NDA 18-738

NDA 18-738

AUG 30 1985

Jean Strand, Ph.D.
Syntex Laboratories, Inc.
3401 Hillview Avenue
Palo Alto, California 94304

Dear Dr. Strand:

Reference is made to your New Drug Application dated June 1, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulcosyn (sulconazole nitrate) Solution, 1.0%.

Reference is also made to your submission of final printed labeling on May 20, 1985.

We have completed the review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Please submit one market package of the drug when available.

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

Sincerely yours,

cc: SAN-DO
ORIG. NDA 18-738
HFN-82
HFN-710
HFN-220
~~HFN-800/3~~Minor
HFN-815 ST 8/19/85
HFN-815/TBostwick/tcd/7/23/85
HFN-815/MO/CCEvans/7/17/85
HFN-815/CHFM
HFN-PHARM/JMDavitt
R/D init. by: ETabor/7/18/85
ARCasola, Ph.D./7/17/85 DRM
F/T: 7/24/85 ARC 8/5/85 7-23-85
C.C.
8/5/85

APPROVAL 0050u

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 18-738

DATE APPROVAL LETTER ISSUED: AUG 30 1985

TO: Press Relations Staff (HFI-40)

FROM:
- ☐ [redacted] CDB
- ☐ Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- ☒ ORIGINAL NDA
- ☐ SUPPLEMENT TO NDA
- ☐ ABBREVIATED ORIGINAL NDA
- ☐ SUPPLEMENT TO ANDA

CATEGORY
- ☒ HUMAN
- ☐ VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Sulcosyn (sulconazole nitrate)

DOSAGE FORM: Topical Solution

HOW DISPENSED
- ☒ RX
- ☐ OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

1.0% sulconazole nitrate

NAME OF APPLICANT *(Include City and State)*

Syntex Laboratories, Inc.
Palo Alto, CA

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Antifungal

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: [signature]

DATE: July 23, 1985

FORM APPROVED BY

NAME

DATE

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

NDA 18-[redacted]

DEC 20 19[redacted]

Mr. Vir[redacted]
Synte[redacted], Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

Dear Mr. Thompson:

Reference is made to your New Drug Application dated June 1, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sulcosyn (sulconazole nitrate) Solution, 1.0%.

Reference is made to your additional communications dated July 1, 1982 and June 7, 1983.

We have completed the review of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy with the following exceptions:

1. The phrase, "for the treatment of cutaneous candidiasis (moniliasis)" should be deleted from the INDICATIONS AND USAGE section. No evidence of effectiveness of Sulcosyn in this indication has been submitted.

2. The indication "tinea pedis (athlete's foot)" should be deleted from the INDICATIONS AND USAGE section. There are insufficient patients in the tinea pedis studies to justify approval. The following sentence should be added to the end of the first paragraph of that section:

   Effectiveness has not been proven in tinea pedis (athlete's foot).

3. Reference to the unapproved Sulcosyn Cream should be deleted wherever it appears in the labeling.

4. This drug should be classified as "Pregnancy Category C". The labeling should accurately summarize the highlights of the results of the Segments I, II and III animal reproduction studies.

5. The references to tinea pedis and candida infections in the DOSAGE AND ADMINISTRATION section should be deleted.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labels and other labeling.

In addition, we request that you submit copies of the introductory promotional materials proposed for this product. Copies should be submitted with a cover letter to the Division of Anti-Infective Drug Products and the Director of Drug Advertising and Labeling. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission. This form is for routine use, not proposed materials.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

J. Bristol 12/20/84

for Elaine C. Esber, M.D.
Acting Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: LOS-DO
ORIG. NDA 18-738
HFN-800/JMinor
HFN-815
HFN-815/CSO/DCBostwick/sdj/9/19/84
R/D init. by: RCBieneman/6/10/84
ARCasola, Ph.D./6/11/84
JMDavitt
WAPowell, M.D.
CCEvans, M.D./8/23/84
ETabor, M.D./10/18/84
F/T: 10/23/84

APPROVABLE 1623b

FPL

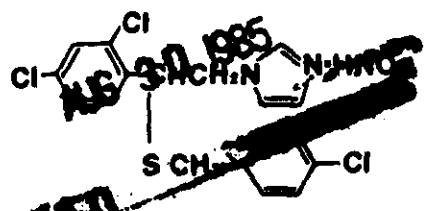
SULCOSYN Solution
NDA 18-738

Package Insert
Code: 02-2536-44

SULCOSYN®
(sulconazole nitrate)
Topical Solution 1.0%

description

SULCOSYN® (sulconazole nitrate) solution 1.0% is a broad-spectrum antifungal agent intended for topical application. Sulconazole nitrate, the active ingredient in SULCOSYN solution, is an imidazole derivative with antifungal and antiyeast activity. Its chemical name is (±)-1-[2,4-dichloro-β-[(p-chlorobenzyl)-thio]-phenethyl] imidazole mononitrate and it has the following chemical structure:



[redacted] a white to off-white crystalline powder with a molecular [redacted]. It is freely soluble in pyridine; slightly soluble in ethanol, [redacted], and chloroform; and very slightly soluble in water. It has a melting point of about 130°C.

SULCOSYN solution contains sulconazole nitrate 10 mg/ml in a solution of propylene glycol, poloxamer 407, polysorbate 20, butylated hydroxyanisole, and purified water, with sodium hydroxide and, if necessary, nitric acid added to adjust the pH.

clinical pharmacology

Sulconazole nitrate is an imidazole derivative that inhibits the growth of the common pathogenic dermatophytes including *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis*. It also inhibits the organism responsible for tinea versicolor, *Malassezia furfur*, and certain gram positive bacteria.

A maximization test with sulconazole nitrate solution showed no evidence of irritation or contact sensitization.

indications and usage

SULCOSYN® (sulconazole nitrate) topical solution 1.0% is a broad-spectrum antifungal agent indicated for the treatment of tinea cruris and tinea corporis caused by *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; and for the treatment of tinea versicolor. Effectiveness has not been proven in tinea pedis (athlete's foot).

Symptomatic relief usually occurs within a few days after starting SULCOSYN solution and clinical improvement usually occurs within one week.

contraindications

SULCOSYN topical solution 1.0% is contraindicated in patients who have a history of hypersensitivity to any of the ingredients.

precautions

General

SULCOSYN® (sulconazole nitrate) topical solution 1.0% is for external use only. Avoid contact with the eyes. If irritation develops, the solution should be discontinued and appropriate therapy instituted.

Information for Patients

Patients should be told to use SULCOSYN solution as directed by the physician, to use it externally only, and to avoid contact with the eyes.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term animal studies to determine carcinogenic potential have not been performed. In vitro studies have shown no mutagenic activity.

Pregnancy – Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Sulconazole nitrate should be used during pregnancy only if clearly needed. Sulconazole nitrate has been shown to be embryotoxic in rats when given in doses of 125 times the adult human dose (in mg/kg). The drug was not teratogenic in rats or rabbits at oral doses of 50 mg/kg/day.

Sulconazole nitrate given orally to rats at a dose 125 times the human dose resulted in prolonged gestation and dystocia. Several females died during the perinatal period, most likely due to labor complications.

Nursing Mothers

Use with caution in nursing mothers since it is not known if sulconazole nitrate appears in breast milk.

Pediatric Use

Safety and effectiveness in children have not been established.

adverse reactions

There were no systemic effects and only infrequent cutaneous adverse reactions in 370 patients treated with sulconazole nitrate solution in controlled clinical trials. Approximately 1% of these patients reported itching and 1% burning or stinging. These complaints did not usually interfere with treatment.

dosage and administration

A small amount of the solution should be gently massaged into the affected and surrounding skin areas once or twice daily.

Symptomatic relief usually occurs within a few days after starting SULCOSYN® (sulconazole nitrate) topical solution 1.0%, and clinical improvement usually occurs within one week. To reduce the possibility of recurrence, tinea cruris, tinea corporis, and tinea versicolor should be treated for 3 weeks.

If significant clinical improvement is not seen after 4 weeks of treatment, an alternate diagnosis should be considered.

how supplied

SULCOSYN® (sulconazole nitrate) topical solution 1.0%:
Plastic bottles
10 cc – NDC #0033-2536-40
20 cc – NDC #0033-2536-44
Avoid excessive heat, above 40°C (104°F), and protect from light.

