

Medical Officer's Review of NDA 19-821
(Original Submission, dated February 26, 1988)

Sponsor: Hoffmann-La Roche, Inc.
Nutley, N.J.

3e7

Product: SoriataneTM (acitretin) Capsules

Composition:

<u>Ingredient</u>	<u>10mg Capsule</u> (mg/capsule)	<u>25mg Capsule</u> (mg/capsule)
Acitretin spray-dried powder, 25%		
Microcrystalline cellulose (Avicel PH 102)		
*includes 1% overage.		

Purpose: "Soriatane is indicated for the treatment of significant psoriasis, including erythrodermic and pustular types. Significant psoriasis is a condition that involves more than 10% of body surface area or is physically, occupationally or psychologically disabling."

Dosage: Initial dose 25 or 50mg/day given in one dose with the main meal. Dose may be increased to 75mg/day maximum or decreased to minimize side effects.

Package: Brown and white 10mg capsules (bottles of 100, prescription packs of 30, Tel-E-Dose^R packages of 100). Brown and yellow 25mg capsules (bottles of 100, prescription packs of 30, Tel-E-Dose packages of 100).

Background: Acitretin is the principal metabolite of etretinate (Tegison^R), which was approved for the treatment of severe, recalcitrant psoriasis, including the erythrodermic and pustular types. Etretinate has the marked disadvantage of a long elimination half-life of 120 days. It is stored in fat tissue and has been detected in blood as long as 2.9 years after chronic therapy was discontinued. Because etretinate is a potent teratogen, this long half-life has meant that pregnancy must be avoided for 3 years after therapy is discontinued. Acitretin was found to have similar therapeutic effects, but a much shorter half-life, varying between 33 and 96 hours and it was not detectable in 67 patients three weeks after therapy was discontinued.

Related submissions are:

IND
IND
IND
IND

Manufacturing Controls: The chemist concluded the following: "This application is not approvable from a manufacturing and control standpoint. Deficiencies are outlined in the Review Notes and the Draft Letter to the Applicant. The CSO is to convey these deficiencies to the Applicant."

Pharmacology: The pharmacologist made the following comments and recommendation:

1. Acitretin is a major metabolite of etretinate (Tigason^R), a drug already marketed by the applicant for similar indications.
2. Acitretin offers two main advantages over etretinate; it has a relatively short elimination half-life, and it does not accumulate in the adipose tissue.
3. Its toxicologic profile (target organ toxicity) is, in general, similar to that of etretinate.
4. This application may be approved. Not having reviewed the pharmacokinetic data in depth, however, I am unsure with regard to adequacy of its labelling—since this drug is also a teratogen. Specifically, the proposed one month washout period following withdrawal of drug therapy, as proposed in the labelling, should be commensurate with the virtually total elimination of drug and its retinoid metabolites, as established by the available human data."

Clinical Studies

Controlled Clinical Studies

- A. Pivotal Studies: Two well-controlled multicenter pivotal studies were done.

Protocol No. N2 916D: This study was begun March 1985 and is ongoing.

Title: A double-blind comparison of varying dosage schedules with Ro 10-1670 in patients with severe psoriasis.

Investigators:

Charles N. Ellis, M.D. (21 pts)
Univ. of Michigan Medical Center
Ann Arbor, MI 48105-0314

Virginia C. Fiedler, M.D. (21 pts)
Univ. of Illinois Medical School
Chicago, ILL. 60612

Jon M. Hanifin, M.D. (21 pts)
Oregon Health Sciences University
Portland, Oregon 97201

Gerald S. Lazarus, M.D. (24 pts)
Univ. of Pennsylvania School of Medicine
Philadelphia, PA 19104

Nicholas Lowe, M.D. (24 pts)
 Univ. of California at Los Angeles
 Los Angeles, CA. 90025

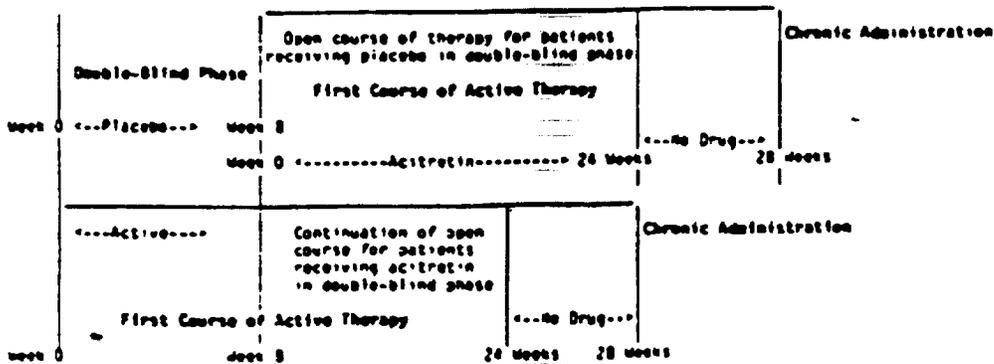
Method: This study was randomized, double-blind, placebo-controlled, parallel group.

