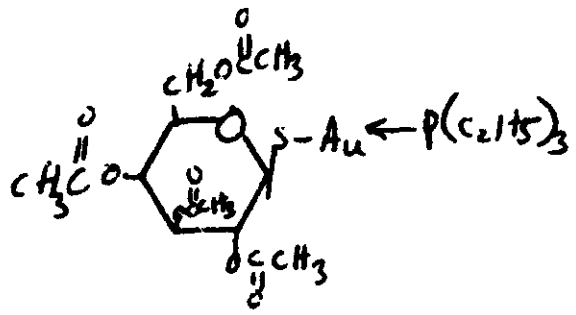
2. Product Name(s)

Proprietary: Ridaura
Non-proprietary: auranofin
USAN: auranofin
Compendium: N/A

3. Dosage Form and Route of Administration: Oral, Tablets

4. Pharmacological Category: Antirheumatic

5. Structural Formula and Chemical Name(s):



(1) Gold, (2,3,4,6-tetra-O-acetyl-1-thio-B-D-glucopyranosato-S) (triethylphosphine)-;

(2) (1-Thio-B-D-glucopyranosato) (Triethylphosphine) gold 2,3,4,6-tetraacetate.

B. 2. Amendment: 3/1/85
2/28/85 (Received)

C. Remarks:

The applicant submitted the controls information on 3/1/85 as was requested by telephone on 2/22 & 26/85. The information as submitted is found acceptable and concluded the remaining dificiencies with the exception of one (1) request. This request involves a limit specification for aranofin "B" which the applicant refused to include in the specifications. A meeting on 2/28/85 appeared to resolve the differences (see Memo 3/3/85). However, as for Telecon on 3/1/85, this request remains not resolved.

(Refer to Chemist Review Notes for additional controls information).

D Conclusion and/or Recommendations:

From a manufacturing and controls standpoint, approval of the controls information will depend on whether the firm will include the remaining information as stated above or whether the applicant can convince the Division and Agency that this request is not needed.

Chemist Review #6 dated 2/12/85 indicated the application is approvable pending the applicant's correction of the controls deficiencies which still remain. Since the deficiencies have not totally been corrected, approval of the controls portion of the NDA will not be allowed at this time.

Ernest G. Pappas 3/13/85

Ernest G. Pappas
3/4/85

cc: Orig NDA 18-689
HFN 150/Div File
HFN-140/Pappas
HFN-150/Peaga
R/D endorsed by: REWood/3/6/85
F/T by P. Amoss/3/12/85
Wang #0262B

REWood 3/13/85 RA Jenssi 3/19/85

Please

Division of Oncology and Radiopharmaceutical Drug Products

Chemist's Review #8

A. 1. NDA 18-689

ADD 7 2 [illegible]

Applicant: Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

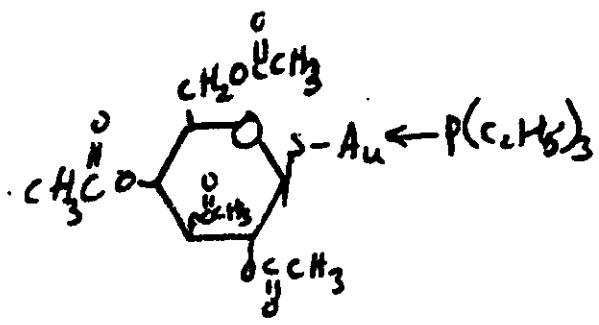
2. Product Name(s):

Proprietary: Ridaura
Non-proprietary: auranofin
USAN: auranofin
Compendium: N/A

3. Dosage Form and Route of Administration: Oral, Tablets

4. Pharmacological Category: Antirheumatic

5. Structural Formula and Chemical Name(s):



(1) Gold, (2,3,4,6-tetra-O-acetyl-1-thio-B-D-glucopyranosato-S) (triethylphosphine)-;

(2) (1-Thio-B-D-glucopyranosato) (Triethylophosphine) gold 2,3,4,6-tetraacetate.