CAUTION: Federal law prohibits dispensing without a prescription.

SYNTEX

SYNTEX LABORATORIES, INC. © APRIL 1985
PALO ALTO, CA 94304

02-2536-44

U.S. Patent No. 4,055,652

Medical Reviews

Medical Officer's Review of NDA 18,738
(Original Submission, dated June 1, 1983)

Sponsor: Syntex Laboratories, Inc.
3401 Hillview Ave.
Palo Alto, CA 94304

Product: SulcosynR (sulconazole nitrate) Solution 1%

Composition:

	% w/v

Purpose: Topical antifungal agent.

Dosage: "A small amount should be massaged gently into the affected and surrounding skin areas once daily."

Packaging: 10cc and 20 cc plastic bottles.

Related Submissions:

Manufacturing Controls:

The chemist concluded in his Review (August 25, 1983) as follows: "Controls remain complete and approvable, validation is complete. Memo from HFN-322 indicated the plants in compliance (They have not appeared on the alert list so no update is required) and the basis for approval was included in the October review."

Pharmacology:

The pharmacologist recommended the following:

1. The liver is a target organ for this drug in animal species, as with other imidazole antifungal drugs. If the clinical studies support the animal findings, the M.O. may wish to institute some kind of warning in the labeling of this drug.

2. Possible potential target organs in humans as predicted by results in animals, especially dogs, are the intestine, eye, kidney and testis/sperm (motility/viability). The labeling of this drug should include the eye and sperm effects (see draft of letter to applicant).

3. The pregnancy portion of the labeling should be Category C. Moreover, the labeling of this drug should accurately summarize the highlights of the findings in preclinical animal reproduction studies (segments I, II and III). See draft of letter to applicant.

Conclusions

On the basis of safety, this application is approvable. The labeling should, however, be modified as recommended above."

Clinical Studies:

A. Special Studies

1. Study #767. Maximization Test of Sulconazole Nitrate 1% Solution

Investigator: Albert M. Kligman, M.D., Ph.D.
Philadelphia, PA

Method: The study used 25 adults and compared sulconazole nitrate sol. with its vehicle and with 1% clotrimazole sol. in accordance with the standard method.

Results: No contact sensitization. No adverse reactions.

The following studies were all done with sulconazole nitrate cream 1% and were submitted as part of NDA [redacted] Results were evaluated in the medical officer's review of NDA [redacted] dated March 11, 1983.

2. Study #613. Percutaneous absorption and metabolism.

Investigators: Melvin Chaplin, PH.D., and Lewis Tannenbaum, M.D. of Syntex Research.

Method: Tritium labeled 1% sulconazole cream was applied under occlusion to 6 adults, using both intact and stripped skin.

Results: About 80% of the applied dose was measured from both stripped and intact skin. During a 7-day period following application, approximately equal amounts were recovered from the urine and feces of all the subjects. About 12% of the total dose applied was recovered from urine and feces, with no significant difference between intact and stripped skin. Blood chemistries and urinalyses before and after showed no significant change, except the SGOT in 2 subjects was 61 and 62 at one week after dosing (normal = 50); these reverted to normal in 2 weeks. Other liver function tests were normal.

3. Study #821. Percutaneous absorption and metabolism.

Investigator: Thomas Franz, M.D., Seattle, Wash.

Method: Tritium-labeled 1% sulconazole cream was applied to 7 adults with normal skin.

Results: The level of radioactivity in plasma and urine increased steadily until the cream was removed at 24 hours. Radioactivity was detectable in the plasma of all patients for 4 days and in the urine and feces for 7 days. The investigator thought this may indicate a sizable sulconazole reservoir in the stratum corneum. Total drug recovery was only 43% of the dose applied, because of lack of occlusive dressings. Recovery of the applied dose from skin was 34% and from urine and feces an average of 8%.

4. Study #663. Maximization Test.

Investigator: Albert M. Kligman, M.D., Ph.D.

Method: In the standard manner, 1% sulconazole cream, the cream vehicle, and 2% miconazole nitrate cream were tested for sensitization.

Results: No sensitization or other reaction.

5. Study #814.

Investigator: Albert M. Kligman, M.D., Ph.D.

Method: Two formulations of 1% sulconazole cream (one an "improved" version) and 2% miconazole cream were tested for sensitization.

Results: No sensitization or other reaction.

6. Study #593. Modified Draize Sensitization Test.

Investigator: William Epstein, M.D.

Method: The standard repeat insult appplication method was employed using 179 subjects.

Results: Ten subjects had some irritation but no sensitization. On first challenge, an 11th subject reacted with a 1+ reaction to 1% sulconazole and a 2+ reaction to 2% sulconazole. He refused further testing.

7. Study #656. Exaggera[illegible] Exposure Study

Investigator: Lewis Tannenbaum, M.D., of Syntex.

Method: Five subjects received 1% sulconazole cream, 5 received the cream base and 5 received 2% miconazole cream. The creams were applied to the back in 5 gm amounts BID, 5 days/week X 3 weeks. [illegible] tests done before and after included hemograms, bilirubin, AP, SGOT, [illegible], LDH, creatinine, BUN, glucose, cholesterol and electrolytes.

Results: Itching and burning were reported in all 5 sulconazole patients and in 2 miconazole patients and one vehicle patient. Pustules appeared in 2 sulconazole patients. Lab. results were normal except for slight transient rise in SGOT in one sulconazole patient and one miconazole patient. This was thought to be caused by a sudden increase in physical activity.

8. Study #670. Phototoxicity.

Investigator: John Parrish, M.D.

Method: 1% sulconazole, the cream vehicle and 2% miconazole cream were tested using 10 subjects. Occlusive patches were applied to abraded and normal skin in each subject and left on 24 hours. After the patches were removed, the sites were either shielded from light or xposed to suberythema doses of UVB or UVA.

Results: Tests were negative for sulconazole. One subject showed faint erythema at an irradiated miconazole site. No eczematous reactions occurred.

B. Controlled Clinical Studies

I. Study #852. Tinea cruris/corporis. May 1981 - March 1982.

Investigators:

Stanley I. Cullen, M.D., Gainesville, Florida
Marvin F. Engel, M.D., Brunswick, Georgia
David L. McCaffree, M.D., Dallas, Texas
Harold M. Rehbein, M.D., Jacksonville, Florida
George Sanchez, M.D., Rio Piedras, Puerto Rico
Isaac Willis. M.D., Atlanta, Georgia

Objective: To compare the safety and efficacy of sulconazole nitrate solution 1% to that of its vehicle when used once a day in the treatment of tinea cruris/corporis.

Method: This was a double-blind, parallel group, randomized study using adults of both sexes with KOH and culture positive tinea cruris and/or corporis. Each investigator was to enroll a maximum of 24 patients, with a goal of 20 patients per investigator. Patient exclusions included pregnancy, patients taking oral antifungals (unless off therapy for at least 2 weeks), patients using topical antifungals (unless off therapy for at least 2 days), patients with uncontrolled diabetes, and patients on concomitant therapy. Medications were applied once daily for 3 weeks. Patients were seen and evaluated clinically and by repeat KOH and culture at 2, 3, and 7 weeks. Also, at each visit, the overall clinical improvement compared to baseline was evaluated as worse, none, partial clearing, or complete clearing. Before treatment and at each return visit, symptoms were evaluated as present or absent and included the following: erythema, scaling, itching, pustules, fissuring, maceration and vesiculation. Adverse reactions were noted.

Results: I consider KOH and culture conversions the most important indices of efficacy. Next in importance is the overall clinical improvement.

I do not consider changes in the individual signs and symptoms to be of much value; consequently, I have not listed them under Results.

1. Demographics.

96 patients were enrolled. 85 of these were evaluated.

	Sulconazole	Vehicle
Number	42	43
Sex		
Male	25 (60%)	32 (74%)
Female	17 (40%)	11 (26%)
Age		
Range	18-84	
Mean	41	

2. Organisms cultured at initial visit

	Sulconazole	Vehicle
Trichophyton rubrum	31	25
Trichophyton mentagrophytes	1	4
Candida albicans	2	3
	34	32

3. Mycological Results

Note: The sponsor has evaluated separately those patients who had a positive initial KOH, those who had a positive initial culture, and those patients who had both a positive KOH and a positive culture initially (joint KOH and culture).