Adults with extensive psoriasis (greater than 20% of body surface) or disabling psoriasis (unable to carry out daily activities in a normal manner) entered the study—85 males and 29 females, aged 26 to 78 years. Patient exclusions were appropriate and included women of childbearing potential and nursing mothers.

The study consisted of 3 phases, as follows:

1. Eight weeks of double-blind, placebo-controlled treatment.
2. Twenty-four weeks of open active treatment (referred to as the "First Course of Active Therapy").
3. Chronic administration, consisting of multiple 6-month courses of open treatment with acitretin.

Treatment Flow Chart



Double-Blind Phase: Patients were assigned randomly to four dosage groups—10mg, 50mg, 75mg or placebo.

If patients experienced significant adverse experiences or failed to respond to treatment, the code could be broken and patients assigned to open treatment. Initially, doses were individualized according to clinical response or to adverse reactions, but after amendment B (May 1985), patients followed specific dosing procedures.

Patients on 10mg/day who had intolerable adverse reactions were removed from the study. Patients on 50 or 75mg/day who reported adverse reactions were reduced to 30 to 50mg/day, respectively. Further reductions of these to 10 or 30mg/day, respectively, were made only if adverse reactions were intolerable. If patients had their dosage reduced to 10mg/day and failed to respond clinically or experienced adverse effects, they were removed from the study.

Patients assigned to 10mg/day or to placebo and who failed to improve were given acitretin 50mg/day in an open-label fashion.

No dosage increases were allowed.

Open Therapy: After the double-blind phase was completed, those patients on acitretin continued on acitretin in an open fashion. Placebo patients were put on acitretin. This open phase lasted 24 weeks, followed by a 4-week off-drug observation period.

Dosages were individualized before Amendment B (May 1985). Amendment B, however, specified that doses of 10, 30, 50 or 75mg/day only be used. Dose reductions were not permitted unless adverse reactions were intolerable, in which case stepwise reductions were allowed to 50, 30 or 10mg/day. No increases in dosages were allowed. Patients who had received placebo during the double-blind phase were given 50mg/day. Patients who had been on 10mg/day remained at this dose unless there was no improvement, in which case they were given 50 mg/day.

After these stepwise dose adjustments were made, if 10mg/day was ineffective or if adverse reactions became intolerable, patients were removed from the study.

This 24 week open course of therapy is called the "First Course of Active Therapy."

Chronic Administration: Following the open course of therapy, those patients who had responded to treatment and later relapsed during the 4-week off-drug period were eligible to received additional courses of therapy. Each course could last a maximum of 6 months, followed by a 4-week off-drug observation period. During the off-drug period, if a patient had a severe relapse, acitretin could be resumed at the therapeutic level without further interruption.

Dosing for each patient was individualized for each patient before Amendment C (July 1985). Amendment C restricted doses to 10, 30, 50 or 75mg/day, and dosing procedures followed those explained above under Open Therapy. Amendment D (Jan. 1986) then permitted dosage adjustments up or down to permit a maximum clinical response with minimal adverse reactions for each patient.

Scoring:

Double-Blind Phase: Scale, erythema, lesion thickness and presence of pustules were evaluated at baseline and at weeks 1, 2, 4, 6 and 8 as follows:

0 - absent, 1 - trace, 2 - mild, 3 - mild to moderate,
4 - moderate, 5 - moderate to severe 6 - severe.

A global evaluation was made at baseline and at the end of the 8 weeks, as follows:

1 - almost clear, 2 - mild, 3 - mild to moderate
4 - moderate, 5 - moderate to severe, 6 - severe

The extent of skin involvement was assessed by estimating the percentage of body surface area involved at baseline and at the end of the 8 weeks.

Open Therapy: Scale, erythema, lesion thickness and presence of pustules were evaluated every 4 weeks for 16 weeks (total course of active therapy was 24 weeks) in patients who had received acitretin during the double-blind phase. And these parameters were evaluated in patients who had received placebo at weeks 1, 2, 4, 6, 8 and then every 4 weeks for a maximum of 24 weeks. And at the end of the 4-week off-drug observation period, the same efficacy ratings were repeated in all patients.

A global evaluation and an estimate of the extent of the disease were made at the end of the open therapy phase and at the end of the 4-week off-drug observation period.

Chronic Administration: Scale, erythema, lesion thickness and pustules were rated before treatment, every 3 months while receiving acitretin, at the end of each course of chronic treatment and at the end of the 4-week off-drug observation periods.

A global evaluation was made at the end of each course of chronic therapy and at the end of the 4-week off-drug observation periods.

The extent of the disease was assessed before the start of the chronic treatment, at the end of each course of chronic treatment and at the end of the 4-week off-drug observation periods.

Evaluation of Safety: The following examinations and lab tests were done at entry into the study:

1. Medical history and physical exam (including ophthalmologic exam).
2. Radiologic exam (including lateral views of the cervical, thoracic and lumbar portions of the spine).