B. 2. Amendments: 3/26/85, 3/29/85 and 4/2/85

3. Supporting IND, NDA, MF, and Letters of Authorization:

4. Related Documents (IND's, NDA's, etc.).

C. Remarks:

Chemist review dated 3/19/85 indicated that the controls remain deficient since the applicant did not totally correct the controls deficiencies as stipulated in chemist review 2/12/85. In this regard, the applicant met with FDA on 3/19/85 to discuss the remaining deficiency which would be tantamount to an approvable action from a controls standpoint if the issue could be resolved (see memo of 3/19/85). The issue that was discussed during (continued on page 3).

D. Conclusions and/or Recommendations:

The applicant has satisfied our request of 3/19/85. The manufacturing and controls are fully met. An approvable letter should issue from a manufacturing and controls standpoint.

Ernest G. Pappas 4/5/85
Ernest G. Pappas
4/3/85

cc: Orig NDA 18-689
HFN-150/Div File
HFN-150/Pease
HFN-140/Pappas
R/D endorsed by: RHWood/4/4/85
F/T by P. Amoss/4/4/85
Wang #0614B

RHWood 4/5/85

R.A. Jewett 4/18/85

FINISHED REVIEW 6/26/82 AUG 2 - 1982

Division of Oncology and Radiopharmaceutical Drug Products
Chemist's Review #2
Date Completed: June 26, 1982
Classification: 1E

pg 31
7-27-82
deg

NDA 18-689

Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

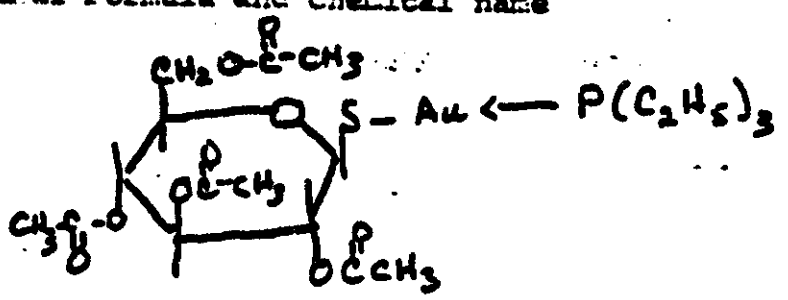
2 Product Names

Proprietary: Ridaura
Non-proprietary Auranofin
USAN: Auranofin
Code Number: SKF-D-29162

3 Dosage Form and Route of Administration:
Oral, tablets and Capsules

4 Pharmacological Category and/or Principal Indication.
Antirheumatic

5. Structural Formula and Chemical name



(2,3,4-6-Tetra-o-acetyl-1-thio- -D-Glucopyranosato-S)(Triethylphosphine) Gold

B.1 Initial Submission

Dated: September 30, 1981
Received: October 5, 1981

2. Resubmission:

Dated: April 22, 1982
Received: April 22, 1982
Assigned: June 15, 1982

3. Supporting Documents: See Chemist's Review #1

4 Related Documents: See Chemist's Review #1

150 FILE

FINISHED REVIEW Ira Jennie 1/11/83

JAN 13 1983

Division of Oncology and
Radiopharmaceutical Drug Products
Chemist's Review #3
Date Completed: December 9, 1982
Classification: 1B

A. 1. NDA 18-689

Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

2. Product Names:

Proprietary: Ridaura
Non-proprietary: Auranofin
USAN: Auranofin
Code Number: SK&F D-39162

3. Dosage Form and Route of Administration:

Capsules: 3 mg. and 6 mg.