(a) KOH results at end of therapy

	Neg. KOH	Pos. KOH	# pts.
Sulconazole	35 (90%)	4	39
Vehicle	15 (41%)	22	37

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	23 (88%)	3	26
Vehicle	10 (37%)	17	27

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	21 (81%)	5	26
Vehicle	9 (33%)	18	27

4. Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	23 (59%)	9 (24.3%)
Partial clearing	13 (33.3%)	10 (27.0%)
None	0 (0.0%)	16 (43.2%)
Worse	3 (7.7%)	2 (5.4%)
	39	37

5. Post-treatment follow-up at week 7 (4 weeks after treatment)

(a) KOH results

	Neg.	Pos.	# pts.
Sulconazole	13 (92.9%)	1 (7.1%)	14
Vehicle	7 (77.8%)	2 (22.2%)	9

(b) Joint KOH/culture results

	Neg.	Pos.	# pts.
Sulconazole	13 (92.9%)	1 (7.1%)	14
Vehicle	7 (77.8%)	2 (22.2%)	9

(b) Overall clinical evaluation (week 7 compared with week 3)

	Sulconazole	Vehicle
Relapse	1 (4.6%)	4 (30.8%)
Unchanged	10 (45.4%)	1 (7.7%)
Improved	11 (50.0%)	8 (61.5%)
	22	13

II. Study #890. Tinea cruris/corporis. Dec. 1981 - Nov. 1982.

Investigators:
Marvin F. Engel, M.D., Brunswick, Georgia
Phillip Frost, M.D., Miami Beach, Florida
Jorge L. Sanchez, M.D., Rio Piedras, Puerto Rico
Lawrence A. Schachner, M.D., Miami, Florida

Objective: Same as that of foregoing Study #852.

Method: Same as Study #852, except that each investigator was to enroll a maximum of 36 patients, with a goal of 30 completed cases (total 150 cases).

Results:

1. Demographics.

83 patients were enrolled, 76 of whom were evaluated.

	Sulconazole	Vehicle
Number	39	37
Sex		
Male	27 (69%)	24 (65%)
Female	12 (31%)	13 (35%)
Age		
Range	18-85	
Mean	43.5	

2. Organisms cultured at Initial Visit

	Sulconazole	Vehicle
T. rubrum	21	24
C. albicans	4	1
E. floccosum	1	3
M. canis	1	0
T. mentagrophytes	1	1
M. ferruginosum	1	0
	29	29

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	27 (87%)	4	31
Vehicle	13 (42%)	18	31

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	20 (91%)	2	22
Vehicle	7 (29%)	17	24

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	19 (83%)	4	23
Vehicle	4 (17%)	20	24

4. Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	18 (58.1%)	6 (19.4%)
Partial clearing	12 (38.7%)	10 (32.3%)
None	0 (0.0%)	14 (45.2%)
Worse	1 (3.2%)	1 (3.2%)
	31	31

5. Post-treatment follow-up at week 7 (4 weeks after treatment)

(a) KOH results

	Neg.	Pos.	# pts.
Sulconazole	18 (85.7%)	3 (14.3%)	21
Vehicle	9 (75.0%)	3 (25.0%)	12

(b) Joint KOH/culture results

	Neg.	Pos.	# pts.
Sulconazole	14 (77.8%)	4 (22.2%)	18
Vehicle	7 (77.8%)	2 (22.2%)	9

(c) Overall clinical evaluation (week 7 compared with week 3)

	Sulconazole	Vehicle
Relapse	4 (19.0%)	4 (33.3%)
Unchanged	11 (52.4%)	5 (41.7%)
Improved	6 (28.6%)	3 (25.0%)
	21	12

III. Study #764. Tinea cruris. June 1980 - July 1981.

Investigators:

Gregory J. Coleman, M.D., Santa Monica, California
Dennis J. Doud, M.D., Greenwood, South Carolina
Michael Fisher, M.D., Bronx, New York
Henry E. Jones, M.D., Atlanta, Georgia
Charles Lewis, M.D., San Antonio, Texas
Lafayette G. Owen, M.D., Louisville, Kentucky
Daryl E. Vander Ploeg, San Antonio, Texas
Isaac Willis, M.D., Atlanta, Georgia

Objective: To evaluate the safety and efficacy of sulconazole nitrate sol. 1% as compared with clotrimazole sol. 1% in tinea cruris.

Method: Same as in study #852, except that sulconazole was compared with an active, marketed reference drug (Clotrimazole sol. 1%) instead of with the vehicle.

Results:

1. Demographics

100 patients were enrolled, of whom 90 were evaluated.

		Sulconazole	Clortimazole
		47	43
Number			
Sex			
	Male	36 (77%)	33 (77%)
	Female	11 (23%)	10 (23%)
Age			
	Range	17-92	
	Mean	43.2	

2. Organisms cultured at Initial Visit

	Sulconazole	Clotrimazole.
T. rubrum	21	16
T. mentagrophytes	11	5
E. floccosum	2	1
T. schoenleinii	1	0
T. tonsurans	1	0
M. ferruginosum	0	1
	36	23

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	37 (97%)	1	38
Clotrimazole	32 (91%)	3	35

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	28 (97%)	1	29
Clotrimazole	15 (94%)	1	16

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	28 (93%)	2	30
Clotrimazole	14 (88%)	2	16

4. Overall clinical evaluation at end of therapy

	Sulconazole	Clotrimazole
Complete clearing	34 (89.5%)	29 (80.6%)
Partial clearing	4 (10.5%)	7 (19.4%)
None	0 (0.0%)	0 (0.0%)
Worse	0 (0.0%)	0 (0.0%)
	38	36

5. Post-treatment follow-up at week 7.

(a) KOH results

	Neg.	Pos.	# pts.
Sulconazole	31 (91%)	3	34
Clotrimazole	28 (88%)	4	32

(b) Culture results

	Neg.	Pos.	# pts.
Sulconazole	27 (93%)	2	29
Clotrimazole	16 (80%)	4	20

(c) Joint KOH/culture results

	Neg.	Pos.	# pts.
Sulconazole	25 (89%)	3	28
Clotrimazole	16 (80%)	4	20

(c) Overall clinical evaluation

	Sulconazole	Clotrimazole
Worse	8 (23.5%)	7 (21.2%)
Unchanged	20 (58.8%)	18 (54.6%)
Improved	6 (17.7%)	8 (24.2%)
	34	33

IV. Study #857. Tinea pedis. April 1981 - Dec. 1981

Investigators:
German Camargo, M.D., 4th Brigade, Columbia Army, Columbia, South America
David Taplin, Professor, Univ. of Miami, Florida.

Objective: To confirm the safety and efficacy of sulconazole nitrate 1% sol. in the treatment of symptomatic tinea pedis in adult men.

Method: A randomized double-blind, paired-comparison study of adult males with symptomatic tinea pedis. Lesions of comparable severity and location on each foot were treated once daily in the presence of the investigator X 4 weeks. Sulconazole was applied to one foot and its vehicle was applied to the other foot. KOH and cultures were taken before treatment and at 2 and 4 weeks. At each visit, symptoms were noted as positive or negative (including erythema, scaling, maceration, vesiculation, pustules) and the overall clinical status of each foot compared with baseline was evaluated at 2 and 4 weeks as worse, none, partial clearing, or complete clearing. Adverse reactions were monitored. Also, at 2 and 4 weeks the right and left feet of each patient were compared with each other, as follows: sulconazole better, vehicle better, no difference.

Results

1. Demographics

52 patients were enrolled, of whom 45 were evaluated. These were all men in the Columbian army, stationed in the jungles of Columbia, South America.

Number	45
Age	
Range	17-26
Mean	20.2

2. Organisms cultured at initial visit

	Sulconazole site	Vehicle site
E. floccosum	36 (90.0%)	36 (83.7%)
Candida sp.	3 (7.5%)	3 (7.0%)
T. mentagrophytes	1 (2.5%)	2 (4.6%)
T. rubrum	0 (0.0%)	2 (4.6%)
	40	43

Note: According to the sponsor, "Two cultures were taken at each site for each patient. Each different organism isolated for a given patient is counted once in the table. A total of 40 patients contributed organisms to the table; 38 patients contributed for the sulconazole site, 39 patients for the vehicle site and 37 patients contributed organisms for both the sulconazole and vehicle sites."