3. CBC (including a differential WBC, reticulocyte count and platelet count).
4. Blood chemistries (including fasting blood sugar, BUN, serum creatinine, serum albumin, total protein, serum bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, calcium, phosphorus, uric acid, chloride, sodium, potassium, creatine phosphokinase) and two determinations 24h apart of fasting levels of triglycerides, cholesterol and HDL cholesterol.
5. Urinalysis

The laboratory tests were repeated at the following times:

1. Double-blind phase—weeks 1, 2, 4, 6 and 8.
2. Open therapy—every 4 weeks for 16 weeks (total course of active therapy was 24 weeks) in patients who had received acitretin during the double-blind phase. At weeks 1, 2, 4, 6 and 8 and then every 4 weeks for a maximum of 24 weeks in patients who had received placebo. And at the end of the 4-week off-drug observation period in all patients.
3. Chronic administration—at the start of each course, every 3 months during treatment, and at the end of the 4-week off-drug observation period.

Ophthalmologic and radiologic exams were made at the end of open therapy (24 weeks) or whenever a patient discontinued treatment. A one-year follow-up safety evaluation was made in these patients and included lab tests, ophthalmologic and radiologic exams.

During chronic administration, an ophthalmologic exam was made at the end of each 6-month course and a radiologic exam at yearly intervals.

Adverse experiences were recorded on the case report forms and were graded by the investigator as mild, moderate or severe.

Results: The most significant scoring methods are the investigators' global evaluations and the reductions in the mean scores for scale, erythema and lesion thickness.

Double-Blind Phase (results)

One hundred-fourteen patients entered this phase and could be evaluated for efficacy. The double-blind code was broken early for 38 patients. Seventy-six completed the double-blind phase.

Reasons for Breaking the Double-Blind Code Early
acitretin mg/day

<u>Reasons</u>	<u>10</u>		<u>50</u>		<u>75</u>		<u>Placebo</u>	
	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
adverse experiences	1	3.6	6	20.7	9	32.1	3	10.3
insuff. response	6	21.4	0	0.0	0	0.0	6	20.7
protocol violation	0	0.0	1	3.4	0	0.0	1	3.4
intercurrent illness	1	3.6	0	0.0	0	0.0	0	0.0
not specified	3	10.7	0	0.0	0	0.0	1	3.4
broken code early	11	39.3	7	24.1	9	32.1	11	37.9
completed double-blind phase	17	60.7	22	75.9	19	67.9	18	62.1
Total Treated		28		29		28		29

Only 6 patients of the 114 withdrew from the study: 2 in the placebo group (one adverse experience and one refused treatment), 2 in the 10mg group (one adverse reaction and one intercurrent illness) and 2 in the 75mg group (one adverse experience and one protocol violation). The remaining 108 patients continued receiving acitretin in the open phase of the study.

Percentage Reduction of Mean Scores of Disease Parameters
during Double-Blind Phase

Treatment Group

acitretin (mg/day)

	10		50		75		Placebo	
	n	mean	n	mean	n	mean	n	mean
<u>Scale</u>								
Baseline	28	3.75	29	3.76	28	4.25	29	4.10
Week 8	20	4.10	21	1.95	17	1.59	18	3.72
% reduction	20	0.0%	21	48.1%	17	62.6%	18	9.3%
<u>Erythema</u>								
Baseline	28	4.14	29	4.59	28	4.36	29	4.21
Week 8	20	3.80	21	2.48	17	2.35	18	3.72
% reduction	20	8.2%	21	46%	17	46.1%	18	11.6%
<u>Thickness</u>								
Baseline	28	3.86	29	4.10	28	4.14	29	4.10
Week 8	20	3.65	21	1.90	17	1.18	18	3.67
% reduction	20	4.4%	21	53.7%	17	71.5%	18	10.5%

At the end of the 8 weeks, both the 50mg and the 75mg treatments showed clinically significant superiority to both the placebo and the 10mg doses. The 75mg dose was not significantly superior to the 50 mg dose, except for the parameter of thickness.

Percentage Improvement in the Mean Scores of Physicians'
Global Evaluations during the Double-Blind Phase

Treatment Group

acitretin (mg/day)

	10		50		75		Placebo	
	n	mean	n	mean	n	mean	n	mean
Baseline	28	4.36	29	4.55	28	4.61	29	4.62
End of Double-Blind	25	4.20	23	2.39	22	2.32	24	4.38
Mean change from Baseline	25	3.7%	23	47.5%	22	49.7%	24	5.2%

Both the 50mg and 75mg doses showed clinically significant superiority to the 10mg dose and the placebo. There was no significant difference between the 50 and 75mg doses. Both the 50 and 75 mg doses showed a clinically significant improvement over baseline.