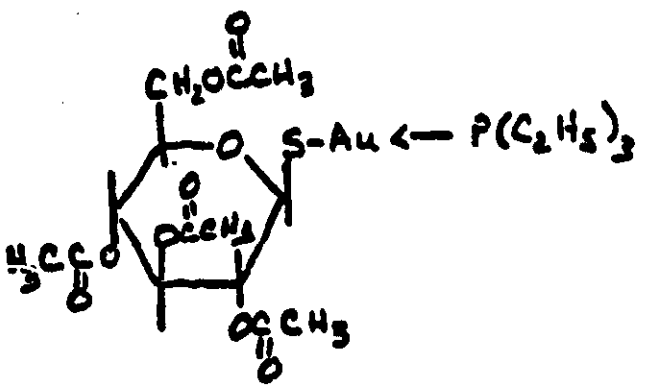
Tablets: 1 mg., 3 mg. and 6 mg.

Oral, Rx

4. Pharmacological Category and/or Principal Indication:

Antirheumatic
(Disease Modifying Antirheumatic Drug - DMARD)

5. Structural Formula and Chemical Name(s):



(1) Gold, (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)-(triethylphosphine).

(2) (1-Thio- -D-glucopyranosato)-(triethylphosphine)gold 2,3,4,6-tetraacetate

Molecular Formula: C H AuO SP

Molecular Weight: 678.488

B 1. Initial Submission: September 30, 1981
Received: October 5, 1981

2. Resubmissions:

Dated:	April 21, 1982	
Received:	April 22, 1982	Package insert
Dated:	April 22, 1982	
Received:	April 22, 1982	Relating to NDS
Assigned:	June 15, 1982	
Dated:	June 22, 1982	
Received:	June 24, 1982	Manufacturing and Control information
Received by Chemist:		
Dated:	October 19, 1982	
Received:	October 29, 1982	Relating to NDS
Received by Chemist:	November 8, 1982	

3. Supporting Documents: See Chemist's Reviews #1 & #2 and [redacted]

4. Related Documents: See Chemist's Reviews #1 & #2 and [redacted]

C. Remarks:

The applicant chose to answer deficiencies in manufacturing and controls information noted in Chemist's Review #1 in two parts, i.e.
Those relating to synthesis were answered 4-22-82. These were reviewed on 6-26-82 - and the additional deficiencies were conveyed to the applicant by Dr. R.H. Wood, Supervisory Chemist, HFD-150. They were answered in a submission dated October 19, 19:

Those relating to other manufacturing and control deficiencies were answered in a submission dated June 22, 1982.

After reviewing current submissions to the application - as well as previously submitted material, the application remains deficient and/or ambiguous in major areas.

1. Formulations:
   a) The application proposes 5 dosage forms: 1, 3, 6 mg. ta: colored, film coated, tablets and 3 and 6 mg. hard shell gelatin capsules.

      Note: Only the 3.0 mg. [redacted] formulation was used in clinical trials. However, 0.34 mg. and 1.0 mg. formulations used in trials are essentially equivalent to the 3.0 mg. [redacted]

      1.0 and 3.0 mg. capsules were of different formulations than proposed in the NDA.

   b) The applicant proposes to initially market a 3 mg. capsule.

   c) It is unclear why the applicant has chosen to color their tablets with [redacted] when manufacturing instructions and current literature cite metal exchange as a possibility for Gold(I) compounds.

2. Synthesis information is deficient as follows:
   a) molar quantities have not been cited.
   b) yields have not been given.
   c) the firm proposes to buy [redacted] used in the last step of the synthesis reaction - but does not consider synthesis at [redacted] necessary to the application.

3. Proof of structure is deficient. The basic information relied on for proof of structure is NMR. (Mass Spec reveals no sulfur fragments, Au-S vibration frequencies are not identified in IR and X-ray crystallographic data has not been submitted (though requested)) However, NMR interpretations are not consistent between submissions nor are they consistent with data for the intermediate, 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl carbamimidothioate monobromide.

4. Impurities/Degradates:
The applicant does not see a problem with impurities or degradates. and HPLC procedures used for control do not identify them any. However, TLC pictorials all show 'impurities/degradation' profiles and hypothetical materials have been identified by the applicant (without proof).

5. Stability of the NDS:
The only instabilities noted are those formed on exposure to light or in basic solution - (They are not identified except for $(C_2H_5)_3$-P=S (unproved)) - and these have been dismissed as of academic interest only - or as controllable.

6. Controls for the NDS and dosage form(s) are inadequate or not described in sufficient detail to permit duplication in our laboratories.

7. Packaging configurations are cited which are not included in the HOW SUPPLIED Section of the package insert and for which no stability data has been submitted.

D. Recommendations/Conclusions:

1. The application is inadequate under 505(b)(2)(3) and (4) of the Act

See Chemists Review Notes and "Draft of Chemists Part, Letter to the Applicant."

2. The Division is to consider the appropriateness of dosage forms in this application which have no basis in IND submissions or which the applicant does not currently plan to market/manufacture

3. The CSO is to be aware that final container labels should correlate with those in the HOW SUPPLIED Section of the Package Insert

cc: Orig NDA
HFD-150
HFN-150/Jarosz
HFN-150/Morris

RAWood
12/10/82

Mary Ann Jarski
Chemist, HFD-150
12/9/82

R.A. Jenner
1/11/83

N 5 - 196

Chemist's Review

Divisions Name: DORDP
Chemist's Review: 5
Date Completed: 12/13/83

A. 1. NDA 18-689
Applicant: Smith, Kline and French Laboratories
Address: Philadelphia, PA 19101

2. Product Name(s):

Proprietary: Ridaura
Non proprietary (generic): Auranofin
Code name and/or number: SKF D 39162

3. Dosage Forms(s), potencies and Route(s) of Administration:

Rx: 3 and 6 mg capsules, 1, 3, and 6 mg tablets oral

4. Pharmacological Category and/or Principal Indication:

Anti-rheumatic

B. Amendments: Resubmission 10/12/83; received HFN-150, 10/13/83; reassigned to this reviewing chemist 10/19/83; received from CSO 10/31/83.

C. This NDA was originally submitted 9/30/81 and the first chemists review (4/12/81) considered it not approvable. Subsequent chemist's review (6/26/82, 12/9/82, 5/6/83) found substantial deficiencies. A non-approval letter was issued 2/28/83. The current submission was orginally classified as an amendment and then reclassified as WD/RS 10/19/83. This is a 1 B drug and per memo from the supervisory chemist, the review should be given priority.

A methods validation report was received 11/16/83, but details from the two district labs containing specific comments were not included.

D. A non-approvable letter should be sent to the applicant containing the material contained in the draft chemist's part.

John C Leak

John C. Leak, Ph.D.
Chemist

cc: Orig NDA 18-689
HFN-150/Div File
HFN-150/JCLeak
HFN-150/Pease
R/D endorsed by: RHWood/12/15/84
F/T by P. Amoss and S. Hill/2/23/84
Wang #1394P

RHWood 2/28/84

RA Jewin 3/2/84

· FINISHED REVIEW
RA Jennis 5/24/83

Division of Oncology and
Radiopharmaceutical Drug Products
Chemists Review: # 4
Date Completed: May 6, 1983
Classification: 1B

5/24

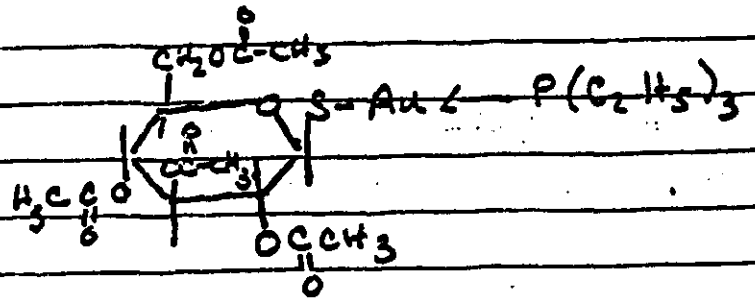
A. 1 NDA 18-689
Applicant: Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, PA 19101

2. Product Names:
Proprietary: Ridaura
Non-proprietary:
· USAN: Auranofin
Code Number: SK+F D-39162

3. Dosage Form and Route of Administration:
Capsules: 3 and 6 mg. R
Tablets: 1, 3 and 6 mg. R

4. Pharmacological Category and/or Principal Indication:
Anti-rheumatic
(Disease Modifying Anti-rheumatic Drug - DMARD)

5. Structural Formula and Chemical Name(s):



$C_{20}H_{34}AuO_9SP$
M.W: 678.488

(1) Gold, (2,3,4,6-tetra-O-acetyl-1-Thio-β-D-glucopyranosato-S)(triethylphosphine)

(2) (1-Thio-β-D-glucopyranosato)-(triethylphosphine)gold 2,3,4,6-tetraacetate.

B. 1. Initial Submission: 9-30-81

2. Resubmissions / Amendments: See prior chemist's review and

Dated: April 13, 1983
Received BD: April 13, 1983
Received by Chemist: April 13, 1983

3 Supporting Documents: See prior chemists review

4. Related Documents: See prior chemists review and .

a) Synthesis of Salts and Their subsequent conversion to S-Diethylalkoxyphosphine Gold 2,3,4,6-Tetra-O-Acetyl-1-Thio-β-D-Glucopyranosides. - F. Ouiroga et al.

b) ACS Symposium Series # 209, American Chemical Society 1983, Ligand Exchange Reactions of Gold Drugs in Model Systems and in Red Cells - M. Tahir Razi, et. al.

(Facsimiles contained in Attachment J. of 4-13-83 submission)

NDA 18-689 Page 3.

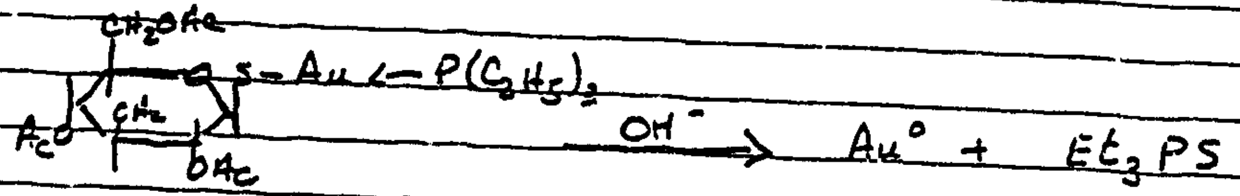
Remarks:

Pending methods validation and a satisfactory inspection report, the manufacturing and controls portion of the application is basically adequate.

However, there are some issues relating to the 'Chemistry of auranofin that require clarification. These are mainly:

- The existance of
  noted in ACS Symposium Series # 209, 1983 paper pages 376 and 378

- The proposed degradation of auranofin particular in basic solution, i.e



See chemist's review notes (pg. 3 + 4)

Additional deficiencies relate to controls applied to auranofin and stability protocols; stability commitments; proposed expiration dating. See chemist's review notes

Insert

Conclusions and/or Recommendations:

The application is inadequate under 505(b)(4) of the Act.

ent.

Also, refer to Recommendations/Conclusions 2., 3. In Chemist's Review # 3.

cc:
Orig NDA 18-689
HFN-150
HFN-150/MAJork
HFN-150/CSO/DMcCORE

[illegible] to deficiencies as outlined in [illegible] 5/16/83 ← Fr. R.U. [illegible] 5/24/83 RKWood 5/18/83

Mary Ann Jurski
Chemist, HFN-150

MAR 1 [illegible]

NDA 18-689

Division Name: DORDP
Chemist's Review: 6
Date Completed: 2/12/85

A. 1. NDA 18-689
Applicant: Smith, Kline and French Laboratories
Address: Philadelphia, PA, 19101

2. Product Name(s):

Proprietary: Ridaura
Non proprietary (generic): Auranofin
Code name and/or number: SKF D 39162

3. Dosage Forms(s), potencies and Route(s) of Administration:

Rx: 3 and 6 mg. capsules, i, 3, and 6 mg. tablets oral

4. Pharmacological Category and/or Principal Indication:

Anti-rheumatic

B. Amendments: Resubmission 10/12/83; received HFN-150 10/13/83; reassigned to this reviewing chemist 10/19/83; received from CSO 10/31/83.
Resubmission 6/6/84; Received Bureau 6/6/84; received 11/19/84 by chemist.

C. Remarks:

The applicant amended their New Drug application on 6/6/84 with additional information on manufacturing and controls as requested on March 27, 1984. This information was reviewed and found to comply; however, an additional correction to the raw materials controls should be made via telecon (see "Draft"). Methods Validation from District Laboratories were found suitable for regulatory purposes (see memo 11/10/83 from HFO-620).Establishment Inspection Report from the Office of Compliance for EIR of 5/6/83 is still pending; however, telecon with Compliance indicated the firm is approved. (see memo of telecon dated 2/11/85).

D. Conclusion and/or Recommendations:

From a manufacturing and controls standpoint, the NDA is approvable pending FPL. The firm should be notified by telecon of additional revisions in the controls which should be made (see "Draft").

Ernest G. Pappas 3/13/85
Ernest G. Pappas

Orig. NDA 18-689
HFN-102
HFN-150/Div File
HFN-150/CSO
HFN-140/EPappas
R/D endorsed by:RHWood 2-21-85
F/T by SA 3-6-85 ;rev.by dwp 3-12-85

RHWood 3/13/85
Wang # 0226B

R.A. Jenssi 3/18/85

MAR 19 1985

Division of Oncology and Radiopharmaceutical Drug Products

Chemist's Review #7

A. 1. NDA 18-689

Applicant: Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

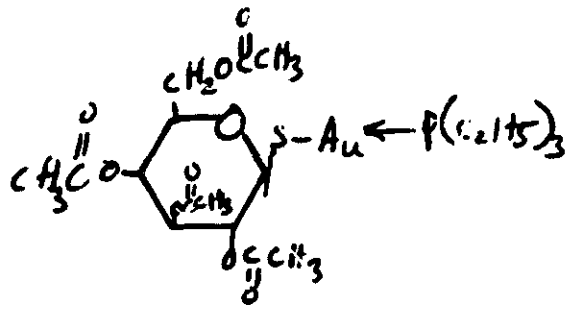
2. Product Name(s)

Proprietary: Ridaura
Non-proprietary: auranofin
USAN: auranofin
Compendium: N/A

3. Dosage Form and Route of Administration: Oral, Tablets

4. Pharmacological Category: Antirheumatic

5. Structural Formula and Chemical Name(s):



(1) Gold, (2,3,4,6-tetra-O-acetyl-1-thio-B-D-glucopyranosato-S) (triethylphosphine -;

(2) (1-Thio-B-D-glucopyranosato) (Triethylphosphine) gold 2,3,4,6-tetraacetate.

B. 2. Amendment: 3/1/85
2/28/85 (Received)

C. Remarks:

The applicant submitted the controls information on 3/1/85 as was requested by telephone on 2/22 & 26/85. The information as submitted is found acceptable and concluded the remaining dificiencies with the exception of one (1) request. This request involves a limit specification which the applicant refused to include in the specifications. A meeting on 2/28/85 appeared to resolve the differences (see Memo 3/3/85). However, as for Telecon on 3/1/85, this request remains not resolved.

D Conclusion and/or Recommendations:

From a manufacturing and controls standpoint, approval of the controls information will depend on whether the firm will include the remaining information as stated above or whether the applicant can convince the Division and Agency that this request is not needed.

Chemist Review #6 dated 2/12/85 indicated the application is approvable pending the applicant's correction of the controls deficiencies which still remain. Since the deficiencies have not totally been corrected, approval of the controls portion of the NDA will not be allowed at this time.

Ernest G. Pappas 3/13/85

Ernest G. Pappas
3/4/85

cc: Orig NDA 18-689
HFN 150/Div File
HFN-140/Pappas
HFN-150/Pease
R/D endorsed by: RHWood/3/6/85
F/T by P. Amoss/3/12/85
Wang #0262B

RHWood 3/13/85 Ra Jenssi 3/19/85