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.
Sulconazole	33 (92%)	3
Vehicle	29 (81%)	7

(b) Culture results at end of therapy

	Neg.	Pos.
Sulconazole	29 (100%)	0
Vehicle	25 (86%)	4

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.
Sulconazole	27 (93%)	2
Vehicle	19 (66%)	10

4. Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Worse	0 (0%)	0 (0%)
None	0 (0%)	0 (0%)
Partial clearing	24 (67%)	26 (72%)
Complete clearing	12 (33%)	10 (28%)
	36	36

5. Comparative clinical improvement

Sulconazole better	Vehicle better	No difference
12 (33%)	8 (22%)	16 (44%)

V. Study #889. Tinea pedis. November 1981 - October 1982

Investigtors

Marvin F. Engel, M.D., Brunswick, Georgia
Phillip Frost, M.D., Miami Beach, Florida
Jose Mendez, M.D., Hato Rey, PR
Jorge L. Sanchez, M.D., Rio Piedras, PR
Lawrence A. Schachner, M.D., Miami, Florida

Objectfve: To compare the safety and efficacy of sulconazole nitrate solution 1% with that of its vehicle in the treatment of tinea pedis.

Method: A randomized, double-blind, parallel group, multicenter trial of adults with KOH pos., symptomatic, acute (present attack no longer than 6 months) tinea pedis. KOH examination and cultures were done before treatment and at 2 and 4 weeks. Patients who were KOH negative at the end of treatment were examined again 4 weeks later. Test drugs were applied once daily for 4 weeks. At 2 and 4 weeks, the overall skin change was assessed as "worse, none, partial clearing, or complete clearing." Adverse reactions were reported at each visit.

Results:

1. Demographics

126 patients were enrolled, of whom 107 were evaluated.

	Sulconazole	Vehicle
Number	54	53
Sex		
Male	27	28
Female	27	25
Age		
Range	19-86	
Mean	50.5	

2. Organisms cultured at Initial Visit

	Sulconazole	Vehicle
T. rubrum	19 (55.9%)	16 (72.7%)
C. albicans	2	0
E. floccosum	2	2
T. mentagrophytes	7	4
T. tonsurans	1	0
C. guilliermondi	3	0
	34	22

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	25 (61%)	16	41
Vehicle	18 (39%)	28	46

Objectfve: To compare the safety and efficacy of sulconazole nitrate solution 1% with that of its vehicle in the treatment of tinea pedis.

Method: A randomized, double-blind, parallel group, multicenter trial of adults with KOH pos., symptomatic, acute (present attack no longer than 6 months) tinea pedis. KOH examination and cultures were done before treatment and at 2 and 4 weeks. Patients who were KOH negative at the end of treatment were examined again 4 weeks later. Test drugs were applied once daily for 4 weeks. At 2 and 4 weeks, the overall skin change was assessed as "worse, none, partial clearing, or complete clearing." Adverse reactions were reported at each visit.

Results:

1. Demographics

126 patients were enrolled, of whom 107 were evaluated.

		Sulconazole	Vehicle
Number		54	53
Sex			
	Male	27	28
	Female	27	25
Age			
	Range	19-86	
	Mean	50.5	

2. Organisms cultured at Initial Visit

	Sulconazole	Vehicle
	19 (55.9%)	16 (72.7%)
T. rubrum	2	0
C. albicans	2	2
E. floccosum	7	4
T. mentagrophytes	1	0
T. tonsurans	3	0
C. guilliermondi	34	22

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	25 (61%)	16	41
Vehicle	18 (39%)	28	46

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	26 (96%)	1	27
Vehicle	13 (68%)	6	19

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	17 (63%)	10	27
Vehicle	5 (26%)	14	19

4. Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	9 (22.0%)	1 (2.1%)
Partial clearing	27 (65.9%)	28 (59.5%)
None	5 (12.2%)	10 (21.2%)
Worse	0 (0.0%)	8 (17.0%)
	41	47

5. Post-treatment follow-up at week 8

(a) KOH results

	Neg.	Pos.	# pts.
Sulconazole	21 (100%)	0	21
Vehicle	12 (85.7%)	2 (14.3%)	14

(c) Joint KOH/culture relapse

	Neg.	Pos.	# pts.
Sulconazole	15 (79.0%)	4 (21.1%)	19
Vehicle	9 (75.0%)	3 (25.0%)	12

(c) Overall clinical results

	Sulconazole	Vehicle
Relapse	0 (0.0%)	5 (33.3%)
Unchanged	14 (63.6%)	5 (33.3%)
Improved	8 (36.4%)	5 (33.3%)
	22	15

6. Results in T. rubrum patients

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	8 (57%)	6	14
Vehicle	4 (29%)	10	14

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	13 (93%)	1	14
Vehicle	9 (64%)	5	14

(c) Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	3 (21.4%)	0 (0.0%)
Partial clearing	9 (64.3%)	11 (73.3%)
None	2 (14.3%)	3 (20.0%)
Worse	0 (0.0%)	1 (6.7%)
	14	15

VI. Study #856. Tinea pedis. July 1981 - March 1982.

Investigators:
Carlton L. Carpenter, M.D., Baton Rouge, LA
Stanley I. Cullen, M.D., Gainesville, FL
Lynn Annette Drake, M.D., Atlanta, GA
Martin Engel, M.D., Brunswick, GA
David Harris, M.D., Los Gatos, CA
David Lee McCaffree, M.D., Dallas, TX
William Rosenberg, M.D., Memphis TN

Objective: To compare the safety and efficacy of sulconazole nitrate solution 1% with that of clotrimazole solution 1% in the treatment of tinea pedis.

Method: Like that in Study #889, except that sulconazole was used by one group and clotrimazole solution 1% was used by the parallel group.

Results:

1. Demographics

81 patients were enrolled, of whom 67 were evaluated.

	Sulconazole	Clotrimazole
Number	35	32
Sex		
Male	24	18
Female	11	14
Age		
Range	12-70	
Mean	39.0	

2. Organisms cultured at initial visit

	Sulconazole	Clotrimazole.
T. rubrum	13 (86.7%)	17 (81.0%)
E. floccosum	0 (0.0%)	1 (4.8%)
T. mentagrophytes	1 (6.7%)	3 (14.3%)
T. tonsurans	1 (6.7%)	0 (0.0%)

3. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	16 (64%)	9	25
Clotrimazole	14 (58%)	10	24

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	7 (100%)	0	7
Clotrimazole	7 (58%)	5	12

(c) Joint KOH and culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	3 (43%)	4	7
Clotrimazole	4 (29%)	10	14

4. Overall clinical evaluation at end of therapy

	Sulconazole	Clotrimazole
Complete clearing	5 (20.0%)	5 (20.8%)
Partial clearing	17 (68.0%)	15 (62.5%)
None	2 (8.0%)	3 (12.5%)
Worse	1 (4.0%)	1 (4.2%)
	25	24

5. Post-treatment follow-up at week 8.

(a) KOH results

	Neg.	Pos.	# pts.
Sulconazole	9 (81.8%)	2 (18.2%)	11
Clotrimazole	8 (72.7%)	3 (27.3%)	11

(b) Joint KOH/culture relapse

	Neg.	Pos.	# pts.
Sulconazole	8 (80.8%)	2 (20.0%)	10
Clotrimazole	5 (71.4%)	2 (28.6%)	7

(c) Overall clinical evaluation

	Sulconazole	Clotrimazole
Relapse	2 (18.2%)	5 (45.5%)
Unchanged	4 (36.4%)	3 (27.3%)
Improved	5 (45.5%)	3 (27.3%)
	11	11

6. Results in T. rubrum patients

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	3 (43%)	4	7
Clotrimazole	7 (54%)	6	13

(b) Culture results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	7 (100%)	0	7
Clotrimazole	6 (55%)	5	11

(c) Overall clinical evaluation at end of therapy

	Sulconazole	Clotrimazole
Complete clearing	1 (14.3%)	2 (15.4%)
Partial clearing	5 (71.4%)	8 (61.5%)
None	1 (14.3%)	2 (15.4%)
Worse	0 (0.0%)	1 (7.7%)
	7	13

VII. Study #763. Tinea versicolor. June 1980 - April 1981.

Investigators
Michael Fisher, M.D., Bronx, N.Y.
Henry E. Jones, M.D., Atlanta, GA
Charles Lewis, M.D., San Antonio, TX
Edgar B. Smith, M.D., Galveston, TX
Daryl E. Vander Ploeg, M.D., San Antonio, TX
Isaac Willis, M.D., Atlanta, GA

Objective: To evaluate the safety and efficacy of sulconazole nitrate solution 1% as compared with its vehicle in the treatment of tinea versicolor

Method: A randomized, double-blind, parallel group comparison of sulconazole nitrate with its vehicle in adults of both sexes. Medications were applied once daily for 3 weeks. Patients were examined

before therapy and at 2 and 3 weeks, and those who were negative at 3 weeks were re-examined at 7 weeks for relapse. At each visit a KOH exam was done and all sites were examined for signs and symptoms (itching, erythema, scaling, hypopigmentation). Cultures were not done, because M. furfur cannot be readily cultured. At 2 and 3 weeks, the overall clinical change was evaluated as "worse, none, partial clearing, clear except for abnormal pigmentation, or complete clearing." Abnormal reactions were noted at each visit.