Physicians' Global Evaluations during the Double-Blind Phase
(% of patients in each category)

	Treatment Group							
	acitretin (mg/day)							
	10		50		75		Placebo	
	no.	%	no.	%	no.	%	no.	%
End of Double-Blind	pts.		pts.		pts.		pts.	
Worsened	4	16	0	0	1	5	6	25
No Change	11	44	2	8	2	9	11	46
Improved	10	40	22	92	19	86	7	29

Only 40% of the 10mg patients and 29% of the placebo patients improved. But over 85% of the 50mg and 75mg groups improved.

First Course of Active Open Therapy (results)

112 patients received a first course of active therapy. The mean duration of therapy was 148 days, and the mean dose of acitretin was 42.8mg/day.

Percentage Reduction from Baseline of Mean Scores of Disease Parameters during First Course of Active Therapy

	n	Scale	Erythema	Thickness
Baseline	112	---	---	---
Week 24	59	55.2%	50.1%	59.7%
4 week post-drug	79	35.3%	40.0%	39.2%

Both at the end of 24 weeks and after the following 4 weeks off therapy, the scores showed clinically significant improvement over baseline scores.

Percentage Reductions from Baseline in Physicians' Global Evaluation Ratings

	n	mean
Baseline	112	--
week 4	39	49.4%
4 week post-drug	76	39.7%

Physicians' global evaluations showed a clinically significant improvement over baseline scores at week 24 and at 4 weeks postdrug.

First Course of Chronic Administration (results)

55 patients had received acitretin therapy at the time of data cutoff in this study (44 males, 11 females, aged 30 to 74 years).

Percentage Reduction from Baseline of Mean Scores
of Disease Parameters during First Chronic Course

	n	Scale	Erythema	Thickness
Baseline	54	---	---	---
6 months	41	48.5%	41.7%	50.6%
4 weeks post-drug	39	26.3%	21.4%	25.0%

Disease parameter scores showed clinically significant reductions from baseline at the end of 6 months of treatment and also after 4 months off treatment.

Percentage Reductions from Baseline in Physicians' Global
Evaluation Ratings

	n	BRAD
Baseline	53	--
6 months	39	43.4%
4 weeks post-drug	38	17.1%

Improvements in the physicians' global evaluation scores were clinically significant at the end of 6 months of treatment and after 4 weeks off treatment.

Second Course of Chronic Administration (results)

Only 4 patients had received a second course of chronic therapy at the time of data cutoff.

Protocol No. 3019 A: This study was begun Nov. 10, 1985 and is ongoing.

Investigators:

Eugene A. Bauer, M.D. (15 pts)
Washington University School of Medicine
St. Louis, Missouri 63110

Paul R. Bergstresser, M.D. (15 pts)
UTHSCD
Dallas, Texas 75235

Charles Camisa, M.D. (15 pts)
The Ohio State University
Columbus, Ohio 43210

Lynn Drake, M.D. (15 pts)
Emory University Clinic
Atlanta, Georgia 30322

Charles M. Ellis, M.D. (18 pts)
University of Michigan Medical Center
Ann Arbor, Michigan 48105

Janet Fairley, M.D. (15 pts)
University of Rochester Medical Center
Rochester, New York 14642

Jon M. Hanifin, M.D. (15 pts)
The Oregon Health Sciences University
Portland, Oregon 97201

Tabitha Henderson, M.D. (9 pts)
University of Pittsburgh
Pittsburgh, Pennsylvania 15261

Stephen N. Horwitz, M.D. (17 pts)
Mt. Sinai Medical Center of Greater Miami
Miami Beach, Florida 33140

Gerald G. Krueger, M.D. (15 pts)
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

O. Fred Miller, M.D. (15 pts)
Mayo Clinic
Rochester, Minn. 55905

Elise Olsen, M.D. (15 pts)
Duke University Medical Center
Durham, North Carolina 27710

Jerome L. Shupack, M.D. (16 pts)
New York University Medical Center
New York, New York 10016

Title: "A double-blind comparison of varying dosage schedules with Ro 10-1670 in patients with severe psoriasis.

Objective: To compare the efficacy and safety of two dosages (25 and 50 mg/day) of acitretin and placebo in the treatment of severe psoriasis and to evaluate long-term efficacy and safety of acitretin.

Method: The same as in the foregoing study (Protocol No. N 2916D) except that patients were assigned randomly to 3 groups - 25mg or 50 mg of acitretin or placebo.

If severe adverse experiences occurred or if the patient failed to respond to treatment, the code could be broken.

If the code was broken because of adverse reactions, patients who were on 50mg/day or 25mg/day were given 25mg/day or 10mg/day, respectively. Further reductions to 10 mg/day were allowed only in case of intolerable adverse reactions. If the reactions persisted at 10mg/day, treatment was stopped.

If the code was broken because of lack of efficacy, patients were put on 50mg/day in an open fashion.

All patients were eligible for open therapy at the end of the double-blind phase. During open therapy, only doses of 75, 50, 25, or 10mg/day were allowed. Dosages were adjusted to achieve maximum benefit and minimum adverse reactions.