Results: 137 patients were enrolled, of whom 127 were evaluated.

1. Demographics

	Sulconazole	Vehicle
Number	64	63
Sex		
Male	41	27
Female	23	36
Age		
Range	16-80	
Mean	31.1	

2. Mycological Results

(a) KOH at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	37 (76%)	12	49
Vehicle	7 (15%)	41	48

(b) Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	3 (6.1%)	2 (4.2%)
Only abn. pigmentation	34 (69.4%)	4 (8.3%)
Partial clearing	8 (16.3%)	13 (27.1%)
None	4 (8.2%)	27 (56.2%)
Worse	0 (0.0%)	2 (4.2%)
	49	48

3. Post-treatment follow-up

(a) KOH relapse

	Neg.	Pos.	# pts.
Sulconazole	21 (70.0%)	9 (30.0%)	30
Vehicle	5 (71.4%)	2 (28.6%)	7

(b) Overall clinical evaluation

	Sulconazole	Vehicle
Relapse	9 (30.0%)	2 (28.6%)
Only abn. pigmentation	18 (60.0%)	3 (42.9%)
Complete clearing	3 (10.0%)	2 (28.6%)
	30	7

before therapy and at 2 and 3 weeks, and those who were negative at 3 weeks were re-examined at 7 weeks for relapse. At each visit a KOH exam was done and all sites were examined for signs and symptoms (itching, erythema, scaling, hypopigmentation). Cultures were not done, because M. furfur cannot be readily cultured. At 2 and 3 weeks, the overall clinical change was evaluated as "worse, none, partial clearing, clear except for abnormal pigmentation, or complete clearing." Abnormal reactions were noted at each visit.

Results: 13/ patients were enrolled, of whom 127 were evaluated.

1. Demographics

	Sulconazole	Vehicle
Number	64	63
Sex		
Male	41	27
Female	23	36
Age		
Range	16-80	
Mean	31.1	

2. Mycological Results

(a) KOH at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	37 (76%)	12	49
Vehicle	7 (15%)	41	48

(b) Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	3 (6.1%)	2 (4.2%)
Only abn. pigmentation	34 (69.4%)	4 (8.3%)
Partial clearing	8 (16.3%)	13 (27.1%)
None	4 (8.2%)	27 (56.2%)
Worse	0 (0.0%)	2 (4.2%)
	49	48

3. Post-treatment follow-up

(a) KOH relapse

	Neg.	Pos.	# pts.
Sulconazole	21 (70.0%)	9 (30.0%)	30
Vehicle	5 (71.4%)	2 (28.6%)	7

(b) Overall clinical evaluation

	Sulconazole	Vehicle
Relapse	9 (30.0%)	2 (28.6%)
Only abn. pigmentation	18 (60.0%)	3 (42.9%)
Complete clearing	3 (10.0%)	2 (28.6%)
	30	7

VIII. Study #871. Tinea versicolor. November 1981 - October 1982

Investigators
Richard B. Greene, M.D., Hallandale, FL
Terry P. Hadley, M.D., Concord, MA
Eric W. Kraus, M.D., San Antonio, TX

Objective: Same as in Study #763.

Method: Same as in Study #763.

Results:

1. Demographics
76 patients were enrolled, of whom 72 were evaluated.

	Sulconazole	Vehicle
Number	33	39
Sex		
Male	21	26
Female	12	13
Age		
Range	16-75	
Mean	31.4	

2. Mycological Results

(a) KOH results at end of therapy

	Neg.	Pos.	# pts.
Sulconazole	22 (79%)	6	28
Vehicle	12 (31%)	27	39

(b) Overall clinical evaluation at end of therapy

	Sulconazole	Vehicle
Complete clearing	7 (25,0%)	3 (7.7%)
Only abn. pigmentation	14 (50.0%)	76 (18.0%)
Partial clearing	6 (21.4%)	13 (33.3%)
None	1 (3.6%)	14 (35.9%)
Worse	0 (0.0%)	2 (5.1%)
	28	39

3. Post-treatment follow-up

(a) KOH relapse

	Neg.	Pos.	# pts.
Sulconazole	15 (68.2%)	7 (31.8%)	22
Vehicle	4 (36.4%)	7 (63.6%)	11

(b) Overall clinical evaluation

	Sulconazole	Vehicle
Relapse	7 (31.8%)	8 (72.7%)
Only abn. pigmentation	6 (27.3%)	2 (18.2%)
Complete clearing	9 (40.9%)	1 (9.1%)
	22	11

Adverse Reactions

A total of 370 patients returned for at least one visit after using sulconazole solution.

A. Probably related to Sulconazole Solution - 7 patients (1.9%)

	# Patients	Severity		
		Mild	Moderate	Severe
Itching	4 (1.1%)	1	2	1
Skin burning/stinging	4 (1.1%)	1	3	2
Red eruption	1 (0.3%)	0	1	0
Increased crusting	1 (0.3%)	0	0	1
Draining (skin)	1 (0.3%)	0	0	1

B. Unknown Relationship to Sulconazole Solution - 3 patients (0.8%)

Itching	2 (0.51%)	0	1	1
Skin burning/stinging	1 (0.3%)	1	0	0
Bumps/nodules	2 (0.5%)	2	1	0
Skin fissures	1 (0.3%)	0	0	1

Only 4 patients discontinued therapy because of adverse reactions. In 2 of these, the relationship to sulconazole treatment was unknown (one had fissures and one had increased itching). In the other 2, the reactions were probably related to sulconazole. (One had increased itching, burning, crusting and draining, and one had a red eruption).

Laboratory tests were performed during clinical studies with sulconazole cream 1% and were reviewed in the medical officer's review of NDA 18-737. The medical officer concluded, "Results showed no evidence of a drug effect on any parameter. Values at the end of therapy were either normal or comparable to pre-treatment values, or, in the few cases of alteration, e.g., in SGOT, glucose, BUN, were attributable to other disease conditions."

Labeling

I shall defer review of labeling until the NDA becomes approvable.

The submitted labeling gives the following indications: "...for the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis; for the treatment of cutaneous candidiasis (monilliasis); and for the treatment of tinea versicolor."

Directions for use say that a small amount should be gently massaged into the affected areas once or twice a day but that tinea pedis should be treated twice a day. Tinea pedis should be treated for 4 weeks and the other conditions for 3 weeks.

Evaluation and Comment:

Safety does not appear to be a problem. Skin reactions were infrequent and mostly mild. Human pharmacology studies revealed nothing remarkable. Note the pharmacologist's recommendations concerning labeling.

My conclusions concerning efficacy conform to the recommendations agreed upon by Drs. Evans, Huene, Powell and Sanders of this Division, and by Drs. Mary Johnson and Richard Stein of the Division of Biometrics [redacted]. The recommendations are as follows:

1. For a claim of effectiveness in tinea cruris, tinea corporis, and tinea pedis, the minimal requirement would be two well-controlled studies in tinea pedis, both of which show effectiveness for this condition. Since this is the most difficult of the conditions to treat, effectiveness in tinea corporis and cruris would also be considered to have been demonstrated.

2. If effectiveness in tinea pedis has not been demonstrated, but effectiveness for tinea cruris and corporis has been demonstrated, the product may be labeled for tinea cruris and corporis, with the disclaimer that the product has not been shown to be effective in tinea pedis.

3. All patients evaluated should have a positive KOH exam and a positive culture with identification of the dermatophyte prior to therapy, and a KOH exam and culture with identification of the dermatophyte at the end of therapy.

4. For a claim of effectiveness in tinea pedis, clinical effectiveness should be shown against T. rubrum, since this is the most difficult organism to treat. A claim of effectiveness may be extrapolated to the other dermatophytes based on the effectiveness against T. rubrum plus the results of in vitro studies on the other individual dermatophytes.

Evaluation of tinea cruris/corporis studies

Study #852. Tinea cruris/corporis

(a) KOH results at end of therapy showed 90% (35 of 39) of the sulconazole patients and 41% (15 of 37) of the vehicle patients had become negative. Sulconazole was significantly better than the vehicle, with a 49% margin of superiority.

(b) Culture results at end of therapy showed 88% (23 of 26) of the sulconazole patients and 37% (10 of 27) of the vehicle patients had become negative. Sulconazole was 51% better than the vehicle, a significant difference.

(c) Joint KOH and culture results at end of therapy showed 81% (21 of 26) of the sulconazole patients and 33% (9 of 27) of the vehicle patients had become negative. Sulconazole was significantly better than vehicle by 48%.

(d) Overall clinical evaluation at end of therapy showed sulconazole to be 34.7% better than the vehicle in the complete clearing category and 41% better than the vehicle in the complete clearing plus partial clearing categories. Sulconazole was clinically significantly better than the vehicle.

(e) Post-treatment follow-up at week 7. In the KOH results category and in the overall clinical evaluation category, 44% of the sulconazole patients and 65% of the vehicle patients failed to return. In the joint KOH/culture results category, 54% of the sulconazole patients and 67% of the vehicle patients failed to return. The post-treatment results, therefore, have no significance.

Study #890. Tinea cruris/corporis.

(a) KOH results at end of therapy showed 87% (27 of 31) of the sulconazole patients and 42% (13 of 31) of the vehicle patients had become negative. Sulconazole was significantly better than the vehicle, with a 45% margin of superiority.

(b) Culture results at the end of therapy showed 91% (20 of 22) of the sulconazole patients and 29% (7 of 24) of the vehicle patients had become negative. Sulconazole was significantly better than the vehicle, with a 62% margin of superiority.

(c) Joint KOH culture results at end of therapy showed 83% (19 of 23) of the sulconazole patients and 17% (4 of 24) of the vehicle patients had become negative. Sulconazole was significantly better than the vehicle by 66%.

(d) Overall clinical evaluation at end of therapy showed that in the complete clearing category, sulconazole was 58.1% compared with 19.4% for the vehicle (a 38.7% difference). In the complete plus partial clearing categories, sulconazole was 96.8% and vehicle was 51.7%, s significant difference in favor of sulconazole (45.1%).

(e) Post-treatment follow-up at week 7. In the KOH results category 32% of the sulconazole patients and 61% of the vehicle patients failed to return. In the KOH/culture results category, 22% of the sulconazole patients and 63% of the vehicle patients failed to return. There were too few returnees to be significant.

Study #764. Tinea cruris.

(a) KOH results at end of therapy showed 97% (37 of 38) of the sulconazole patients and 91% (32 of 35) of the clotrimazole patients had become negative. Sulconazole was, thus, slightly better than its control drug.

(b) Culture results at the end of therapy showed 97% (28 of 29) of the sulconazole patients and 94% (15 of 16) of the clotrimazole patients had become negative. Sulconazole was, therefore, at least as good as its active control drug.

(c) Joint KOH and culture results at end of therapy showed 93% (28 of 30) of the sulconazole patients and 88% (14 of 16) of the clotrimazole patients had become negative. Sulconazole was, therefore, at least as effective as its active control.

(d) Overall clinical evaluation at end of therapy showed sulconazole slightly superior to clotrimazole in the complete clearing category and equal to clotrimazole in the complete plus partial clearing categories.

(e) Post-treatment follow-up at week 7 showed sulconazole to be slightly superior to its active control drug in KOH results, culture results, joint KOH/culture results, and in the overall clinical results.

Evaluation of the tinea pedis studies

Study #857. Tinea pedis.

(a) KOH results at end of therapy showed 92% (33 of 36) of the sulconazole sites and 81% (29 of 36) of the vehicle sites had become negative. I consider that this 11% difference in favor of sulconazole probably lacks significance.

(b) Culture results at the end of therapy showed 100% (39 of 39) of the sulconazole sites and 86% (25 of 29) of the vehicle sites had become negative. I think this 14% difference in favor of sulconazole may be significant, but is borderline.

(c) Joint KOH culture results at end of therapy showed 93% (27 of 29) of the sulconazole sites and 66% (19 of 29) of the vehicle sites had become negative. This 25% difference in favor of sulconazole is significant, in my opinion.

(d) Overall clinical evaluation at end of therapy showed no essential difference between sulconazole and vehicle. For partial clearing, the vehicle was 5% better than sulconazole. For complete clearing, sulconazole was 5% better than the vehicle.

(e) Comparative clinical improvement showed sulconazole to be 11% better than the vehicle. This is not clinically significant.

Conclusion: The results show a trend in favor of sulconazole but I do not consider them conclusive of clinical efficacy. In any event, this study had only two patients with T. rubrum infections and, therefore, does not qualify as evidence for the efficacy of sulconazole lotion in tinea pedis (in accordance with conference recommendation #4 as stated above).

Study #889. Tinea pedis.

(a) KOH results at end of therapy showed 61% (25 of 41) of the sulconazole patients and 39% (18 of 46) of the vehicle patients had become negative. I consider the 22% difference in favor of sulconazole to be significant.

(b) Culture results at the end of therapy showed 96% (26 of 27) of the sulconazole patients and 68% (13 of 19) of the vehicle patients had become negative. I consider the 28% difference in favor of sulconazole to be significant.

(c) Joint KOH and culture results at end of therapy showed 63% (17 of 27) of the sulconazole patients and 26% (5 of 19) of the vehicle patients had become negative. I consider the 37% difference in favor of sulconazole to be significant.

(d) Overall clinical evaluation at end of therapy showed sulconazole about 20% superior to the vehicle in the complete clearing category and 26.3% superior to the vehicle in the complete clearing plus partial clearing categories. I consider these differences to be clinically significant in favor of sulconazole.

(e) Post-treatment follow-up at week 8. The results have no significance. In the KOH results category, for example, approximately 49% of the sulconazole and 70% of the vehicle patients failed to return at 8 weeks. About 30% of the sulconazole patients and 37% of the vehicle patients in the joint KOH/cult. group failed to return at 8 weeks. In the overall clinical evaluation category, about 46% of the sulconazole patients and 68% of the vehicle patients failed to return at 8 weeks.

Results in T. rubrum patients:

(a) KOH results at end of therapy showed 57% (8 of 14) of the sulconazole patients and 29% (4 of 14) of the vehicle patients had become negative. This may show a trend in favor of sulconazole but I consider the numbers too small to have any significance.

(b) Culture results at the end of therapy showed 93% (13 of 14) of the sulconazole patients and 64% (9 of 14) of the vehicle patients had become negative. Again, I think these figures may show a trend in favor of sulconazole, but they are too small to be significant.

(c) Overall clinical evaluation at end of therapy showed 21.4% (3 of 14) of the sulconazole patients and 0% (0 of 15) of the vehicle patients had complete clearing. And 64.3% (9 of 14) of the sulconazole patients and 73.3% (11 of 15) of the vehicle patients showed partial clearing. Here again, I think there may be a trend in favor of sulconazole, but the numbers of patients are too small to have significance.

Study #856. Tinea pedis.

(a) KOH results at end of therapy showed 64% (16 of 25) of the sulconazole patients and 58% (14 of 24) of the clotrimazole patients had become negative. Consequently, sulconazole was 6% better than its active reference drug.

(b) Culture results at the end of therapy showed 100% (7 of 7) of the sulconazole patients and 58% (7 of 12) of the clotrimazole patients had become negative. The numbers of patients are too small to be significant.

(c) Joint KOH and culture results at end of therapy showed 43% (3 of 7) of the sulconazole patients and 29% (4 of 14) of the clotrimazole patients had become negative. The numbers here also are too small to have significance.

(d) Overall clinical results at end of therapy showed 88% (22 of 25) of the sulconazole patients and 83.3% (20 of 24) of the clotrimazole patients were in the complete plus partial clearing categories. Thus, sulconazole was 4.7% better than its active reference drug, clotrimazole.

(e) Post-treatment follow-up at week 8. Results lack significance because fewer than half the patients returned.

Results in T. rubrum patients:

(a) KOH results at end of therapy showed 43% (3 of 7) of the sulconazole patients and 54% (7 of 13) of the clotrimazole patients had become negative. There were too few patients to have any significance.

(b) Culture results at the end of therapy showed 100% (7 of 7) of the sulconazole patients and 55% (6 of 11) of the clotrimazole patients had become negative. Here again, the numbers are too small to have significance.

(c) Overall clinical results at end of therapy showed 85.7% (6 of 7) of the sulconazole patients and 76.9% (10 of 13) of the clotrimazole patients were in the complete clearing plus partial clearing categories. Patient numbers are not significant.

(d) Post-treatment follow-up at week 8. Results lack significance because fewer than half the patients returned.

Evaluation of the tinea versicolor studies

Study #763. Tinea versicolor.

(a) KOH results at end of therapy showed 76% (37 of 49) of the sulconazole patients and 15% (7 of 48) of the vehicle patients had become negative. Sulconazole was 65% superior to vehicle, a significant difference.

(b) Overall clinical results at end of therapy showed that in the combined categories of complete clearing plus only abnormal pigmentation plus partial clearing, sulconazole was 52% superior to vehicle, a significant difference.

(c) Post-Treatment follow-up results at week 7 have no significance, because 30% of the sulconazole patients and 85% of the vehicle patients failed to return.

Study #871. Tinea versicolor.

(a) KOH results at end of therapy showed 79% (22 of 28) of the sulconazole patients and 31% (12 of 39) of the vehicle patients had become negative. Sulconazole was, therefore, 48% better than the vehicle, a significant difference.

(b) Overall clinical results at the end of therapy showed that in the combined categories of complete clearing plus only abnormal pigmentation plus partial clearing, sulconazole was 37% superior to the vehicle, a significant difference.

(c) Post-treatment follow-up results at week 7 have no significance because 21% of the sulconazole patients and 72% of the vehicle patients failed to return.

Note: A number of patients were excluded from each study following the initial enrollment. In my opinion, these exclusions have no effect on the outcome of the studies. The reasons for the exclusions were as follows:

Study #852:

Eleven patients excluded (96 enrolled, 85 evaluated).

Vehicle: One terminated at week two visit, because of adverse reaction.
Four were lost to follow-up after initial visit.

Sulconazole: Six were lost to follow-up after initial visit.

Study #890:

Seven patients excluded (83 enrolled, 76 evaluated).

Vehicle: Two excluded for non-compliance.
One terminated after one week of treatment (week two visit early). One lost to follow-up after week two.
Two lost to follow-up after admission.

Sulconazole: One excluded for non-compliance.

Study: #764:

Ten patients excluded. (100 enrolled, 90 evaluated).

Clotrimazole: Four lost to follow-up after initial visit.
One had protocol violation (Candida at baseline).

Sulconazole: Three had protocol violation (Candida at baseline).
One lost to follow-up after initial visit.

Study #857:

Seven patients excluded (52 enrolled, 45 evaluated).
Four were lost to follow-up after initial visit.
Two had an adverse reaction within the first week.
One excluded for non-compliance.

Study #889:

Nineteen patients excluded (126 enrolled, 107 evaluated).

Vehicle: Nine lost to follow-up after initial visit.

Sulconazole: One excluded because week two and week four visits late.
Nine lost to follow-up after initial visit.

Study #856:

Fourteen patients excluded (81 enrolled, 67 evaluated).

Clotrimazole: One excluded for non-compliance. One excluded because of hospitalization for intercurrent disease. One late for week two and week four and lost to follow-up. Four lost to follow-up after initial visit.

Sulconazole: Two excluded for non-compliance. One hospitalized for intercurrent disease. One had adverse reaction. Three lost to follow-up after initial visit.

Study #763

Ten patients excluded (137 enrolled, 127 evaluated).

Vehicle: Two lost to follow-up after initial visit. One lost to follow-up after week two and week two visit excessively early. Two missed week two, week three late. One withdrew voluntarily after initial visit.

Sulconazole: Two lost to follow-up after initial visit. One excluded for non-compliance. One missed week two, late for week three, lost to follow-up after week three.

Study #871:

Four patients excluded (76 enrolled, 72 evaluated).

Vehicle: One excessively late for weeks two, and three.

Sulconazole: Two excluded for non-compliance. One voluntarily withdrew after initial visit.

Conclusions:

1. Sulcosyn Solution appears to be reasonably safe when used as directed.

2. The sponsor has failed to show efficacy of Sulcosyn Solution 1% against T. rubrum infections of the feet. The NDA is, therefore, not approvable for tinea pedis (in accordance with our recommendations of Dec. 13 and 14, 1982).

3. Two vehicle-controlled studies (#852 and #890) and one active drug-controlled study (#764) show Sulcosyn Solution 1% to be effective against tinea cruris and tinea corporis.

4. Two vehicle-controlled studies (#763 and #871) show Sulcosyn Solution 1% to be effective against tinea versicolor.

Recommendations:

This NDA should be made approvable for the following indications: tinea cruris, tinea corporis and tinea versicolor.

It should be declared not approvable for tinea pedis.

Wilson A. Powell, Jr., M.D.
HFN-140

cc:
Orig NDA
HFN-815 5/14/84
HFN-815/CSO
HFN-220
HFN-815/WAPowell:js/3/26/84
Retyped:WAPowell:js/5/04/84
1905a

Chemist Reviews

Division of Anti-Infective Drugs

NDA 18-738

October 29, 1982

Syntex Laboratories, Inc.
3401 Hillview Ave.
Palo Alto, CA. 94304

Propretary Name: SULCOSYN (sulconazole nitrate) Solution 1%.

Dosage Form & Route of Administration:

Product is a solution formulation for topical (dermal) use.

Pharmacological Catagory / Principal Indication :

The new drug substance is an anti-fungal.
The dosage form of the drug is indicated for the treatment of tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis and tinea versicolor.

Structural Formula & Chemical Name:

See page 2 for this drug & selected similar compounds.
Sulconazole is the thio analog of Econazole (see page 2).

Related NDA's etc. [redacted]

Remarks:

Conclusions: Controls are complete and approvable, validation was done and is adequate with minor points to be transmitted to the firm. Memo from HFD-322 indicates that the plants involved are in compliance. [redacted]
Data supports granting the use of a 24 month expiry for the trade package and a 12 month expiry for the sample tube.
Labeling is adequate from a controls standpoint in draft.

cc:
Original NDA
HFD-102
HFN-140 File Copy
HFN-140/Bostwick
HFN-140 Dr. Casola
10/29/82RCBieneman

R. C. Bieneman Chemist HFN-140

RCB 11/1/82

Division of Anti-Infective Drugs Review

NDA 18-738 August 25, 1983

Syntex Laboratories , Inc.
3401 Hillview Ave.
Palo Alto, CA. 94304

Proprietary Name: SULCOSYN (sulconazole nitrate) Solution 1%.

Dosage Form & Route of Administration:

Product is a solution formulation for topical (dermal) use.

Pharmacological Catagory / Principal Indication:

The new drug substance is an antifungal.
The dosage form of the drug is indicated for the treatment of tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis and tinea versicolor.

Structural Formula and Chemical name:

See review of October 29, 1982 .

Related NDA's etc. See review of October 29, 1982.

Remarks:

The present submission of clinical etc. portions of the NDA on June 1, 1983 has not altered the conclusions found in our October review.

Conclusions: Controls remain complete and approvable, validation is complete, Memo from HFN-322 indicated the plants in compliance (they have not appeared on the alert list so no update is required) and the basis for approval was included in the Octo'er review.

R. C. Bieneman Chemist HFN-140

cc:
Original NDA
HFN-102
HFN-140 File Copy
HFN-140 CSO/Bostwick
HFN-140 Dr. Casola
8/25/83RCBieneman

ADEC 8/26/83
MDS 8/30/83

Pharmacology Review's

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-738 (Original Submission, dated 6/1/83)

Date Received: 7/5/83

Date Review Completed: 10/27/83

Applicant: Syntex Laboratories, Inc.
Palo Alto, CA 94304

Drug: Sulcosyn^{R} (sulconazole nitrate) Solution 1%

Related Submissions:

Background Information

Chemical Structure & Description: See NDA [redacted]

DESCRIPTION OF DOSAGE FORM

Sulconazole nitrate will be marketed as a solution in which the active ingredient remains completely solubilized. The solution has the following quantitative composition:

	Percent w/v

Proposed Clinical Indications & Dosage: Sulcosyn^{R} (sulconazole nitrate) Topical Solution 1% is a broad spectrum antifungal agent indicated for topical application in the treatment of tinea pedia (athlete's foot), tinea cruris, and tinea corporis caused by Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis; for the treatment of cutaneous candidiasis (moniliasis); and for the treatment of tinea versicolor.

A small amount should be gently massaged into the affected and surrounding skin areas once or twice daily, except in tinea pedis, where administration should be twice daily. Symptomatic relief is supposed to occur within a few days and clinical improvement should occur within one week. To reduce the possibility of recurrence, candida infections and tinea cruris, corporis, and versicolor should be treated for 3 weeks and tinea pedis for 4 weeks. If significant clinical improvement is not seen after 4 weeks of treatment, an alternate diagnosis should be considered.

NDA 18-738

Preclinical Studies

1. Preclinical studies previously submitted [redacted]

2. Studies Not Previously Submitted [redacted]

Percutaneous Absorption of Sulconazole Nitrate (RS-44822-00-10-3) in A Formulated Solution in Rats, Guinea Pigs, Rabbits & Dogs: (AT 2252)

Methods: A 1% sulconazole nitrate (SCZ) formulated solution containing ^{14}C SCZ was applied once dermally to the shaved skin of rats, rabbits, guinea pigs and dogs. The composition of this solution was as follows:

Component	grams/100 ml

The number of animals and dosing regimen are illustrated in table below.

AMOUNT OF [^{14}C]-SULCONAZOLE NITRATE APPLIED DERMALLY TO RATS, GUINEA PIGS, RABBIT & DOGS AS THE 1% FORMULATED SOLUTION

Species	Sex	N[1]	Amount of [^{14}C]-Sulconazole Nitrate Applied Dermally (mg)	Dose of Sulconazole Nitrate mg/kg	mg/cm^2
Rat[2]	M	47	2.04 ± 0.02	8.5 ± 0.1	0.17 ± 0.00
Guinea Pig[3]	M	47	2.01 ± 0.02	4.4 ± 0.1	0.17 ± 0.00
[illegible]	M	5	6.21 ± 0.00	1.7 ± 0.0	0.10 ± 0.0
[illegible]	F	5	1075.8 ± 17.0	1.1 ± 0.1	0.11 ± 0.00

Values are mean + SE.
[1]N = Number of animals
[2]Ca. 0.2ml (0.2g) formulated sol'n spread over a 12 cm^2 area of skin.
[3]Ca. 0.2ml (0.2g) " " " " " 60 " " " " .
[4]Ca. 0.6ml (0.6g) " " " " " 96 " " " " .
[5]Ca. 1.0ml (1.0g)

Only open studies (dosed areas of skin covered with a protective shield) were conducted, and the dose was left on the skin for 24 hrs, then washed off with soap and warm water.

Also in separate experiments, all species received a single IV (rat, rabbit, dog) or IP (guinea pig) dose of ^{14}C SCZ (rat, dog, 5mg/kg; rabbit, guinea pig 1 mg/kg) so as to more completely describe the disposition of the drug and to support the interpretation of the percutaneous absorption study.

Results

IV Studies: In rabbits and dogs, the decline of radioactivity (RA) in plasma was biphasic; the terminal plasma half-life ($t_{1/2}$) of total RA was ca. 75, 27 & 28 hrs in rabbits, dogs & rats, respectively. Peak plasma RA was obtained at 1 hr in guinea pigs after IP dosing and the plasma $t_{1/2}$ was ca. 35 hrs. In each of the 4 species, the plasma levels of RA had declined within 2-4 days to less than 5% of the highest level. Fecal excretion was the major route of elimination in rats, guinea pigs & dogs (55-72% of administered dose), whereas in rabbits, roughly equal amounts of RA were recovered in urine and feces, respectively 47 & 39% of the administered dose.

Dermal Studies: In the 4 species studied, the amount of unabsorbed drug (in skin washing plus or minus skin hydrolyzates) during the 24-hr dosing period ranged from 58-84% of that applied topically. Less than 2% of the applied dose remained on the skin at 24 hrs after washing with soap and water.

In all 4 species, plasma levels (sampled at 2, 4, 7 & 24 hrs post-dosing, and daily thereafter for 1 wk) of RA were not above background levels.

Urine and feces were collected quantitatively for 7 days after dosing. In all species, by the 5th day, only small amounts of RA were being excreted. After 7 days of collection, about 7.32, 6.2 & 2.5% of the dermally applied dose was recovered in excreta of rats, guinea pigs, rabbits and dogs, respectively. Total recovery of the dose from skin & excreta was about 77, 85, 83 & 82% in rats, guinea pigs, rabbits and dogs, respectively.

"Because the dosed areas of skin were covered with a protective shield, thereby preventing oral ingestion of the dermally applied dose and minimizing the possibility of contamination of excreta with the dose, we estimated the extent of absorption of [^{14}C]-sulconazole nitrate through the skin into the systemic circulation by measuring the amount of radioactivity recovered in excreta. In rats, guinea pigs, rabbits and dogs exposed for 24 hr to a single dermal dose of 0.10 to 0.17 mg sulconazole nitrate per square centimeter of skin area delivered in the formulated solution, percutaneous absorption was estimated to be approximately 7.0%, 3.2%, 5.2% and 2.5%, respectively."

Comments

Sulcosyn^{R} (sulconazole nitrate, SCZ) solution 1% and cream 1% are broad spectrum antifungal agents. These are both intended for dermal application and differ only in terms of the vehicles used. Both the solution and cream formulations are to be indicated for the treatment of tinea pedis, tinea cruris, tinea corporis and Candida albicans infection. The duration of treatment is for a few days up to 4 weeks.

From results of studies in rats, guinea pigs, rabbits and dogs, it was estimated that 2.5-7% of the topically applied dose was percutaneously absorbed using the 1% SCZ solution formulation.

[redacted]

The Division had directed to the applicant several questions and recommendations concerning the toxicology of this drug; [redacted] These were in relation to development of cataracts in dogs; and also the possibility that this drug would cause a decrease in sperm motility and/or viability in this species. It was recommended that the eye and sperm effects seen in dogs be mentioned in the NDA labeling; [redacted] the applicant has adequately addressed these issues [redacted]

Consequently, our earlier recommendations regarding the inclusion of the eye and sperm effects in dogs in the labeling are no longer warranted.

Recommendations

1. The liver is a target organ for toxicity of this drug in experimental animals; in this regard it is similar to other imidazole antifungal drugs. If the results of clinical studies support the animal findings, an appropriate warning in the labeling may be needed.

2. Possible potential target organs as predicted by results in animals (especially dogs) are the intestine and kidney. The ocular findings, seen only in dogs, occurred only at very high oral doses and hence, any such risk to humans receiving SCZ topically would be highly unlikely.

3. The pregnancy portion of the labeling should be Category C. Moreover, the labeling of this drug should accurately summarize the highlights of the findings in preclinical animal reproduction studies (segments I, II & III); see letter to applicant.

Conclusions: On the basis of preclinical evidence of safety, this application is approvable. However, the labeling should be modified as recommended above.

Gamil C. Debbas

Gamil C. Debbas, Ph.D.

cc: Orig. IND
HFN-140 cT 1/3/84
HFN-140/MO
CSO
HFN-220
HFN-102/Glocklin
HFN-140/
R/d init.by:JMDavitt
0524a

Attachment