Results: The most significant scoring methods are the investigators' global evaluations and the reductions in the mean scores for scale, erythema and lesion thickness.

Double-Blind Phase (results): 219 patients entered this phase. Data on 217 were evaluable for efficacy. 184 patients completed the double-blind phase of the study. The code was broken early by 35 patients for the reasons given in the following table:

<u>Reasons</u>	<u>Acitretin mg/day</u>					
	<u>25</u>		<u>50</u>		<u>Placebo</u>	
	no.	%	no.	%	no.	%
Adverse experiences	1	1.3	4	5.6	0	---
Insufficient response	5	6.7	3	4.2	16	22.2
Lost to follow-up	3	4.0	0	---	0	---
Protocol violation	1	1.3	0	---	0	---
Not specified	1	1.3	1	1.4	0	---
Broke code early	11	14.7	8	11.1	16	22.2
Completed double-blind phase	64	85.3	64	88.9	56	77.8
Number of patients treated	75	---	72	---	72	---

Only 5 of the 219 patients withdrew from the double-blind phase, 4 in the 25mg/day group (3 lost to follow-up and 1 protocol violation) and 1 in the 50mg/day group (adverse experience).

Percentage Reductions of Mean Scores of Disease Parameters
during Double-Blind Phase

Treatment Group

Acitretin mg/day

	<u>25</u>		<u>50</u>		<u>Placebo</u>	
	n	mean	n	mean	n	mean
<u>Scale</u>						
Baseline	74	4.11	71	4.10	72	3.97
Week 8	60	2.60	63	2.27	56	3.66
% reduction	--	36.7%	--	44.6%	--	7.8%
<u>Erythema</u>						
Baseline	74	4.24	71	4.45	72	4.42
Week 8	60	3.12	63	2.81	56	3.98
% reduction	--	26.4%	--	36.9%	--	9.9%
<u>Thickness</u>						
Baseline	74	4.11	71	4.20	72	4.03
Week 8	60	2.70	63	2.08	56	3.77
% reduction	--	34.3%	--	50.5%	--	6.5%

The 25mg and 50mg treatments were clinically significantly superior to the placebo at 8 weeks. The 50 mg was significantly superior to the 25mg dose in reducing erythema and thickness. Both the 25mg and the 50mg doses showed clinically significant improvement of all 3 parameters compared with baseline.

Percentage Improvement in the Mean Scores of Physicians' Global
Evaluations during the Double-Blind Phase

Treatment Group

Acitretin mg/day

	<u>25</u>		<u>50</u>		<u>Placebo</u>	
	n	mean	n	mean	n	mean
Baseline	73	4.37	71	4.49	72	4.43
End of double-blind	66	3.33	70	2.91	68	4.32
Mean change from baseline	66	23.8%	70	35.2%	68	2.5%

The 25mg and 50mg doses showed clinically significant improvement compared with the placebo group. Both the 25mg and 50mg groups showed clinically significant improvement compared with baseline. And the 50mg dose was significantly better than the 25mg dose.

Physicians' Global Evaluations during the Double-Blind Phase
(% of patients in each category)

Treatment Group

Acitretin mg/day

	<u>25</u>		<u>50</u>		<u>Placebo</u>	
	no.	%	no.	%	no.	%
<u>End of Double-Blind</u>						
Worsened	7	11	4	6	14	21
No change	13	20	11	16	37	54
Improved	46	70	55	79	17	25

Seventy percent of the 25mg patients and 79% of the 50mg patients showed improvement. Only 25% of the placebo patients improved.

First Course of Active Open Therapy (results)

Two-hundred seventeen patients received a first course of active therapy. The mean duration of therapy was 158.4 days and the mean daily dose was 43.1mg.

Percentage Reduction from Baseline of Mean Scores of Disease Parameters during First Course of Active Therapy

	<u>n</u>	<u>Scale</u>	<u>Erythema</u>	<u>Thickness</u>
Baseline	215	---	-----	-----
week 24	132	57.7%	52.4%	62.6%
4 weeks post-drug	171	39.8%	39.3%	42.2%

There were clinically significant reductions of scores of all 3 disease parameters both at the end of 24 weeks and after 4 weeks off-drug.

Percentage Reductions from Baseline in Physicians' Global Evaluation Ratings

	<u>n</u>	<u>mean</u>
Baseline	214	---
Week 24	99	58.9%
4 weeks post-drug	165	40.5%

There was clinically significant improvement over baseline at the end of 24 weeks of active therapy and at 4 weeks after acitretin was discontinued.

Chronic Administration (results)

No results are reported for patients on chronic administration.

B. Supportive Studies**1. Protocol No. D 10250**

Title: Etretin (Ro 10-1670) in the Treatment of Severe Psoriasis.

Investigators: Drs. Orfanos, Ehlert and Gollnick-Berlin.

Objectives: To compare the efficacy and the safety of three doses of Ro 10-1670 and one dose of etretinate in patients with severe psoriasis.

Method: Randomized, double-blind, positive controlled, parallel-group, multicenter study involving 182 patients (131 males and 51 females, ages 10 to 82 years). Patients received Ro 10-1670 in doses of 10 mg, 25mg or 50mg, or 50mg of etretinate, once daily for 8 weeks.

Results: No dose-response relationship between doses of Ro 10-1670 could be established for efficacy, although a dose-response relationship was demonstrable for safety. All 4 treatment regimens, however, showed significant improvements in the extent and severity of the disease.

2. Protocol No. D 10251

Title: Ro 10-1670 in the Treatment of Severe Psoriasis.

Investigator: A. Lassus, M.D.
Helsinki University Central Hospital
Helsinki, Finland

Objectives: To determine a dose-response relationship of Ro 10-1670 regarding therapeutic activity in psoriasis and tolerability compared with placebo.

Method: Study was randomized, double-blind, placebo-controlled, parallel-group six month phase followed by a six-month open-label phase. A total of 80 patients (42 males, 38 females, aged 21 to 79 years); 40 patients were assigned to each of 4 dose groups (10mg, 25mg, 50mg or placebo).

Results: Ro 10-1670 was effective in severe psoriasis in a dose-dependent manner. During the double-blind phase, the optimal dose for most patients was 25mg/day. The open phase is in progress.

Adverse Reactions:

- A. Laboratory Test Abnormalities: The following results were taken from the 329 patients who received acitretin in the domestic trials.

Most of the lab abnormalities are known effects of therapy with retinoids. In the 50mg/day dosage groups, the most frequent abnormalities of significance were elevations of serum triglyceride levels (56.4%), SGPT (17.8%), SGOT (15.8%) and LDH (14.9%). Therapy was discontinued in 14 patients because of lab abnormalities-elevated triglycerides in 5; elevated liver function tests in 8; and elevated triglycerides, liver function tests and hypoglycemia in a patient with preexisting diabetes.

Lab test abnormalities did not tend to be dose-related.

Percent of Patients in Whom Lab Abnormalities Reported

Hematologic

25 - 50%

- Increased:
- reticulocytes

10 - 25%

- Increased:
- neutrophils
- WBC
- Decreased:
- Lymphocytes

1 -10%

- Increased:
- eosinophils
- bands
- lymphocytes
- basophils
- monocytes
- Decreased:
- WBC
- neutrophils
- Increased or Decreased:
- Hgb
- platelets
- Hct
- RBC

Urinary

1 -10%

- RBC in urine
- WBC in urine
- glycosuria
- acetonuria
- proteinuria

Hepatic

25% - 50%

Increased:

- SGPT

Decreased:

- HDL cholesterol

10 - 25%

Increased:

- SGOT

- alkaline phosphatase

- direct bilirubin

- LDH

- GGTP

Decreased:

- serum albumin

1 - 10%

Increased:

- total bilirubin

- globulin

Renal

10 - 25%

Increased:

- uric acid

1 - 10%

Increased:

- creatinine

- BUN

Electrolytes

10 - 25%

Increased:

- phosphorus

- potassium

Increased and Decreased:

- magnesium

1 - 10%

Decreased:

- phosphorus

- potassium

Increased and Decreased:

- sodium

- chloride

- calcium

Miscellaneous

50 - 75%

Increased:
- triglycerides

25 - 50%

Increased:
- CPK

10 - 25%

Increased:
- fasting blood sugar

1 - 10%

Decreased:
- fasting blood sugar
Increased and Decreased:
- iron

- B. Clinical Abnormalities: The following results were taken from the 329 patients who received acitretin in the domestic clinical trials. Most of these reactions are typical of hypervitaminosis A and of retinoid therapy. The highest incidence of reactions involved the skin and appendages (89.1%), mucous membranes (80.9%), eye (30.1%), musculoskeletal system (30.1%) and CNS (24.9%). Of the 329 patients, 315 reported adverse events totalling 1,968. In general, the frequency of adverse reactions increases with increasing dosage. The placebo itself, however, has a 66% adverse event rate.

Adverse Reactions Occurring in 10% or more of Patients,
Probably or Possibly Related to Treatment

<u>Clinical Adverse Reaction</u>	<u>No. of Pts.</u>	<u>% of Pts.</u>
Chellitis	251	76.3
Skin Peeling	199	60.5
Alopecia	187	56.8
Pruritus	98	29.8
Rhinitis	88	26.7
Sticky skin	84	25.5
Nail Disorder	82	24.9
Dry Skin	73	22.2
Arthralgia	61	18.5
Xerophthalmia	58	17.6
Rigors	49	14.9
Dry Mouth	48	14.6
Erythematous Rash	38	11.6
Atrophy of Skin	34	10.3
Hyperesthesia	34	10.3
Epistaxis	33	10.0

Adverse Reactions Reported in 1-10% of Patients
(some of which may have no relation to acitretin)

Paronychia	Nausea
Paresthesia	Abdominal Pain
Psoriasiform Rash	Conjunctivitis/Irrit.
Photosensitivity Reaction	Abnormal/Blurred Vision
Pyogenic Granuloma	Blepharitis
Bullous Eruption	Eye Pain
Skin Ulceration	Photophobia
Cold/Clammy Skin	Tinnitus
Increased Sweating	Taste Perversion
Purpura	Earache
Abnormal Hair Texture	Insomnia
Skin Fissures	Nervousness
Hypoesthesia	Myalgia
Infection	Spinal Hyperostosis
Seborrhea	Back Pain
Thirst	Hypertonia
Stomatitis	Arthritis
Gingivitis	Headache
Increased Saliva	Pain
Gingival Bleeding	Fatigue
Anorexia	Increased Appetite
Edema	

There was also a large number of possible reactions reported in fewer than 1.0% of patients. I have not listed these here. They can be found listed in the package insert.

C. Special Topics

1. Teratogenicity Worldwide: One pregnancy was reported (European). The patient had received acitretin for 14 days and her pregnancy was then terminated. Because the stage of pregnancy was so early, the tissue could not be evaluated histologically.
2. Deaths Worldwide: There was none reported among the approximately 1080 patients who received acitretin.
3. Radiologic Evaluations in the Domestic Studies: X-ray examinations of the cervical, thoracic and lumbar spine of 262 patients were made and reviewed by radiologists.

Seven percent of patients who had abnormalities before treatment showed new changes or progression of preexisting changes. Patients who had normal pre-treatment radiographs showed no bone changes.

The commonest changes were degenerative spurring of the spine in 4% of patients, and anterior bridging of the spine and increased diffuse idiopathic skeletal hyperostosis (DISH) occurring in 2% and 1% of patients, respectively. One patient had narrowing and destruction of cervical disk margins.

4. Ophthalmologic Evaluations in Domestic Studies: Of 331 patients who had eye exams, 252 (76%) had at least one follow-up exam that could be compared with baseline. Eighty-two drug-related adverse reactions occurred in 72 (29%). Data from the eye exams were reviewed by Dr. Paul Lichter of the Kellogg Eye Center, University of Michigan. The following were reported:

- dry eyes (17%)
- eye irritation (6%)
- loss of eyebrows or eyelashes (4%)
- photophobia, blepharitis, lid crusting, redness and recurrent styes (less than 1% each)
- pannus in one patient
- subepithelial corneal lesions in one patient
- cataracts seen in 3 patients, but not attributed to acitretin

Most reactions were reversible and not considered serious.

Other possibly or probably related events reported on medical forms other than the eye exam form were pseudotumor cerebri (1 patient), decrease in night vision (2 patients), blurred vision (3 patients).

Labeling: In the boxed Contraindication section and in the Precautions section (under Information for Patients and under Pregnancy), the statement is made that women of childbearing potential must use an effective form of contraception "for at least one month after cessation of treatment". I question whether one month is long enough. In 67 patients, soriatane plasma levels were non-measurable 3 weeks after cessation of therapy. Elimination half-life was reported to vary from 33 to 96 hours in 22 persons.

The Indications and Usage section states: "Soriatane is indicated for the treatment of significant psoriasis, including erythrodermic and pustular types". And the labeling defines "significant" psoriasis as "a condition that involves more than 10% of body surface area or is physically, occupationally or psychologically disabling". The labeling for Tegison (etretinate, the parent compound) seems to me to be more appropriate. It states: "...is indicated for the treatment of severe, recalcitrant psoriasis, including the erythrodermic and generalized pustular types. Because of significant adverse effects associated with its use, Tegison should be prescribed only by physicians knowledgeable in the systemic use of retinoids and reserved for patients with severe, recalcitrant psoriasis who are unresponsive to or intolerant of standard therapies; topical tar plus UVB light; psoralens plus UVA light; systemic corticosteroids; and methotrexate."

Under Dosage and Administration, the initial dose is given as "25 or 50 mg per day", and this can be "increased for inadequate response to a maximum of 75mg per day." Only the 50mg dose, however, is supported by the two double-blind, pivotal studies.

Statistical Review: The statistician made the following conclusions:

1. The results of the two studies are in agreement. The statistical results support the conclusion that Soriatane (acitretin) is effective in treatment of Psoriasis.
2. The effective dose causes a statistically significant increase, compared to placebo, in clinical and laboratory adverse events. However, the reviewing medical officer states these are less severe than currently approval treatment products [i.e., than etretinate].
3. The combined results show that the safest effective dose may be between 35mg/day and 40mg/day. The company can probably better define this by evaluating the open study data."

Summary and Evaluation:

Efficacy: Two studies were performed. Both were domestic, double-blind, placebo-controlled, parallel group, multicenter studies designed to compare different Soriatane dosage schedules in psoriasis. The design was similar in both studies, but in study N2916D 10mg, 50mg and 75mg tablets were compared to a placebo, and in study 3019A, 25mg and 50mg tablets were compared to the placebo. Thus, only the 50mg/day dosage was compared to the placebo in each of the studies. Since two studies are required of the sponsor, these critical studies are compared below when using the 50mg/day dose.

Study N2916D

Percent Reduction in Mean Scores in Double-Blind Phase

	Acitretin 50mg			Placebo		
	n	% reduct.	p-value	n	% reduct.	p-value
Scale	21	48.1	≤ 0.05	18	9.3	NS
erythema	21	46.0	≤ 0.05	18	11.6	NS
thickness	21	53.7	≤ 0.05	18	10.5	NS

Percent Improvement in Mean Scores of Physician's Global Evaluations in Double-Blind Phase

	Acitretin 50mg			Placebo		
	n	% impr.	p-value	n	% impr.	p-value
mean change from bsline	23	47.5	≤ 0.05	24	5.2	NS

Study 3019A

Percent Reduction in Mean Scores in Double-Blind Phase

	Acitretin 50mg			Placebo		
	n	% reduct.	p-value	n	% reduct.	p-value
Scale	63	44.6	≤ 0.05	56	7.8	NS
erythema	63	36.9	≤ 0.05	56	9.9	NS
thickness	63	50.5	≤ 0.05	56	6.5	NS

Percent Improvement in Mean Scores of Physician's Global Evaluations in Double-Blind Phase

	Acitretin 50mg			Placebo		
	n	% impr.	p-value	n	% impr.	p-value
mean change from bsline	70	35.2	≤ 0.05	68	2.5	NS

Thus, both studies show that Soriatane 50mg/day is statistically superior in efficacy to placebo in the treatment of psoriasis.

Recommendation: I recommend this NDA be made approvable, pending submission of satisfactory FPL and satisfactory manufacturing and controls information.

Wilson A. Powell

Wilson A. Powell, M.D.
Medical Officer

cc: Orig NDA
HFD-340
HFD-520
HFD-520/WAPowell:elp/11/22/88:01/13/89
HFD-520/Chem
HFD-520/Pharm
HFD-520/DCBostwick
4405m

16 9/89

Date Review Begun: March 12, 1990
Date Review Completed: March 16, 1990

Addendum to Medical Officer's Review of NDA 19-821

Sponsor: Hoffmann-LaRoche, Inc.
Nutley, N.J.

Drug: Soriatane (acitretin) Capsules

Indication: The original indication for the product was "significant" psoriasis, including erythrodermic and pustular types.

Dosage: Initial dose 25 or 50 mg/day given in one dose with the main meal. Dose may be increased to 75 mg/day maximum or decreased to minimize side effects.

Dates of Submission: The original application was submitted February 26, 1988. Labeling revisions dated August 4, 1989 and September 18, 1989 are the subject of this review.

Other Reviews:

A. Medical

In his original medical officer review, Dr. Wilson Powell noted that clinical studies in severe psoriasis have established the clear superiority of 50 mg of acitretin per day over placebo. However, he raised two labeling issues:

1. Contraception was mandated for only one month after cessation of Soriatane therapy. Dr. Powell felt that this time period should be longer.
2. He felt that the indications should be the same as for Tegison.

B. Statistical

In his review dated November 21, 1988, Dr. Ralph Harkins agreed that efficacy had been established by the two pivotal clinical studies.

C. Biopharmaceutics

Dr. Jim McDowell was generally favorable in his review of the submitted biopharmaceutics data. His review made a number of labeling recommendations (see below) and recommended additional studies to be performed before or after NDA approval at the discretion of this Division.

D. Pharmacology

In his original review dated June 8, 1988 (addenda dated August 29, 1988, May 25, 1989 and October 17, 1989), Dr. Sewa Joshi recommended approval of the NDA. He also questioned whether one month of contraception following cessation of therapy was adequate (subsequent labeling revisions provide for a two-month "washout" period).

E. Epidemiology

Dr. Charles Anello of FDA's Epidemiology group has registered serious concerns about the approval of Soriatane because of the potential for greater exposure to women (due to the shorter half-life) in his memo dated September 5, 1989.

F. Chemistry.

Ms. Mary Ann Jarski found multiple deficiencies in her first two chemistry reviews, dated September 16, 1988 and August 23, 1989. In her third review, (to be added when review is available).

Background:

On August 10, 1989, we met with Roche to discuss some of our concerns. A number of issues were discussed, including animal pharmacology, the biopharmaceutics data, adverse reactions, and labeling.

A second meeting was held September 22, 1989. This meeting concerned labeling issues, biopharmaceutics, and animal carcinogenicity studies.

Finally, an in-house meeting was held October 19, 1989. At this meeting, labeling and biopharmaceutics data were discussed. It was agreed that if the labeling were revised and certain other conditions met, an approvable letter could issue.

Labeling Review:

- A. We have received some informal comments from Dr. Burlington and Dr. Peck which we will incorporate into this review. The comments below pertain to the physician insert submitted September 18, 1989: