CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

Trade Name: SORIATANE

Generic Name: acitretin

Sponsor: Hoffman-LaRoche, Inc.

Approval Date: April 18, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-821/S-002
NDA 19-821/S-006

Hoffmann-La Roche, Inc.
Attention: Lisa Luther
Group Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Luther:

Please refer to your supplemental new drug applications dated August 16, 1999, received August 18, 1999 (S-002) and May 17, 2002, received May 21, 2002 (S006), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SORIATANE ® (acitretin) Capsules, 10 mg and 25mg.

We acknowledge receipt of your submissions dated March 6, February 27, 11, 6, 2003, December 19, 17, 4, 2002 and November 26, 2002.

These supplemental new drug applications provide for revisions which include changes to the Boxed Warning, Contraindications, Warnings, Precautions, Overdosage, Drug Interactions, Adverse Reactions, the Informed Consent Form for Females, the addition of Clinical Studies and Geriatric sections, a Medication Guide, and revisions to the Soriatane Pregnancy Prevention program booklet. This approval also contains wording for the Dear Professional Letters.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. Please note on page 5 of the Package Insert placement of the following table under Information for Males Taking Soriatane:

Timing of paternal acitretin treatment relative to conception	Delivery of healthy neonate	Spontaneous abortion	Induced abortion	Total
At time of conception	5*	5	1	11
Discontinued ~ 4 weeks prior	0	0	1**	1
Discontinued ~ 6-8 months prior	0	1	0	1

* Four of 5 cases were prospective
**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)

Please include the appropriate reference for the above data and re-number all subsequent references accordingly.

FDA considers the patient brochure (including Pregnancy Prevention Program [PPP] booklet), like the Informed Consent Form and the Medication Guide on which it is based, part of the approved labeling for Soriatane. As such, the FPL for the PPP booklet should reflect the revisions in the approved Informed Consent Form and the approved wording for the Medication Guide.

Your submitted plan for implementing new labeling and the Medication Guide into the marketplace is acceptable; please make every effort to exchange patient materials and package inserts in prescribers' offices at next marketing representative call.

As a reminder, FDA expects the post-marketing agreement in the original 1997 approval action to be completed as agreed upon at that time (study of acitretin and etretinate levels in 100 women of child-bearing potential).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container, and carton labels) and must be formatted in accordance with the requirements of 21 CFR 201.66. Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-821/S-002 AND S-006." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter(s) communicating important information about this drug product (such as the agreed upon "Dear Health Care Professional" letters), we request that you submit a copy of the letter(s) to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Kathryn A. O'Connell, M.D., Ph.D.
Medical Officer
acting for
Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine OConnell
4/18/03 03:54:30 PM
acting today for Jonathan Wilkin, M.D., Dvision Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-821/S-002
NDA 19-821/S-006

Hoffmann-La Roche, Inc.
Attention: Lisa Luther
Group Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Luther:

Please refer to your supplemental new drug applications dated August 16, 1999, received August 18, 1999 (S-002) and May 17, 2002, received May 21, 2002 (S006), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SORIATANE ® (acitretin) Capsules, 10 mg and 25mg.

We acknowledge receipt of your submissions for S-006 dated July 19, 2002.

These supplemental new drug applications provide for revisions which include changes to the Boxed Warning, Contraindications, Warnings, Precautions, Overdosage, Drug Interactions, Adverse Reactions, the Informed Consent Form for Females, and the addition of Clinical Studies and Geriatric sections, and a Medication Guide.

We completed our review of these applications, as amended, and they are approvable. Before these application(s) may be approved, however, you must submit draft labeling for the drug. The labeling should reflect revisions sent to you electronically on November 18, 2002, with the following exceptions.

1. Minor editorial changes/corrections of typographical error.
2. Changes of substance that has been agreed upon in principle via teleconference November 21, 2002, for which final wording remains for future discussions.

    a. Boxed Warning for Birth Defects: Clarification of the basis for changes in listed fetal outcome
    b. Clinical studies efficacy data
    c. Precautions: Wording for psychiatric events
    d. Adverse Reactions: Wording for psychiatric adverse events

Please include in your submission:

1. A proposal for Dear Prescriber and Dear Pharmacists Letter
2. Clarification of the method for medication guide distribution.

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

b. Present tabulations of the new safety data combined with the original NDA data.

c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110.

If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, please call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
11/21/02 05:41:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

APPROVED LABELING

Professional Package Insert

SORIATANE®
(acitretin)
CAPSULES

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS: Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment or for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected.

Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.

Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.

Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae.

Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.

Important Information for Women of Childbearing Potential:

Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.

- Must have selected and have committed to use 2 effective forms of contraception [birth control] simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly post menopausal.

- Patients must use 2 effective forms of contraception [birth control] simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors
associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed.

Effective forms of contraception include both primary and secondary forms

of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception [birth control] simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[2] Microdosed "minipill" progestin preparations are not recommended for use with Soriatane. It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.

Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:

Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.

- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,

  - greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean

elimination half-life of 120 days.

- greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days.

However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.[1]

♦ Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.

- There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred after the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.

- There are also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia and stillbirth.

- Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer marketed in the U.S.; for information, call Roche at 1-800-526-6367.

- Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

Important Information For Males Taking Soriatane:

♦ Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

  There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome):

  NOTE to HLR: I had technical difficulties inserting the data table here that is based on your *Dermatology* 2002 paper. Please insert here exactly as in the approval letter. Please also insert the reference for the data and adjust reference numbers that follow in the labeling accordingly)

For All Patients: A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.

DESCRIPTION: Soriatane (acitretin), a retinoid, is available in 10 mg and 25 mg gelatin capsules for oral administration. Chemically, acitretin is all-*trans*-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. It is a metabolite of etretinate and is related to both retinoic acid and retinol (vitamin A). It is a yellow to greenish-yellow powder with a molecular weight of 326.44. The structural formula is:

[[graphic: molecular structure]]

Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides).

Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

CLINICAL PHARMACOLOGY: The mechanism of action of Soriatane is unknown.

Pharmacokinetics: *Absorption:* Oral absorption of acitretin is optimal when given with food. For this reason, acitretin was given with food in all of the following studies. After administration of a single 50 mg oral dose of acitretin to 18 healthy subjects, maximum plasma concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in 2 to 5 hours (mean 2.7 hours). The oral absorption of acitretin is linear and proportional with increasing doses from 25 to 100 mg. Approximately 72% (range 47% to 109%) of the administered dose was absorbed after a single 50 mg dose of acitretin was given to 12 healthy subjects.

Distribution: Acitretin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism (see Pharmacokinetic Drug Interactions: Ethanol): Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-*cis* form (*cis*-acitretin). The formation of *cis*-acitretin relative to parent compound is not altered by dose or fed/fast conditions of oral administration of acitretin. Both parent compound and isomer are further metabolized into chain-shortened breakdown products and conjugates, which are excreted. Following multiple-dose administration of acitretin, steady-state concentrations of acitretin and *cis*-acitretin in plasma are achieved within approximately 3 weeks.

Elimination: The chain-shortened metabolites and conjugates of acitretin and *cis*-acitretin are ultimately excreted in the feces (34% to 54%) and urine (16% to 53%). The terminal elimination half-life of acitretin following multiple-dose administration is 49 hours (range 33 to 96 hours), and that of *cis*-acitretin under the same conditions is 63 hours (range 28 to 157 hours). The accumulation ratio of the parent compound is 1.2; that of *cis*-acitretin is 6.6.

Special Populations: Psoriasis: In an 8-week study of acitretin pharmacokinetics in patients with psoriasis, mean steady-state trough concentrations of acitretin increased in a dose proportional manner with dosages ranging from 10 to 50 mg daily. Acitretin plasma concentrations were nonmeasurable (<4 ng/mL) in all patients 3 weeks after cessation of therapy.

Elderly: In a multiple-dose study in healthy young (n=6) and elderly (n=8) subjects, a two-fold increase in acitretin plasma concentrations were seen in elderly subjects, although the elimination half-life did not change.

Renal Failure: Plasma concentrations of acitretin were significantly (59.3%) lower in end-stage renal failure subjects (n=6) when compared to age-matched controls, following single 50 mg oral doses. Acitretin was not removed by hemodialysis in these subjects.

Pharmacokinetic Drug Interactions (see also boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS: *Drug Interactions*): In studies of in vivo pharmacokinetic drug interactions, no interaction was seen between acitretin and cimetidine, digoxin, phenprocoumon or glyburide.

Ethanol: Clinical evidence has shown that etretinate (a retinoid with a much longer half-life, see below) can be formed with concurrent ingestion of acitretin and ethanol. In a two-way crossover study, all 10 subjects formed etretinate with concurrent ingestion of a single 100 mg oral dose of acitretin during a 3-hour period of ethanol ingestion (total ethanol, approximately 1.4 g/kg body weight). A mean peak etretinate concentration of 59 ng/mL (range 22 to 105 ng/mL) was observed, and extrapolation of AUC values indicated that the formation of etretinate in this study was comparable to a single 5 mg oral dose of etretinate. There was no detectable formation of etretinate when a single 100 mg oral dose of acitretin was administered without concurrent ethanol ingestion, although the formation of etretinate without concurrent ethanol ingestion cannot be excluded (see boxed CONTRAINDICATIONS AND WARNINGS). Of 93 evaluable psoriatic patients on acitretin therapy in several foreign studies (10 to 80 mg/day), 16% had measurable etretinate levels (>5 ng/mL).

Etretinate has a much longer elimination half-life compared to that of acitretin. In one study the apparent mean terminal half-life after 6 months of therapy was approximately 120 days (range 84 to 168 days). In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 0.5 to 12 ng/mL) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

Progestin-only Contraceptives: It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of

microdosed progestin preparations.[2] Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

CLINICAL STUDIES: In two double-blind placebo controlled studies, Soriatane was administered once daily to patients with severe psoriasis (ie, covering at least 10% to 20% of the body surface area). At 8 weeks (see Table 1) patients treated in Study A with 50 mg Soriatane per day showed significant improvements ($p \leq 0.05$) relative to baseline and to placebo in the physician's global evaluation and in the mean ratings of severity of psoriasis (scaling, thickness, and erythema). In study B, differences from baseline and from placebo were statistically significant ($p \leq 0.05$) for all variables at both the 25 mg and 50 mg doses; it should be noted for Study B that no statistical adjustment for multiplicity was carried out.

Table 1. Summary of the Soriatane Efficacy Results of the 8-Week Double-Blind Phase of Studies A and B

	Study A		Study B		
	Total daily dose		Total daily dose		
Efficacy Variables	**Placebo (N=29)**	**50 mg (N=29)**	**Placebo (N=72)**	**25 mg (N=74)**	**50 mg (N=71)**
Physician's Global Evaluation					
Baseline	4.62	4.55	4.43	4.37	4.49
Mean Change After 8 Weeks	-0.29	-2.00*	-0.06	-1.06*	-1.57*
Scaling					
Baseline	4.10	3.76	3.97	4.11	4.10
Mean Change After 8 Weeks	-0.22	-1.62*	-0.21	-1.50*	-1.78*
Thickness					
Baseline	4.10	4.10	4.03	4.11	4.20
Mean Change After 8 Weeks	-0.39	-2.10*	-0.18	-1.43*	-2.11*
Erythema					
Baseline	4.21	4.59	4.42	4.24	4.45
Mean Change After 8 Weeks	-0.33	-2.10*	-0.37	-1.12*	-1.65*

*Values were statistically significantly different from placebo and from baseline ($p \leq 0.05$). No adjustment for multiplicity was done for Study B.

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema, and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0=none, 1=trace, 2=mild, 3=mild-moderate, 4=moderate, 5=moderate-severe, 6=severe).

A subset of 141 patients from both pivotal studies A and B continued to receive Soriatane in an open fashion for up to 24 weeks. At the end of the treatment period, all efficacy variables, as indicated in Table 2, were significantly improved ($p \leq 0.01$) from baseline, including extent of psoriasis, mean ratings of psoriasis severity and physician's global evaluation.

Table 2. Summary of the First Course of Soriatane Therapy (24 Weeks)

Variables	Study A	Study B
Mean Total Daily Soriatane Dose (mg)	42.8	43.1
Mean Duration of Therapy (Weeks)	21.1	22.6
Physician's Global Evaluation	**N=39**	**N=98**
Baseline	4.51	4.43
Mean Change From Baseline	-2.26*	-2.60*
Scaling	**N=59**	**N=132**
Baseline	3.97	4.07
Mean Change From Baseline	-2.15 *	-2.42*
Thickness	**N=59**	**N=132**
Baseline	4.00	4.12
Mean Change From Baseline	-2.44*	-2.66*
Erythema	**N=59**	**N=132**
Baseline	4.35	4.33
Mean Change From Baseline	-2.31*	-2.29*

*Indicates that the difference from baseline was statistically significant ($p \leq 0.01$).

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema; and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0=none, 1=trace, 2=mild, 3=mild-moderate, 4=moderate, 5=moderate-severe, 6=severe).

All efficacy variables improved significantly in a subset of 55 patients from Study A treated for a second, 6-month maintenance course of therapy (for a total of 12 months of treatment); a small subset of patients (n=4) from Study A continued to improve after a third 6-month course of therapy (for a total of 18 months of treatment).

INDICATIONS AND USAGE: Soriatane is indicated for the treatment of severe psoriasis in adults. Because of significant adverse effects associated with its use, Soriatane should be prescribed only by those knowledgeable in the systemic use of retinoids. In females of reproductive potential, Soriatane should be reserved for non-pregnant patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments (see Boxed CONTRAINDICATIONS AND WARNING: Soriatane can cause severe birth defects).

Most patients experience relapse of psoriasis after discontinuing therapy. Subsequent courses, when clinically indicated, have produced efficacy results similar to the initial course of therapy.

CONTRAINDICATIONS: Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).

Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values (see boxed WARNINGS, *Hepatotoxicity*; WARNINGS, *Lipids*; and PRECAUTIONS).

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate.] Consequently, the combination of methotrexate with Soriatane is also contraindicated (see PRECAUTIONS: *Drug Interactions*).

Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see WARNINGS: *Pseudotumor Cerebri*).

Soriatane is contraindicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

WARNINGS: (See also boxed CONTRAINDICATIONS AND WARNINGS)

Hepatotoxicity: Of the 525 patients treated in US clinical trials, 2 had clinical jaundice with elevated serum bilirubin and transaminases considered related to Soriatane treatment. Liver function test results in these patients returned to normal after Soriatane was discontinued. Two of the 1289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal 2 months after Soriatane was discontinued.

The potential of Soriatane therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For 6 patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for 7 patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for 1 patient, the change was from class II to class IIIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found.

Elevations of AST (SGOT), ALT (SGPT), GGT (GGTP) or LDH have occurred in approximately 1 in 3 patients treated with Soriatane. Of the 525 patients treated in clinical trials in the US, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with Soriatane, the drug should be discontinued and the etiology further investigated.

Ten of 652 patients treated in US clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for a month or less before presenting with hepatic symptoms or signs.

Hyperostosis: In adults receiving long-term treatment with Soriatane, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see ADVERSE REACTIONS). Because the frequency and severity of iatrogenic bony abnormality in adults is low, periodic radiography is only warranted in the presence of symptoms or long term use of Soriatane. If such disorders arise, the continuation of therapy

should be discussed with the patient on the basis of a careful risk/benefit analysis. In clinical trials with Soriatane, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column, knees and ankles.

Vertebral Results: Of 380 patients treated with Soriatane, 15% had preexisting abnormalities of the spine which showed new changes or progression of preexisting findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification and narrowing and destruction of a cervical disc space. De novo changes (formation of small spurs) were seen in 3 patients after 1½ to 2½ years.

Skeletal Appendicular Results: Six of 128 patients treated with Soriatane showed abnormalities in the knees and ankles before treatment that progressed during treatment. In 5, these changes involved the formation of additional spurs or enlargement of existing spurs. The sixth patient had degenerative joint disease which worsened. No patients developed spurs de novo. Clinical complaints did not predict radiographic changes.

Lipids and Possible Cardiovascular Effects: Blood lipid determinations should be performed before Soriatane is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% of patients. These effects of Soriatane were generally reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridemia included those with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions. Because of the risk of hypertriglyceridemia, serum lipids must be more closely monitored in high-risk patients and during long-term treatment.

Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. Although no causal relationship has been established, there have been post-marketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with fatal fulminant pancreatitis. Therefore, dietary modifications, reduction in Soriatane dose, or drug therapy should be employed to control significant elevations of triglycerides. If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Soriatane should be considered.

Ophthalmologic Effects: The eyes and vision of 329 patients treated with Soriatane were examined by ophthalmologists. The findings included dry eyes (23%), irritation of eyes (9%) and brow and lash loss (5%). The following were reported in less than 5% of patients: Bell's Palsy, blepharitis and/or crusting of lids, blurred vision, conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties and subepithelial corneal lesions.

Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation.

Pancreatitis: Lipid elevations occur in 25% to 50% of patients treated with Soriatane. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported. There have been rare reports of pancreatitis during Soriatane therapy in the absence of hypertrigyceridemia.

Pseudotumor Cerebri: Soriatane and other retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Some of these events involved concomitant use of isotretinoin and tetracyclines. However, the event seen in a single Soriatane patient was not associated with tetracyline use. Early signs and symptoms include papilledema, headache, nausea and vomiting and visual disturbances. Patients with these signs and symptoms should be examined for papilledema and, if present, should discontinue Soriatane immediately and be referred for

neurological evaluation and care. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS).

PRECAUTIONS: ***Information for Patients*** **(see Medication Guide for all patients and Patient Agreement/Informed Consent for Female Patients at end of professional labeling):**

Patients should be instructed to read the Medication Guide supplied as required by law when Soriatane is dispensed.

Females of reproductive potential: **Soriatane can cause severe birth defects.** Female patients must not be pregnant when Soriatane therapy is initiated, they must not become pregnant while taking Soriatane, and for at least 3 years after stopping Soriatane so that the drug can be eliminated to below a blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely (see boxed CONTRAINDICATIONS AND WARNINGS).

Females of reproductive potential should also be advised that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued. This allows for elimination of the acitretin which can be converted to etretinate in the presence of alcohol.

Female patients should be advised that any method of birth control can fail, including tubal ligation, and that microdosed progestin "minipill" preparations are not recommended for use with Soriatane. Data from one patient who received a very low-dosed progestin contraceptive (levonorgestrel 0.03 mg) had a significant increase of the progesterone level after three menstrual cycles during acitretin treatment.[2]

Female patients should sign a consent form prior to beginning Soriatane therapy (see boxed CONTRAINDICATIONS AND WARNINGS).

Nursing Mothers: Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants.

All Patients:

Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms.

Patients should be advised that a transient worsening of psoriasis is sometimes seen during the initial treatment period. Patients should be advised that they may have to wait 2 to 3 months before they get the full benefit of Soriatane, although some patients may achieve significant improvements within the first 8 weeks of treatment as demonstrated in clinical trials.

Decreased night vision has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see WARNINGS and ADVERSE REACTIONS). Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period and sometimes after treatment has stopped.

Patients should not donate blood during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane.

Because of the relationship of Soriatane to vitamin A, patients should be advised against taking vitamin A supplements in excess of minimum recommended daily allowances to avoid possible additive toxic effects.

Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical UV exposure) because the effects of UV light are enhanced by retinoids.

Patients should be advised that they must not give their Soriatane capsules to any other person.

For Prescribers:

Phototherapy: Significantly lower doses of phototherapy are required when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning). (see DOSAGE AND ADMINISTRATION).
Drug Interactions:

Ethanol: Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see boxed CONTRAINDICATIONS AND WARNINGS and CLINICAL PHARMACOLOGY: *Pharmacokinetics*).

Glibenclamide: In a study of 7 healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide (a sulfonylurea similar to chlorpropamide) in 3 of the 7 subjects. Repeating the study with 6 healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with Soriatane is recommended (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

Hormonal Contraceptives: It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin "minipill" preparations. Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

Methotrexate: An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with acitretin is also contraindicated (see CONTRAINDICATIONS).

Phenytoin: If acitretin is given concurrently with phenytoin, the protein binding of phenytoin may be reduced.

Tetracyclines: Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS AND WARNINGS: *Pseudotumor Cerebri*).

Vitamin A and oral retinoids: Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis A.

Other: There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, or glyburide. Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction.

Laboratory Tests: If significant abnormal laboratory results are obtained, either dosage reduction with careful monitoring or treatment discontinuation is recommended, depending on clinical judgment.

Blood Sugar: Some patients receiving retinoids have experienced problems with blood sugar control. In addition, new cases of diabetes have been diagnosed during retinoid therapy, including diabetic ketoacidosis. In diabetics, blood-sugar levels should be monitored very carefully.

Lipids: In clinical studies, the incidence of hypertriglyceridemia was 66%, hypercholesterolemia was 33% and that of decreased HDL was 40%. Pretreatment and follow-up measurements should be obtained under fasting conditions. It is recommended that these tests be performed weekly or every other week until the lipid response to Soriatane has stabilized (see WARNINGS).

Liver Function Tests: Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. It is recommended that these tests be performed prior to initiation of Soriatane therapy, at 1- to 2-week intervals until stable and thereafter at intervals as clinically indicated (see CONTRAINDICATIONS AND boxed WARNING).

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80 week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m^2 comparison.

Mutagenesis: Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays.

Impairment of Fertility: In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day).

No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[3-5] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[3,4]

Pregnancy: *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).**

In a study in which acitretin was administered to male rats only at a dosage of 5 mg/kg/day for 10 weeks (approximate duration of one spermatogenic cycle) prior to and during mating with untreated female rats, no teratogenic effects were observed in the progeny. (see boxed CONTRAINDICATIONS AND WARNINGS for information about male use of Soriatane.)

Nonteratogenic Effects: In rats dosed at 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison), slightly decreased pup survival and delayed incisor eruption were noted. At the next lowest dose tested, 1 mg/kg/day, no treatment-related adverse effects were observed.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses,

decreases in bone mineral density, and premature epiphyseal closure have been reported in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between these effects and Soriatane has not been established. While it is not known that these occurrences are more severe or more frequent in children, there is special concern in pediatric patients because of the implications for growth potential (see WARNINGS: *Hyperostosis*).

Geriatric Use: Clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A two-fold increase in acitretin plasma concentrations was seen in healthy elderly subjects compared with young subjects, although the elimination half-life did not change (see CLINICAL PHARMACOLOGY: *Special Populations*).

ADVERSE REACTIONS: Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, neuropsychiatric, and central nervous systems. Many of the clinical adverse reactions reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome.

***Adverse Events/Post-Marketing Reports*:** In addition to the events listed in the tables for the clinical trials, the following adverse events have been identified during post-approval use of Soriatane. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Acute myocardial infarction, thromboembolism, (see WARNINGS), stroke

Nervous System: Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug.

Psychiatric: Aggressive feelings and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane (see PRECAUTIONS).

Reproductive: Vulvo-vaginitis due to *Candida albicans*

Skin and Appendages: Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed.

Clinical Trials: During clinical trials with Soriatane, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred sixteen patients (22%) left studies prematurely, primarily because of adverse experiences involving the mucous membranes and skin. Three patients died. Two of the deaths were not drug related (pancreatic adenocarcinoma and lung cancer); the other patient died of an acute myocardial infarction, considered remotely related to drug therapy. In clinical trials, Soriatane was associated with elevations in liver function test results or triglyceride levels and hepatitis.

The tables below list by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis.

Table 3. Adverse Events Frequently Reported During Clinical Trials
Percent of Patients Reporting (N=525)

BODY SYSTEM	>75%	50% to 75%	25% to 50%	10% to 25%
CNS				Rigors
Eye Disorders				Xerophthalmia
Mucous Membranes	Cheilitis		Rhinitis	Dry mouth Epistaxis
Musculoskeletal				Arthralgia Spinal hyperostosis (progression of existing lesions)
Skin and Appendages		Alopecia Skin peeling	Dry skin Nail disorder Pruritus	Erythematous rash Hyperesthesia Paresthesia Paronychia Skin atrophy Sticky skin

Table 4. Adverse Events Less Frequently Reported During Clinical Trials
(Some of Which May Bear No Relationship to Therapy)
Percent of Patients Reporting (N=525)

BODY SYSTEM	1% to 10%	<1%
Body as a Whole	Anorexia Edema Fatigue Hot flashes Increased appetite	Alcohol intolerance Dizziness Fever Influenza-like symptoms Malaise Moniliasis Muscle weakness Weight increase
Cardiovascular	Flushing	Chest pain Cyanosis Increased bleeding time Intermittent claudication Peripheral ischemia
CNS (also see Psychiatric)	Headache Pain	Abnormal gait Migraine Neuritis Pseudotumor cerebri (intracranial hypertension)
Eye Disorders	Abnormal/blurred vision Blepharitis Conjunctivitis/irritation Corneal epithelial abnormality Decreased night vision/night blindness Eye abnormality Eye pain Photophobia	Abnormal lacrimation Chalazion Conjunctival hemorrhage Corneal ulceration Diplopia Ectropion Itchy eyes and lids Papilledema Recurrent sties

BODY SYSTEM	1% to 10%	<1%
		Subepithelial corneal lesions
Gastrointestinal	Abdominal pain Diarrhea Nausea Tongue disorder	Constipation Dyspepsia Esophagitis Gastritis Gastroenteritis Glossitis Hemorrhoids Melena Tenesmus Tongue ulceration
Liver and Biliary		Hepatic function abnormal Hepatitis Jaundice
Mucous Membranes	Gingival bleeding Gingivitis Increased saliva Stomatitis Thirst Ulcerative stomatitis	Altered saliva Anal disorder Gum hyperplasia Hemorrhage Pharyngitis
Musculoskeletal	Arthritis Arthrosis Back pain Hypertonia Myalgia Osteodynia Peripheral joint Hyperostosis (progression of existing lesions)	Bone disorder Olecranon bursitis Spinal hyperostosis (new lesions) Tendonitis
Psychiatric	Depression Insomnia Somnolence	Anxiety Dysphonia Libido decreased Nervousness
Reproductive		Atrophic vaginitis Leukorrhea
Respiratory	Sinusitis	Coughing Increased sputum Laryngitis
Skin and Appendages	Abnormal skin odor Abnormal hair texture Bullous eruption Cold/clammy skin Dermatitis Increased sweating Infection Psoriasiform rash Purpura Pyogenic granuloma Rash Seborrhea Skin fissures Skin ulceration Sunburn	Acne Breast pain Cyst Eczema Fungal infection Furunculosis Hair discoloration Herpes simplex Hyperkeratosis Hypertrichosis Hypoesthesia Impaired healing Otitis media Otitis externa Photosensitivity reaction Psoriasis aggravated Scleroderma

BODY SYSTEM	1% to 10%	<1%
		Skin nodule Skin hypertrophy Skin disorder Skin irritation Sweat gland disorder Urticaria Verrucae
Special Senses/Other	Earache Taste perversion Tinnitus	Ceruminosis Deafness Taste loss
Urinary		Abnormal urine Dysuria Penis disorder

Laboratory: Soriatane therapy induces changes in liver function tests in a significant number of patients. Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% (see WARNINGS). Transient, usually reversible elevations of alkaline phosphatase have been observed.

Table 5 lists the laboratory abnormalities reported during clinical trials.

Table 5. Abnormal Laboratory Test Results Reported During Clinical Trials
Percent of Patients Reporting

BODY SYSTEM	50% to 75%	25% to 50%	10% to 25%	1% to 10%
Electrolytes			Increased: – Phosphorus – Potassium – Sodium Increased and decreased magnesium	Decreased: – Phosphorus – Potassium – Sodium Increased and decreased: – Calcium – Chloride

Hematologic		Increased -Reticulocytes	Decreased: – Hematocrit – Hemoglobin – WBC Increased: – Haptoglobin – Neutrophils – WBC	Increased: – Bands – Basophils – Eosinophils – Hematocrit – Hemoglobin – Lymphocytes – Monocytes Decreased: – Haptoglobin – Lymphocytes – Neutrophils – Reticulocytes Increased or decreased: – Platelets – RBC
Hepatic		Increased: – Cholesterol – LDH – SGOT – SGPT Decreased: – HDL cholesterol	Increased: – Alkaline phosphatase – Direct bilirubin – GGTP	Increased: – Globulin – Total bilirubin – Total protein Increased and decreased: – Serum albumin
Miscellaneous	Increased triglycerides	Increased: – CPK – Fasting blood sugar	Decreased: – Fasting blood sugar – High occult blood	Increased and decreased: – Iron
Renal			Increased: – Uric acid	Increased: – BUN – Creatinine
Urinary		WBC in urine	Acetonuria Hematuria RBC in urine	Glycosuria Proteinuria

OVERDOSAGE: In the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg.

In one reported case of overdose, a 32-year-old male with Darier's disease took 21 x 25 mg capsules (525 mg single dose). He vomited several hours later but experienced no other ill effects.

All female patients of childbearing potential who have taken an overdose of Soriatane must: 1) Have a pregnancy test at the time of overdose. 2) Be counseled as per the b*oxed Contraindications and Warnings* and *Precautions* sections regarding birth defects and contraceptive use for at least 3 years duration after the overdose.

DOSAGE AND ADMINISTRATION: There is intersubject variation in the pharmacokinetics, clinical efficacy and incidence of side effects with Soriatane. A number of the more common side effects are dose related. Individualization of dosage is required to achieve sufficient therapeutic response while minimizing side effects. Soriatane therapy should be

initiated at 25 to 50 mg per day, given as a single dose with the main meal. Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial treatment. Relapses may be treated as outlined for initial therapy.

When Soriatane is used with phototherapy, the prescriber should decrease the phototherapy dose, dependent on the patient's individual response (see PRECAUTIONS: *General*).

Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison.

Information for Pharmacists: A Soriatane Medication Guide must be given to the patient each time Soriatane is dispensed, as required by law.

HOW SUPPLIED: Brown and white capsules, 10 mg, imprinted SORIATANE 10 ROCHE; bottles of 30 (NDC 0004-0288-57).

Brown and yellow capsules, 25 mg, imprinted SORIATANE 25 ROCHE; bottles of 30 (NDC 0004-0289-57).

Store between 15° and 25°C (59° and 77°F). Protect from light. Avoid exposure to high temperatures and humidity after the bottle is opened.

1. **REFERENCES:** Berbis Ph, et al.: *Arch Dermatol Res* (1988) 280:388-389.

2. Maier H, Honigsmann H: Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 348:1107, 1996.

3. Sigg C, et al.: Andrological investigations in patients treated with etretin. *Dermatologica* 175:48-49, 1987.

4. Parsch EM, et al.: Andrological investigation in men treated with acitretin (Ro 10-1670). *Andrologia* 22:479-482, 1990

5. Kadar L, et al.: Spermatological investigations in psoriatic patients treated with acitretin. In: Pharmacology of Retinoids in the Skin; Reichert U. et al., ed, KARGER, Basel, vol. 3, pp 253-254, 1988.

PATIENT AGREEMENT/INFORMED CONSENT for FEMALE Patients:

To be completed by the patient, her parent/guardian*and signed by her prescriber.

Read each item below and initial in the space provided to show that you understand each item and agree to follow your doctor's instructions. **Do not sign this consent and do not take Soriatane if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and initial each item before signing the consent.

_____
(Patient's Name)

1. I understand that there is a very high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Soriatane in any amount even for short periods of time. Birth defects have also happened in babies of women who became pregnant after stopping Soriatane treatment.

2. I understand that I must not take Soriatane if I am pregnant.
Initial: _____

3. I understand that I must not become pregnant while taking Soriatane and for at least 3 years after the end of my treatment with Soriatane.
Initial: _____

4. I know that I must avoid drinks, food, and medicines, including over-the-counter products, that contain alcohol. This is extremely important, because alcohol changes Soriatane in the blood into a drug that takes even longer to leave the body. This means the risk of birth defects may last longer than 3 years if I swallow any form of alcohol during Soriatane therapy or for 2 months after I stop taking Soriatane.

5. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) **at the same time**. The only exception is if I have had surgery to remove the womb (a hysterectomy) or my prescriber has told me I have gone completely through menopause.
Initial: _____

6. I have been told by my prescriber that 2 effective forms of birth control (contraception) must be used at the same time for at least 1 month before starting Soriatane, for the entire time of Soriatane therapy, and for at least 3 years after Soriatane treatment has stopped.

7. I understand that birth control pills and injectable/implantable/insertable/topical (patch) hormonal birth control products are among the most effective forms of birth control. However, any form of birth control can fail. Therefore, I must use 2 different methods at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is birth control pills, injections, or tubal ligation (tube-tying).
Initial: _____

8. I understand that the following are considered effective forms of birth control:
Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills, injectable/implantable/insertable/topical (patch) hormonal birth control products, and an IUD (intrauterine device).
Secondary: Diaphragms, latex condoms, and cervical caps. Each must be used with a spermicide, which is a special cream or jelly that kills sperm.

I understand that at least 1 of my 2 methods of birth control must be a primary method.
Initial: _____

9. I will talk with my prescriber about any medicines or dietary supplements I plan to take during my Soriatane treatment because hormonal birth control methods (for example, birth control pills) may not work if I am taking certain medicines or herbal products (for example, St. John's Wort).
Initial: _____

10. I understand that if I have taken Tegison (etretinate), I must continue to follow the birth control (contraception) recommendations for Tegison.
Initial: _____

11. Unless I have had a hysterectomy or my prescriber says I have gone completely through menopause, I understand that I must have 2 negative pregnancy test results before I can get a prescription for Soriatane. The first pregnancy test should be done when my prescriber decides to prescribe Soriatane. The second pregnancy test should be done during the first 5 days of my menstrual period right before starting Soriatane therapy, or as instructed by my prescriber. I will then have pregnancy tests on a regular basis as instructed by my prescriber during my Soriatane therapy.
Initial: _____

12. I understand that I should not start taking Soriatane until I am *sure* that I am not pregnant and have negative results from 2 pregnancy tests.
Initial: _____

13. I have read and understand the materials my prescriber has given to me, including the Soriatane Pregnancy Prevention Program. My prescriber gave me and asked me to watch the video about contraception (birth control). I was told about a confidential counseling line that I may call at Roche for more information about birth control (1-800-542-6900).

14. I have received information on emergency contraception (birth control).
Initial: _____

15. I understand that I may receive a free contraceptive (birth control) counseling session and pregnancy testing. My prescriber can give me a Soriatane Patient Referral Form for this free consultation.
Initial: _____

16. I understand that I should receive counseling from my prescriber, repeated on a regular basis, about contraception (birth control) and behaviors associated with an increased risk of pregnancy.
Initial: _____

17. I understand that I must stop taking Soriatane right away and call my prescriber if I get pregnant, miss my menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods during and at least 3 years after stopping Soriatane treatment.
Initial: _____

18. If I do become pregnant while on Soriatane or at any time within 3 years of stopping Soriatane, I understand that I should report my pregnancy to Roche at 1-800-526-6367 or to the Food and Drug Administration (FDA) MedWatch program at 1-800-FDA-1088. The information I share will be kept confidential (private) and will help the company and the FDA evaluate the pregnancy prevention program.
Initial: _____

My prescriber has answered all my questions about Soriatane. I understand that it is my responsibility not to get pregnant during Soriatane treatment or for at least 3 years after I stop taking Soriatane. I now authorize my prescriber _____ to begin my treatment with Soriatane.
Patient signature:_____ Date:_____
Parent/guardian signature (if under age 18):_____ Date:_____
Please print: Patient name and address_____
_____ Telephone _____

I have fully explained to the patient, _____, the nature and purpose of the treatment described above and the risks to females of childbearing potential. I have asked the patient if she has any questions regarding her treatment with Soriatane and have answered those questions to the best of my ability.
Prescriber signature: _____ Date:_____

Medication Guide for Patients:

Read this Medication Guide carefully before you start taking Soriatane and read it each time you get more Soriatane. There may be new information.

The first information in this Guide is about birth defects and how to avoid pregnancy. **After this section there is important safety information about possible effects for any patient taking Soriatane.** ALL patients should read this entire Medication Guide carefully.

This information does not take the place of talking with your prescriber about your medical condition or treatment.

What is the most important information I should know about Soriatane?

Soriatane can cause severe birth defects. If you are a female who can get pregnant, you should use Soriatane only if you are not pregnant now, can avoid becoming pregnant, and other medicines do not work for your severe psoriasis or you cannot use other psoriasis medicines. Information about effects on unborn babies and about how to avoid pregnancy is found in the next section: "What are the important warnings and instructions for females taking Soriatane?".

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

What are the important warnings and instructions for females taking Soriatane?

- **Before you receive your Soriatane prescription, you should have discussed and signed a Patient Information/Consent form with your prescriber. This is to help make sure you understand the risk of birth defects and how to avoid getting pregnant. If you did not talk to your prescriber about this and sign the Form, contact your prescriber.**

- **You must not take Soriatane if you are pregnant or might become pregnant during treatment or at any time for at least 3 years after you stop treatment because Soriatane can cause severe birth defects.**
- **During Soriatane treatment and for 2 months after you stop Soriatane treatment, you must avoid drinks, foods, and all medicines that contain alcohol. This includes over-the-counter products that contain alcohol.** Avoiding alcohol is very important, because alcohol changes Soriatane into a drug that may take longer than 3 years to leave your body. The chance of birth defects may last longer than 3 years if you swallow any form of alcohol during Soriatane therapy and for 2 months after you stop taking Soriatane.

- **You and your prescriber must be sure you are not pregnant before you start Soriatane therapy. You must** have **negative** results from **2 pregnancy tests.** A negative result shows you are not pregnant. Because it takes a few days after pregnancy begins for a test to show that you are pregnant, the first negative test may not ensure you are not pregnant. Do not take Soriatane until you have negative results from 2 pregnancy tests.
  - The **first pregnancy test** will be done at the time you and your prescriber decide if Soriatane might be right for you.
  - The **second pregnancy test** will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane. Your prescriber may suggest another time.

- **Discuss effective birth control (contraception) with your prescriber. You must use 2 effective forms of birth control (contraception) at the same time during all of the following:**
  - for at least 1 month before beginning Soriatane treatment
  - during treatment with Soriatane
  - for at least 3 years after stopping Soriatane treatment

- **You must use 2 effective forms of birth control (contraception) at the same time even if you think you cannot become pregnant, unless 1 of the following is true for you:**
  - You had your womb (uterus) removed during an operation (a hysterectomy).
  - Your prescriber said you have gone completely through menopause (the "change of life").
  - You choose a method called "abstinence". This means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during, and for at least 3 years after Soriatane treatment.

- **You can get a free birth control counseling session and pregnancy testing from a prescriber or family planning expert. Your prescriber can give you a Soriatane Patient Referral Form for this free session.**

- **You must use 2 effective forms of birth control (contraception) at the same time every time you repeat Soriatane treatment. You must use birth control for at least 1 month before you start Soriatane, during treatment, and at least 3 years after you stop Soriatane treatment.**

- **The following are considered effective forms of birth control:**

  Primary Forms:
  - having your tubes tied (tubal ligation)
  - partner's vasectomy
  - IUD (intrauterine device)
  - birth control pills that contain both estrogen and progestin (combination oral contraceptives)
  - hormonal birth control products that are injected, implanted, or inserted in your body.
  - birth control patch

  Secondary Forms (use with a Primary Form):
  - diaphragms with spermicide
  - latex condoms with spermicide
  - cervical caps with spermicide

  At least 1 of your 2 methods of birth control must be a primary form.

- **If you have sex at any time without using 2 effective forms of birth control (contraception) at the same time, or if you get pregnant or miss your period, stop using Soriatane and call your prescriber right away.**

- **Consider "Emergency Contraception" (EC) if you have sex with a male without correctly using 2 effective forms of birth control (contraception) at the same time.** EC is also called "emergency birth control" or the "morning after" pill. Contact your prescriber **as soon as possible** if you have sex without using 2 effective forms of birth control (contraception) at the same time, because EC works best if it is used within 1 or 2 days after sex. EC is not a replacement for your usual 2 effective forms of birth control (contraception) because it is not as effective as regular birth control methods.

You can get EC from private doctors or nurse practitioners, women's health centers, or hospital emergency rooms. You can get the name and phone number of EC providers nearest you by calling, the free Emergency Contraception Hotline at 1-888-NOT-2-LATE (1-888-668-2528).

- **Stop taking Soriatane right away and contact your prescriber if you get pregnant while taking Soriatane or at any time for at least 3 years after treatment has stopped. You need to discuss the possible effects on the unborn baby with your prescriber.**

- **If you do become pregnant while taking Soriatane or at any time for at least 3 years after stopping Soriatane, you should report your pregnancy to Roche at 1-800-526-6367 or directly to the Food and Drug Administration (FDA) MedWatch program (1-800-FDA-1088).** Your name will be kept in private (confidential). The information you share will help the FDA and the manufacturer evaluate pregnancy prevention program for Soriatane.

- **Do not take Soriatane if you are breast feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast feed or take Soriatane, but not both.

What should males know before taking Soriatane?

Small amounts of Soriatane are found in the semen of males taking Soriatane. Based upon available information, it appears that these small amounts of Soriatane in semen pose little, if any, risk to an unborn child while a male patient is taking the drug or after it is discontinued. Discuss any concerns you have about this with your prescriber.

All patients should read the rest of this Medication Guide

What is Soriatane?

Soriatane is a medicine used to treat severe forms of psoriasis in adults. Psoriasis is a skin disease that causes cells in the outer layer of the skin to grow faster than normal and pile up on the skin's surface. In the most common type of psoriasis, the skin becomes inflamed and produces red, thickened areas, often with silvery scales. **Because Soriatane can have serious side effects**, you should talk with your prescriber about whether Soriatane's possible benefits outweigh its possible risks.

Soriatane may not work right away. You may have to wait 2 to 3 months before you get the full benefit of Soriatane. Psoriasis gets worse for some patients when they first start Soriatane treatment.

Soriatane has not been studied in children.

Who should not take Soriatane?

- **Do NOT take Soriatane if you can get pregnant:** Do not take Soriatane if you are pregnant or might get pregnant during Soriatane treatment or at any time for **at least 3 years** after you stop Soriatane treatment. (see "What are the important warnings and instructions for females taking Soriatane?").

- **Do NOT take Soriatane if you are breast feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast feed or take Soriatane, but not both.

- **Do NOT take Soriatane if you have severe liver or kidney disease.**

- **Do NOT take Soriatane if you have repeated high blood lipids** (fat in the blood).

- **Do NOT take Soriatane if you take these medicines:**
  - methotrexate
  - tetracyclines

  The use of these medicines with Soriatane may cause **serious** side effects.

- **Do NOT take Soriatane if you are allergic to acitretin,** the active ingredient in Soriatane, to any of the other ingredients (see the end of this Medication Guide for a list of all the ingredients in Soriatane), or to any similar drugs (ask your prescriber or pharmacist whether any drugs you are allergic to are related to Soriatane).

Tell your prescriber if you have or ever had:
- diabetes or high blood sugar
- liver problems
- kidney problems
- high cholesterol or high triglycerides (fat in the blood)
- heart disease
- depression
- alcoholism
- an allergic reaction to a medication

Your prescriber needs this information to decide if Soriatane is right for you and to know what dose is best for you.

Tell your prescriber about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines can cause **serious side effects** if taken while you also take Soriatane. Some medicines may affect how Soriatane works, or Soriatane may affect how your other medicines work. **Be especially sure to tell your prescriber if you are taking the following medicines:**

- methotrexate
- tetracyclines
- phenytoin
- vitamin A supplements
- progestin-only oral contraceptives ("mini-pills")
- Tegison® or Tigason (etretinate). Tell your prescriber if you have ever taken this medicine in the past.

- St. John's Wort herbal supplement

Tell your prescriber if you are getting phototherapy treatment. Your doses of phototherapy may need to be changed to prevent a burn.

How should I take Soriatane?

- Take Soriatane with food.
- Be sure to take your medicine as prescribed by your prescriber. The dose of Soriatane varies from patient to patient. The number of capsules you must take is chosen specially for you by your prescriber. This dose may change during treatment.
- If you miss a dose, do not double the next dose. Skip the missed dose and resume your normal schedule.
- If you take too much Soriatane (overdose), call your local poison control center or emergency room.

You should have **blood tests** for liver function, cholesterol and triglycerides before starting treatment and during treatment to check your body's response to Soriatane. Your prescriber may also do other tests.

Once you stop taking Soriatane, your psoriasis may return. Do *not* treat this new psoriasis with leftover Soriatane. It is important to see your prescriber again for treatment recommendations because your situation may have changed.

What should I avoid while taking Soriatane?

- **Avoid pregnancy.** See "What is the most important information I should know about Soriatane?", and "What are the important warnings and instructions for females taking Soriatane?".

- **Avoid breast feeding.** See "What are the important warnings and instructions for females taking Soriatane?"

- **Avoid alcohol.** Females must avoid drinks, foods, medicines, and over-the-counter products that contain alcohol The risk of birth defects may continue for longer than 3 years if you swallow any form of alcohol during Soriatane treatment and for 2 months after stopping Soriatane (see "What are the important warnings and instructions for females taking Soriatane?").

- **Avoid giving blood. Do not donate blood** while you are taking Soriatane and **for at least 3 years after stopping** Soriatane treatment. Soriatane in your blood can harm an unborn baby if your blood is given to a pregnant woman. Soriatane does not affect your ability to **receive** a blood transfusion.

- **Avoid progestin-only birth control pills ("mini-pills").** This type of birth control pill may not work while you take Soriatane. Ask your prescriber if you are not sure what type of pills you are using.

- **Avoid night driving if you develop any sudden vision problems.** Stop taking Soriatane and call your prescriber if this occurs (see Side Effects).

- **Avoid non-medical ultraviolet (UV) light.** Soriatane can make your skin more sensitive to UV light. Do not use sunlamps, and avoid sunlight as much as possible. If you are taking light treatment (phototherapy), your prescriber may need to change your light dosages to avoid burns.

- **Avoid dietary supplements containing Vitamin A.** Soriatane is related to vitamin A. Therefore, do not take supplements containing vitamin A, because they may add to the unwanted effects of Soriatane. Check with your prescriber or pharmacist if you have any questions about vitamin supplements.

- **DO NOT SHARE Soriatane with anyone else, even if they have the same symptoms.** Your medicine may harm them or their unborn child.

What are the possible side effects of Soriatane?

- **Soriatane can cause birth defects.** See "What is the most important information I should know about Soriatane?" and "What are the important warnings and instructions for females taking Soriatane?"

- Psoriasis gets worse for some patients when they first start Soriatane treatment. Some patients have more redness or itching. If this happens, tell your prescriber. These symptoms usually get better as treatment continues, but your prescriber may need to change the amount of your medicine.

- **Serious side effects.** These do not happen often, but they can lead to permanent harm, or rarely, to death. Stop taking Soriatane and call your prescriber right away if you get the following signs or symptoms:

  - **Bad headaches, nausea, vomiting, blurred vision.** These symptoms can be signs of increased brain pressure that can lead to blindness or even death.

  - **Decreased vision in the dark** (night blindness). Since this can start suddenly, you should be very careful when driving at night. This problem usually goes away when Soriatane treatment stops. If you develop **any** vision problems or eye pain stop taking Soriatane and call your prescriber.

  - **Depression.** There have been some reports of patients developing mental problems including a depressed mood, aggressive feelings, or thoughts of ending their own life (suicide). These events, including suicidal behavior, have been reported in patients taking other drugs similar to Soriatane as well as in patients taking Soriatane. Since other things may have contributed to these problems, it is not known if they are related to Soriatane. It is very important to stop taking Soriatane and call your prescriber right away if you develop such problems.

  - **Yellowing of your skin or the whites of your eyes, nausea and vomiting, loss of appetite, or dark urine.** These can be signs of serious liver damage.

  - **Aches or pains in your bones, joints, muscles, or back; trouble moving; loss of feeling in your hands or feet.** These can be signs of abnormal changes to your bones or muscles.

  - **Frequent urination, great thirst or hunger.** Soriatane can affect blood sugar control, even if you do not already have diabetes. These are some of the signs of high blood sugar.

  - **Shortness of breath, dizziness, nausea, chest pain, weakness, trouble speaking, or swelling of a leg. These may be signs of a heart attack, blood clots, or stroke.** Soriatane can cause serious changes in blood fats (lipids). It is possible for these changes to cause blood vessel blockages that lead to heart attacks, strokes, or blood clots.

Common side effects. If you develop any of these side effects or any unusual reaction, check with your prescriber to find out if you need to change the amount of Soriatane you take. These side effects usually get better if the Soriatane dose is reduced or Soriatane is stopped.

- **Chapped lips; peeling fingertips, palms, and soles; itching; scaly skin all over; weak nails; sticky or fragile (weak) skin; runny or dry nose, or nose bleeds.** Your prescriber or pharmacist can recommend a lotion or cream to help treat drying or chapping.
- **Dry mouth**
- **Joint pain**
- **Tight muscles**
- **Hair loss.** Most patients have some hair loss, but this condition varies among patients. No one can tell if you will lose hair, how much hair you may lose or if and when it may grow back.
- **Dry, eyes.** Soriatane may dry your eyes. Wearing **contact lenses** may be uncomfortable during and after treatment with Soriatane because of the dry feeling in your eyes. If this happens, remove your contact lenses and call your prescriber. Also read the section about vision under "Serious side effects".
- **Rise in blood fats (lipids).** Soriatane can cause your blood fats (lipids) to rise. Most of the time this is not serious. But sometimes the increase can become a serious problem. (See information under "Serious side effects."). You should have blood tests as directed by your prescriber.

These are not all the possible side effects of Soriatane. For more information, ask your prescriber or pharmacist.

How should I store Soriatane?

Keep Soriatane away from sunlight, high temperature, and humidity. **Keep Soriatane away from children.**

What are the ingredients in Soriatane?

Active ingredient: acitretin

Inactive ingredients: microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

General information about the safe and effective use of Soriatane

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Soriatane for a condition for which it was not prescribed. Do not give Soriatane to other people, even if they have the same symptoms that you have.

This Medication Guide summarizes the most important information about Soriatane. If you would like more information, talk with your prescriber. You can ask your pharmacist or prescriber for information about Soriatane that is written for health professionals.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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R_X only

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-

27898424

Revised: March 2003

End of Professional Labeling

Pregnancy Prevention Program (PPP) Booklet

(the section below in yellow highlight is not part of labeling; intended as sponsor communication in Approval)

- The Pregnancy Prevention Program booklet forms are not available in Word format and so the following Comments were sent to sponsor and were agreeable.
  - This first comment regards the Introduction for the self-assessment test. This is a suggestion, it can stand as is at your discretion. Use of the word "test" may discourage some patients from cooperating with this voluntary program. Perhaps you could re-phrase the instructions to say: "Answer the patient self-evaluation questions". On the "test" form itself, it might also intimidate some patients that they are asked to sign and date the completed "test" for the medical record with wrong answers noted. Is this really necessary given that they will already be signing a Consent Form? Also, consider instructing the patient to mark "unsures" and wrong answers with a "X" instead of a checkmark. The reason is that a busy prescriber is apt to misinterpret the checkmark as "OK", whereas a "X" is likely more universally recognized as a problem that needs further counseling.
  - Page 26 of the self-assessment tool states that "Soriatane is a very powerful medicine used to treat severe psoriasis that did not get better with other treatments". This should be deleted. Instead, insert:: "Soriatane can have serious side effects. For that reason, it is used to treat only severe psoriasis. It should NEVER be taken by a pregnant woman".
  - It appears that there is plenty of space in the mock up section for females, so please increase the "white space" between bullets for readability.
  - The automated phone line has a title "what should I do if I think I am pregnant", but this important information should be included as well immediately before the emergency contraception section: insert "What should I do if I think I am pregnant or if I have trouble with my birth control" (answer: STOP taking Soriatane and call prescriber immediately if you suspect you might be pregnant; if problems with birth control, STOP Soriatane, call prescriber immediately, and re-read the next section on emergency contraception").
  - On page 13 of the booklet please delete the words "The facts in this booklet about Soriatane treatment are very important to your health and well-being". Insert instead these words: "It is very important that you understand all of the facts in this booklet because Soriatane can have serious side effects".

*The booklet recommended for approval is as submitted by the sponsor below **with** the changes noted above, including wording changes to match the Medication Guide and Informed Consent* (end of comment):

Soriatane® (acitretin) Pregnancy Prevention Program

((PPP Logo))

Pages

CONTENTS

Soriatane Patient Agreement/Informed Consent for Female Patients..... Inside Back Pocket

INTRODUCTION

Please read this booklet carefully before taking Soriatane (soh-RYE-uh-tane). This booklet provides important facts about Soriatane, but it does not contain all the information about this medication. When you pick up your Soriatane prescription at the pharmacy, you will receive a copy of the Soriatane Medication Guide. If there's anything else you want to know, or if you have any questions or concerns, talk with your prescriber.

Please follow these simple steps to using this booklet:

1. Read the Patient Product Information

• Read this section carefully for important information about this medication. The information presented here is taken from the Soriatane Medication Guide.

2. Next, read the section Preventing Pregnancy: A Guide to Contraception

• Read this section for important information about primary and secondary contraception methods, free contraception counseling, and how to use the Confidential Contraception Counseling Line.

• Talk to your prescriber about getting a referral for contraception counseling. If counseling is desired, your prescriber should complete the Soriatane Patient Referral Form (located in the back pocket of this booklet); you will need to bring this form to your appointment for contraception counseling.

3. Take the patient self-evaluation test

• Test yourself using the self-evaluation form (enclosed in the back pocket of this booklet) to make sure you fully understand the information and to help you and your prescriber decide whether you are ready to start taking Soriatane.

4. Sign the Patient Agreement/Informed Consent for Female Patients form if you and your prescriber have decided that Soriatane treatment is right for you.

• Discuss and complete the Patient Agreement/Informed Consent for Female Patients form with your prescriber.

YOUR PERSONAL RECORD

Name: _____

You MUST have negative results from 2 pregnancy tests done by your prescriber that show you are NOT pregnant before starting Soriatane therapy.

First test will be done at the time you and your prescriber decide if Soriatane might be right for you.

TEST DATE: _____ TEST RESULT: _____

Second test will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane, but your prescriber may suggest another time.

START OF MENSTRUAL PERIOD: _____
TEST DATE: _____ TEST RESULT: _____

DATE SORIATANE THERAPY STARTED: _____

FOLLOW-UP APPOINTMENTS

DATE _____ TIME _____
DATE _____ TIME _____

DATE _____ TIME _____
DATE _____ TIME _____
DATE _____ TIME _____
DATE _____ TIME _____

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SORIATANE?

Soriatane can cause severe birth defects. If you are a female who can get pregnant, you should use Soriatane only if you are not pregnant now, can avoid becoming pregnant, and other medicines do not work for your severe psoriasis or you cannot use other psoriasis medicines. Females should read "What are the important warnings and instructions for females taking Soriatane?" on page 3 and "What should males know before taking Soriatane?" on page 6. Everyone should read this entire booklet carefully.

IMPORTANT INFORMATION FOR FEMALE PATIENTS

What are the important warnings and instructions for females taking Soriatane?

- **Before you received your Soriatane prescription, you should have discussed and signed a Patient Agreement/Informed Consent for Female Patients form with your prescriber. This is to help make sure you understand the risk of birth defects and how to avoid getting pregnant. If you did not talk to your prescriber about this and sign the form, contact your prescriber.**
- **You must not take Soriatane if you are pregnant or might become pregnant during treatment or at any time for at least 3 years after you stop treatment because Soriatane can cause severe birth defects.**
- **During Soriatane treatment and for 2 months after you stop Soriatane treatment, you must avoid drinks, food and all medicines that contain alcohol. This includes over-the-counter products that contain alcohol.** Avoiding alcohol is very important, because alcohol changes Soriatane into a drug that may take longer than 3 years to leave your body. The chance of birth defects may last longer than 3 years if you swallow any form of alcohol during Soriatane therapy and for 2 months after you stop taking Soriatane.
- **You and your prescriber must be sure you are not pregnant before you start Soriatane therapy. You must** have **negative** results from **2 pregnancy tests.** A negative result shows you are not pregnant. Because it takes a few days after pregnancy begins for a test to show that you are pregnant, the first negative test may not ensure you are not pregnant. Do not take Soriatane until you have negative results from **2** pregnancy tests.
  - The **first pregnancy test** will be done at the time you and your prescriber decide if Soriatane might be right for you.
  - The **second pregnancy test** will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane. Your prescriber may suggest another time.
- Discuss effective **birth control** (contraception) with your prescriber. You must use **2 effective forms of birth control (contraception) at the same time during all of the following:**
  - **For at least 1 month before beginning Soriatane treatment**
  - **During treatment with Soriatane**
  - **For at least 3 years after stopping Soriatane treatment**
- You must use 2 effective forms of birth control (contraception) at the same time even if you think you cannot become pregnant, unless 1 of the following is true for you:
  - You have had your womb (uterus) removed during an operation (a hysterectomy).
  - Your prescriber said you have gone completely through menopause (the "change of life").
  - You choose a method called "abstinence." This means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during and for at least 3 years after Soriatane treatment.

• You can get a free birth control counseling session and pregnancy testing from a prescriber or family planning expert. Your prescriber can give you a Soriatane Patient Referral Form for this free session.
• The following are considered effective forms of birth control:

Primary Forms
- having your tubes tied (tubal ligation)
- partner's vasectomy
- IUD (intrauterine device)
- birth control pills that contain both estrogen and progestin (combination oral contraceptives)
- hormonal birth control products that are injected, implanted or inserted in your body
- birth control patch

Secondary Forms (use with a Primary Form)
- diaphragms with spermicide
- latex condoms with spermicide
- cervical caps with spermicide

At least 1 of your 2 methods of birth control must be a primary form.
• You must use 2 effective forms of birth control (contraception) at the same time every time you repeat Soriatane treatment. You must use birth control for at least 1 month before you start Soriatane, during treatment and for at least 3 years after you stop Soriatane treatment.
• **If you have sex at any time without using 2 effective forms of birth control (contraception) at the same time, or if you get pregnant or miss your period, stop using Soriatane and call your prescriber right away.**
• Consider **"Emergency Contraception (EC)"** if you have sex with a male without correctly using 2 effective forms of birth control (contraception) at the same time. EC is also called "emergency birth control" or the "morning after" pill. Contact your prescriber **as soon as possible** if you have sex without using 2 effective forms of birth control (contraception) at the same time, because EC works best if it is used within 1 or 2 days after sex. EC is not a replacement for your usual 2 effective forms of birth control (contraception) because it is not as effective as regular birth control methods.

You can get EC from: **private doctors or nurse practitioners, women's health centers or hospital emergency rooms. You can get the name and phone number of EC providers nearest you by calling the free Emergency Contraception Hotline at 1-888-NOT-2-LATE (1-888-668-2528).**
• **Stop taking Soriatane right away and contact your prescriber if you get pregnant while taking Soriatane or at any time for at least 3 years after treatment has stopped. You need to discuss the possible effects on the unborn baby with your prescriber.**
• **If you do become pregnant while taking Soriatane or at any time for at least 3 years after stopping Soriatane, you should report your pregnancy to Roche at 1-800-526-6367 or directly to the Food and Drug Administration (FDA) MedWatch program (1-800-FDA-1088).**
Your name will be kept in private (confidential). The information you share may help the FDA and the manufacturer support the pregnancy prevention program for Soriatane.
• **Do not take Soriatane if you are breast-feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast-feed or take Soriatane but not both.

IMPORTANT INFORMATION
FOR MALE PATIENTS

What should <u>males</u> know before taking Soriatane?
Small amounts of Soriatane are found in the semen of males taking Soriatane. Based upon available information both during and after the treatment, small amounts of Soriatane in semen do not seem to harm the baby. It is not known for sure that there is a risk. It appears that any small remaining amount of Soriatane in semen poses little, if any, risk to an unborn child while a male patient is taking the drug or after it is discontinued. Discuss

any concerns you have about this with your prescriber.

IMPORTANT INFORMATION
FOR ALL PATIENTS

What is Soriatane (acitretin)?
Soriatane is a medicine used to treat severe forms of psoriasis in adults. Psoriasis is a skin disease that causes cells in the outer layer of the skin to grow faster than normal and pile up on the skin's surface. In the most common type of psoriasis, the skin becomes inflamed and produces red, thickened areas, often with silvery scales. **Because Soriatane can have serious side effects,** you should talk with your prescriber about whether Soriatane's possible benefits outweigh its possible risks.

Soriatane may not work right away. You may have to wait 2 to 3 months before you get the full benefit of Soriatane. Psoriasis gets worse for some patients when they first start Soriatane treatment.

Soriatane has not been studied in children.

Who should not take Soriatane?
- **Do NOT take Soriatane if you can get pregnant:** Do not take Soriatane if you are pregnant or might get pregnant during Soriatane treatment or at any time for **at least 3 years** after you stop Soriatane treatment (see "What are the important warnings and instructions for females taking Soriatane?" on page 3).
- **Do NOT take Soriatane if you are breast-feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast-feed or take Soriatane, but not both.
- **Do NOT take Soriatane if you have severe liver or kidney disease.**
- **Do NOT take Soriatane if you have repeated high blood lipids over time** (fat in the blood).
- **Do NOT take Soriatane if you take the medicines:**
  - methotrexate
  - tetracyclines

The use of these medicines with Soriatane may cause **serious** side effects.

- **Do NOT take Soriatane if you are allergic to acitretin,** the active ingredient in Soriatane, or to any of the other ingredients. (See the end of this section for a list of all the ingredients in Soriatane).

Tell your prescriber if you have or ever had:
- Diabetes or high blood sugar
- Liver problems
- Kidney problems
- High cholesterol or high triglycerides (fat in the blood)
- Heart disease
- Depression
- Alcoholism

Your prescriber needs this information to decide if Soriatane is right for you and to know what dose is best for you.

Tell your prescriber about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines can cause **serious side effects** if taken while you also take Soriatane. Some medicines may affect how Soriatane works, or Soriatane may affect how your other medicines work. **Be especially sure to tell your prescriber if you are taking the following medicines:**
- methotrexate
- tetracyclines
- phenytoin
- vitamin A supplements

- progestin-only oral contraceptives ("mini-pills")
- Tegison® or Tigason® (etretinate). Tell your prescriber if you have ever taken this medicine in the past.
- St. John's Wort herbal supplement

Tell your prescriber if you are getting phototherapy treatment. Your doses of phototherapy may need to be changed to prevent a burn.

How should I take Soriatane?
- Take Soriatane with food.
- Be sure to take your medicine as prescribed by your prescriber. The dose of Soriatane varies from patient to patient. The number of capsules you must take is chosen specially for you by your prescriber. This dose may change during treatment.
- If you miss a dose, do not double the next dose. Skip the missed dose, and resume your normal schedule.
- If you take too much Soriatane (overdose), call your local poison control center or emergency room.

You should have **blood tests** for liver function, cholesterol and triglycerides before starting treatment and during treatment to check your body's response to Soriatane. Your prescriber may also do other tests.

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Once you stop taking Soriatane, your psoriasis may return. Do not treat this new psoriasis with leftover Soriatane. It is important to see your prescriber again for treatment recommendations because your situation may have changed.

What should I avoid while taking Soriatane?
- **Avoid pregnancy.** See "What is the most important information I should know about Soriatane?" on page 2, "What are the important warnings and instructions for females taking Soriatane?" on page 3, and "What should males know before taking Soriatane?" on page 6.
- **Avoid breast-feeding.** See "What are the important warnings and instructions for females taking Soriatane?"
- **Avoid alcohol.** Females must avoid drinks, foods, medicines and over-the-counter products that contain alcohol. The risk of birth defects may continue for longer than 3 years if you swallow any form of alcohol during Soriatane treatment or for 2 months after stopping Soriatane (see "What are the important warnings and instructions for females taking Soriatane?" on page 3).
- **Avoid giving blood. Do not donate blood** while you are taking Soriatane and **for at least 3 years after stopping** Soriatane treatment. Soriatane in your blood can harm an unborn baby if your blood is given to a pregnant woman. Soriatane does not affect your ability to **receive** a blood transfusion.
- **Avoid progestin-only birth control pills ("mini-pills").** They may not work while you take Soriatane. Ask your prescriber if you are not sure what type of pills you are using.
- **Avoid night driving if you develop any sudden vision problems.** Stop taking Soriatane and call your prescriber if this occurs (see the Serious side effects section on the next page).
- **Avoid nonmedical ultraviolet (UV) light.** Soriatane can make your skin more sensitive to UV light. Do not use sunlamps, and avoid sunlight as much as possible. If you are taking light treatment (phototherapy), your prescriber may need to change your light dosages to avoid burns.
- **Avoid dietary supplements containing Vitamin A.** Soriatane is related to vitamin A. Therefore, do not take supplements containing vitamin A, because they may add to the unwanted effects of Soriatane. Check with your prescriber or pharmacist if you have any questions about vitamin supplements.

- **DO NOT SHARE Soriatane with anyone else, even if they have the same symptoms.**

What are the possible side effects of Soriatane?

Soriatane can cause birth defects. See "What is the most important information I should know about Soriatane?" on page 2 and "What are the important warnings and instructions for females taking Soriatane?" on page 3.

Psoriasis gets worse for some patients when they first start Soriatane treatment. Some patients have more redness or itching. If this happens, tell your prescriber. These symptoms usually get better as treatment continues, but your prescriber may need to change the amount of your medicine.

Serious side effects

These do not happen often, but they can lead to permanent harm, or rarely, to death. Stop taking Soriatane and call your prescriber right away if you get the following signs or symptoms:

- **Bad headaches, nausea, vomiting, blurred vision.** These symptoms can be signs of increased brain pressure that can lead to blindness or even death.
- **Decreased vision in the dark** (night blindness). Since this can start suddenly, you should be very careful when driving at night. This problem usually goes away when Soriatane treatment stops. If you develop **any** vision problems or eye pain, stop taking Soriatane and call your prescriber.
- **Depression.** There have been some reports of patients who have taken oral retinoids like Soriatane and have developed mental problems including a depressed mood, aggressive feelings or thoughts of self-harm. Since other factors may have contributed to such events, it is not known if they are related to Soriatane. It is very important to stop taking Soriatane and call your prescriber right away if you experience any of these.
- **Yellowing of your skin or the whites of your eyes, nausea and vomiting, loss of appetite or dark urine.** These can be signs of serious liver damage.
- **Aches or pains in your bones, joints, muscles or back; trouble moving; loss of feeling in your hands or feet.** These can be signs of abnormal changes to your bones or muscles.
- **Frequent urination, great thirst or hunger.** Soriatane can affect blood sugar control, even if you do not already have diabetes. These are some of the signs of high blood sugar.
- **Shortness of breath, dizziness, nausea, chest pain, weakness, trouble speaking or swelling of a leg. These may be signs of a heart attack, blood clots or stroke.** Soriatane can cause serious changes in blood fats (lipids). It is possible for these changes to cause blood vessel blockages that lead to heart attacks, strokes or blood clots.

Common side effects

If you develop any of these side effects or any unusual reaction, check with your prescriber to find out if you need to change the amount of Soriatane you take. These side effects usually get better if you reduce your dose or stop taking Soriatane:

- **Chapped lips; peeling fingertips, palms and soles; itching; scaly skin all over; weak nails; sticky or fragile (weak) skin; runny or dry nose or nose bleeds.** Your prescriber or pharmacist can recommend a lotion or cream to help treat drying or chapping.
- **Dry mouth**
- **Joint pain**
- **Tight muscles**
- **Hair loss.** Most patients have some hair loss, but this condition varies among patients. No one can tell if you will lose hair, how much hair you may lose or if and when it may grow back.
- **Dry eyes.** Soriatane may dry your eyes. Wearing **contact lenses** may be uncomfortable during and after treatment with Soriatane because of the dry feeling in your eyes. If this happens, remove your contact lenses and call your prescriber. Also read about decreased vision in the Serious side effects section on the previous page.

- **Rise in blood fats (lipids).** Soriatane can cause your blood fats (lipids) to rise. Most of the time, this is not serious. But sometimes, the increase can become a serious problem. (See information in the Serious side effects section on the previous page.) You should have blood tests as directed by your prescriber.

These are not all the possible side effects of Soriatane. For more information, ask your prescriber or pharmacist.

How should I store Soriatane?
Keep Soriatane away from sunlight, high temperature and humidity. **Keep Soriatane away from children.**

What are the ingredients in Soriatane?
Active ingredient: acitretin
Inactive ingredients: microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black and red) and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

General information about the safe and effective use of Soriatane
Medicines are sometimes prescribed for purposes other than those listed here. Do not use Soriatane for a condition for which it was not prescribed. Do not give Soriatane to other people, even if they have the same symptoms that you have.

This section of this booklet summarizes the most important information about Soriatane. If you would like more information, talk with your prescriber. You can ask your pharmacist or prescriber for information about Soriatane that is written for health professionals.

PREVENTING PREGNANCY:
A GUIDE TO CONTRACEPTION

Why is this information very important to me?
Your dermatologist may prescribe Soriatane (acitretin) to be used in your treatment. Soriatane is used to treat severe psoriasis in adults. In females of reproductive potential, Soriatane should be reserved for nonpregnant patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Soriatane can cause severe birth defects. Soriatane is indicated only for females who are **not** pregnant. This booklet contains very important facts about Soriatane that **you must know and understand before you can begin treatment with Soriatane.**

This section of the booklet explains the birth control (contraception) steps you must take before you can start taking Soriatane; what you must do during Soriatane treatment; and what you must do for at least 3 years after you stop your Soriatane treatment.

To help you avoid becoming pregnant while taking Soriatane, a special Contraception Counseling Referral Program is available through your prescriber that will pay for you to go to another healthcare professional to receive contraception counseling and pregnancy testing. Details of this program are given in the section called *Contraception Counseling Referral Program,* on page 14.

Emergency Contraception (EC), or emergency birth control, is used to prevent pregnancy following unprotected intercourse or sex. Details on emergency birth control are provided in the section called *Emergency Contraception,* on page 24.

Also, it is *extremely* important that your sexual partner understand that you must use 2 effective forms of birth control (contraception) at the same time for at least 1 month before beginning Soriatane treatment, during treatment with Soriatane and for at least 3 years after stopping Soriatane treatment. It is very important that your sexual partner understand you must not become pregnant and the special precautions that must be taken during Soriatane treatment and for at least 3 years after you completely stop taking Soriatane. The section called *Your sexual partner,* on page 26, is provided to help you as you talk to your sexual partner about his important role in your Soriatane treatment.

Because you need to understand all the facts in this booklet, read it all the way through. Do **NOT** skip any

section of the booklet. After you have read through the booklet once, read it through again. As you read through the second time, write down a list of questions for your prescriber to answer. Do not worry if you think the question is silly or may be unimportant. You have to understand all the facts in this booklet. Your prescriber wants you to understand everything in this booklet and everything that he or she tells you about Soriatane treatment. The facts in this booklet about Soriatane treatment are very important to your health and well-being.

Why must I use 2 effective forms of birth control (contraception)?

You must use 2 effective forms of birth control (contraception) at the same time for at least 1 month before beginning Soriatane treatment, during treatment with Soriatane and for at least 3 years after stopping Soriatane treatment to prevent pregnancy, because any birth control method can fail and your baby could be born with severe birth defects if you are taking Soriatane while you are pregnant.

There is an **extremely high risk** that a deformed baby can result if you become pregnant while taking Soriatane in any amount, even for short periods of time. When an unborn baby is exposed to Soriatane, there is a higher risk of deformities or a miscarriage. This explains the need for the precautions that must be taken at least 1 month before, during and for at least 3 years after stopping Soriatane use. **Remember, not 1 but 2 effective forms of birth control are required while you are taking Soriatane.**

CONTRACEPTION COUNSELING
REFERRAL PROGRAM
Be sure to ask your prescriber about the Contraception Counseling Referral Program

Before you can start taking Soriatane (acitretin), you and your prescriber must be sure that you are not pregnant and that you understand how to avoid becoming pregnant. Because it is so very important that you understand how to avoid becoming pregnant while taking Soriatane, a special Contraception Counseling Referral Program has been established by the manufacturer of Soriatane.

You or your prescriber can arrange for you to see a contraception counselor who specializes in the female reproductive system. This healthcare professional will provide you with expert counseling about birth control and may even do a pregnancy test.

Even if you feel that you know about birth control, and even if you are not having sex or do not plan to have sex, this counseling is very important in planning your treatment with Soriatane. You will not be required to pay for the counseling or any pregnancy testing that they may do. **Be sure to ask your prescriber about the Contraception Counseling Referral Program.**

What is abstinence?
Abstinence means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during, and for at least 3 years after Soriatane treatment.
Abstinence is not considered a method of birth control.

Using abstinence
If you are not currently having sexual intercourse with a male partner, it is extremely important that you ask yourself:

Will I definitely remain abstinent for at least 1 month before, during and for at least 3 years after Soriatane treatment?

If your answer is no, talk to your prescriber immediately.

How can I avoid becoming pregnant?
Any method of birth control can fail. Even if you use one of the most effective birth control methods correctly, there is still a risk of getting pregnant.

Therefore, 2 effective forms of birth control must always be used together at the same time by female patients starting at least 1 month before, during and at least 3 years after Soriatane treatment.

CONTRACEPTION METHODS[1]
Primary (most effective) methods of birth control

At least 1 of the 2 effective forms of birth control must be a primary method of birth control.

This information does not contain all available information about contraception. As always, you should discuss this and any other medical question with your prescriber or contraception counselor.

THE PILL (oral contraception)
Two kinds of birth control pills are available and they work in different ways.

Combination pills, which contain 2 hormones, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. In addition, combination pills prevent eggs from being released. Your healthcare professional will discuss the different types of pills and help you decide which one is right for you.

Mini-pills, which contain only 1 type of hormone, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. Mini-pills are not recommended for birth control during Soriatane (acitretin) use.

With the Pill method of birth control, 1 pill is taken once a day until the package is completed.
The Pill is usually started the first Sunday after a normal menstrual period or as instructed by your healthcare professional. One package is completed every menstrual cycle. Not all pills provide protection from the start; you can become pregnant during the first 4 weeks after you start taking the Pill. Pills should be taken at the same time every day, and it may be helpful to use a calendar. Strike an "X" for the first day of a new package of pills, and check each day thereafter.

With **perfect use** (correctly and consistently), about 1 woman in 1000 becomes pregnant.
For **typical use** (not always correctly or consistently), the rate is 5 in 100.

The Pill can have a variety of side effects; most are considered minor. Some rare, but serious, health risks do exist, including blood clots, heart attack and stroke. Women who are older than 35 years, who smoke or who are greatly overweight are at greater risk for these side effects, so it is important to discuss these issues with your prescriber.

If a dose of the combination pill is missed, you can take one when you realize it and then continue taking the others at their regular time. **If you miss an entire day, it may be okay to take 2 pills together if necessary; however, you should consult the patient information included in your birth control package and contact your healthcare professional. If you miss taking your pills more than 2 days in a row, you can become pregnant. Do not have sexual intercourse at this time. If you miss more than 2 days, you should call your healthcare professional as soon as you realize it. You are at greatest risk for pregnancy if you start a package late or miss taking pills during the first week of each package.**

Remember: If the Pill is your primary method, you must still use a secondary method at the same time.

THE PATCH (topical contraceptive)
The 2 hormones in the contraceptive patch are absorbed through the skin and released into the bloodstream while the patch is worn. The hormones in the contraceptive patch thicken vaginal mucus to keep the sperm from joining the egg and may prevent a fertilized egg from attaching to the womb. They also prevent eggs from being released.

With the 4-week patch method of birth control, 1 patch is used per week for 3 weeks; then, no patch is worn for the fourth week. The first patch may be applied on the first day of a woman's menstrual period (First Day Start) OR on the first Sunday after the woman's menstrual period starts (Sunday Start). If Sunday Start is selected, or the patch is applied on any other day except the first day of the menstrual period, a woman may become pregnant during the first week of her cycle. The patch should be changed on the same day each week.

The effectiveness of the patch is considered to be similar to combination contraceptive pills if used as directed. However, the patch may be less effective for a woman who weighs more than 198 lb (90 kg). Your healthcare professional should discuss your individual needs with you if your weight is more than 198 lb.

The patch may have similar side effects to combination contraceptive pills. Most side effects are considered minor. However, some rare but serious side effects include blood clots, heart attack and stroke. Women who are older than 35 years, who smoke or who are significantly overweight are at greater risk for these side effects.

If the patch falls off or is partially detached for less than 24 hours, a new patch should be put on immediately, and this patch should be changed on the usual change day. If the patch is detached for more than 1 day, a new cycle with a new change day should be started by applying a new patch. Should this occur, you may not be protected from pregnancy for the first week. Do not have sexual intercourse at this time.

If you forget to apply a patch on the first day of your cycle or forget to change a patch for more than 2 days in the middle of the cycle, you should apply a new patch immediately and begin a new 4-week cycle with a new change day. You may not be protected from pregnancy for the next week. It is very important that no more than 7 days elapse during the patch-free week of treatment. Do not have sexual intercourse at this time. Consult your healthcare professional if you forget to follow the instructions in the patient information included with your patch.

Remember: If the patch is your primary method, you must still use a secondary method at the same time.

IMPLANTABLE HORMONES—This method of birth control is no longer available to new patients.

With this birth control method, your healthcare professional puts 6 small rod-shaped capsules under the skin of your upper arm. The procedure is simple and can be done during an office visit. The capsules release small amounts of hormone that stop eggs from being released and thicken vaginal mucus to keep sperm from joining the egg. The capsules remain effective for a number of years, and they can be removed by your healthcare professional at any time.

Generally, the side effects are similar to those that occur if you take the Pill. There is only a small chance of an irritation at the spot where the capsules are implanted. The contraceptive effectiveness of these hormones begins 3 days after being implanted.

With **perfect use,** about 5 women in 10,000 become pregnant.
For **typical use,** the rate is also 5 in 10,000.

Remember: If implantable hormones are your primary method, you must still use a secondary method at the same time.

INJECTABLE HORMONES

This method of birth control is a shot or needle injection of a hormone in your arm or buttocks, given to you by your healthcare professional at specific intervals every 4 to 12 weeks. The hormone shot stops eggs from being released, thickens vaginal mucus to keep the sperm from joining the egg and keeps a fertilized egg from attaching to the womb.

Generally, the side effects are similar to those that occur if you take the Pill. This form of birth control is reversible, but it may take several months after stopping the shots before you can become pregnant.

With **perfect use,** about 2-3 women in 1000 become pregnant.
For **typical use,** the rate is also 2-3 in 1000.

Injectable hormones can take up to 1 week to be fully effective; you can become pregnant during this week. Patients who have certain illnesses, or a family history of some illnesses, may not be suited for this type of birth control, so it is important to discuss these issues with your healthcare professional.

Remember: If injectable hormones are your primary method, you must still use a secondary method at the same time.

THE INTRAUTERINE DEVICE (IUD)
The intrauterine device, which is called the IUD, is a plastic device that contains either copper or hormones. Your healthcare professional puts the small plastic IUD in your womb. The copper or hormones in the IUD keep the sperm from joining the egg and prevent a fertilized egg from attaching to the womb.

IUDs that contain hormones can be left in place for between 1 and 5 years. The copper-containing IUDs can be left in place for up to 10 years. Side effects of all types of IUDs may include increased cramps and heavier and longer periods. Women with new sex partners, women with more than one partner or women whose partners have other partners have an increased chance of tubal infection (which may lead to sterility). These risks should be discussed with your healthcare professional. He or she will also explain how to check the IUD for proper position by feeling for a "tail" or string in the vagina. If the string cannot be felt, the IUD may have been expelled or dislodged from its proper position and a healthcare professional should be consulted. This method is not recommended for women who have not had a child.

With **perfect use,** about 1.5 women in 100 become pregnant.
For **typical use,** the rate is 2 in 100.

Remember: If an IUD is your primary method, you must still use a secondary method at the same time.

INSERTABLE HORMONES
The hormonal vaginal contraceptive ring is inserted by you into your vagina and contains a combination of hormones similar to the Pill. After the ring is inserted, it releases a continuous low dose of hormones into your body. The hormones stop the release of an egg and alter cervical mucus to keep sperm from entering the womb. You leave it in for 3 weeks, and then you remove it for 1 week. During this time, your menstrual period will begin. For your first cycle, the ring should be inserted between day 1 and day 5 of your menstrual period. It may take up to 1 week to become fully effective in the first cycle.

Generally, the side effects are similar to those of the Pill. Other side effects may include vaginal discharge or irritation. Like the Pill, the hormonal vaginal contraceptive ring may increase the risk of blood clots, heart attack and stroke, especially in women who smoke. It should not be used by women with certain types of cancer or other medical conditions, so it is important to discuss these issues with your prescriber.

With **perfect use,** about 7-8 women in 1000 become pregnant.
For **typical use,** the rate is 1-2 in 100.

Remember: If the hormonal vaginal contraceptive ring is your primary method, you must still use a secondary method at the same time. You cannot use the diaphragm as a secondary method because the vaginal contraceptive ring may interfere with correct placement and position of a diaphragm.

STERILIZATION: TUBAL LIGATION AND VASECTOMY
Sterilization of either a man or woman requires an operation. A tubal tying (ligation) is intended to permanently block a woman's tubes where the sperm joins with the egg. A vasectomy is intended to permanently block a man's semen duct that carries sperm. However, it takes 15 to 20 ejaculations after sterilization to clear sperm from the man's semen.

You may become pregnant if your male partner has not had 2 consecutive counts that show there are no sperm in the seminal fluid.

There are no lasting side effects and sterilization has no effect on sexual pleasure. Mild bleeding or infection may occur right after the procedure. Sterilization is intended to be permanent; reversing the operation is very difficult and cannot be guaranteed.

With **perfect use,** about 5 women in 1000 (using female sterilization) or 1 woman in 1000 (using male sterilization) become pregnant.
For **typical use,** the rates are 5 in 1000 (female) and 1.5 in 1000 (male).

Remember: If sterilization is your primary method, you must still use a secondary method at the same time.

Secondary (moderately effective) forms of birth control

CONDOM, DIAPHRAGM OR CERVICAL CAP
Each of these is called a "barrier" method of birth control. They are used with a special gel called a spermicide. A spermicide is a substance that kills sperm. By itself, it is NOT an adequate birth control method for Soriatane (acitretin) users. Spermicides come in several forms—creams, jellies, foams and suppositories, which should be applied with your barrier method 10 to 30 minutes before each intercourse.

Spermicide must be applied each time you have sexual intercourse. Your contraception counselor should explain to you exactly how to use the spermicide with the "barrier" method you choose. The barrier method, plus the spermicide, only count as ONE of the 2 forms of effective birth control you must choose before starting Soriatane. The diaphragm or cervical cap must be left in place for 6 hours after your last sexual act, and a woman should not douche or rinse the vagina during this time.

You should understand exactly how to and how not to use barrier methods of birth control. You need to be aware of common mistakes in their use that may result in pregnancy. These barrier methods of birth control are considered less reliable than the other methods discussed earlier.

CONDOM
The condom, also called a "rubber," is a thin sheath that traps the sperm. Condoms are made of latex, plastic or animal tissue (natural skin). Condoms, when used properly and consistently, and with a spermicide, can be effective in preventing pregnancy. It is also believed that latex condoms reduce the spread of some STDs (sexually transmitted diseases), including HIV. Synthetic and natural skin condoms, or those made from the skin of lamb's intestines, are equally effective at preventing pregnancy. However, natural skin condoms do not protect against STDs.

Proper use of a condom means several things. If you choose this method, it is important to have your contraception counselor explain exactly how to follow these directions. The condom has to have been stored in a cool, dry place and not exposed to heat or pressure. It should be rolled onto the erect penis before any contact with the woman's genitals. The rolled rim should always remain on the outside of the condom. If the condom has been rolled incorrectly (backward), it should be discarded and replaced with a new one. A 1/2 inch of

empty space should be left at the tip, but no air should be trapped. Air at the tip could cause the condom to break.

The condom should be removed immediately after intercourse to prevent spillage of semen. A condom can be used only once. Oil-based lubricants, like petroleum jelly and baby oil, should not be used with a condom. Water-based lubricants are safe to use and will not destroy the condom. However, since it is necessary to use a spermicide with a condom, this can be used as a lubricant. Care should be taken to avoid ripping, tearing or slipping off during sexual activity.

With **perfect use**, about 3 women in 100 become pregnant.
For **typical use**, the rate is 14 in 100.

Remember: Condoms should never be used alone without a primary birth control method.

DIAPHRAGM
The diaphragm is a shallow latex cup. Its purpose is to cover the cervix and prevent sperm from passing up into the womb. Because the size around the cervix varies from woman to woman, a diaphragm has to be custom fit by a healthcare professional. The fit needs to be checked at least once every 2 years, if a weight gain or loss of 10 or more pounds occurs, or after pregnancy or an abortion.

The diaphragm can be inserted into the vagina up to 6 hours before sexual intercourse. Spermicide jelly or cream is placed in the diaphragm and around the rim before insertion. Fresh spermicide should be applied with each sexual intercourse or if 6 hours have elapsed before sexual intercourse occurs. The diaphragm should not be removed when spermicide is reapplied. The diaphragm must be left in place for at least 6 hours after the last sexual intercourse; it should not be left in place for longer than a total of 24 hours because of the risk of serious infection (toxic shock syndrome). Once fitted, the diaphragm is inserted into the vagina so that the dome covers the cervix and the rim fits snugly on the vaginal walls.

With **perfect use** (with spermicide), about 6 women in 100 become pregnant.
For **typical use** (with spermicide), the rate is 20 in 100.

Remember: A diaphragm should always be used with spermicide and only as a secondary method. A separate primary method must always be used.

CERVICAL CAP
The cervical cap is a barrier method that must be individually fitted and prescribed by a healthcare provider. The cervical cap is inserted by the female before each sexual intercourse and must be used in combination with a spermicide to be considered moderately effective as a birth control method. The cervical cap is made of latex and should never be used with an oil-based lubricant, such as petroleum jelly, as this will destroy the cap.

The cervical cap actually fits over the cervix. The cap should be left in place for at least 6 hours after the last sexual intercourse, but not longer than 48 hours because of the risk of toxic shock syndrome. Spermicide is placed in the cap before insertion, but it is best to add more spermicide with each intercourse while the cap is still in place. The cervical cap should not be removed while the spermicide is being reapplied. Inserting and removing the cervical cap can be somewhat more difficult than inserting and removing the diaphragm. However, with sufficient instruction and practice, insertion and removal can usually be accomplished.

With **perfect use**, about 9 women in 100 become pregnant.
For **typical use**, the rate is 20 in 100.

Remember: A cervical cap should always be used with a spermicide and only as a secondary method. A separate primary method must always be used.

Other contraception methods
Do not use less effective methods of birth control such as birth control pills without estrogen, natural family planning, fertility awareness or withdrawal while taking Soriatane (acitretin), a medication that can cause birth defects to your unborn child. Ask your healthcare professional about other contraception methods that you may use or have heard about.

Reference: 1. Trussell J, Card JJ, Rowland Hogue CJ. Adolescent sexual behavior, pregnancy, and childbearing. In: Hatcher RA, Trussell J, Stewart F, et al, eds. *Contraceptive Technology.* 17th ed. New York, NY: Ardent Media, Inc.; 1998:701-744.

[end of PPP booklet]

Dear Prescriber/Pharmacist letter:

Dear Prescriber/Pharmacist:

Please be advised of the following **important changes to the Soriatane (acitretin) labeling**.

The Soriatane Package Insert has been updated to provide additional information collected during the time the product has been marketed. It has also been revised for ease of use. It is important to note the new Medication Guide for all patients taking Soriatane, as well as changes to the informed consent form for female patients.

Prescribers and pharmacists are advised to read the entire Package Insert (enclosed) after reviewing the "Synopsis of Informational Changes" below.

Synopsis of Informational Changes

- The Soriatane **"Patient Agreement/Informed Consent for Female Patients"** has been revised for consistency with the changes made in the Package Insert. After the prescriber has determined that a female patient may be a candidate for Soriatane, and has explained the proper use of this medication, the patient should initial each of the 18 items and sign and date the entire informed consent. This is an important component of the Pregnancy Prevention Program and is included as part of the professional Package Insert.

- To improve the communication regarding Soriatane to all healthcare providers, pharmacists and patients, Roche Laboratories Inc. will be releasing a FDA approved **Medication Guide (MedGuide) for Soriatane**. This document will be sent to prescribers' offices and to all pharmacies in the United States to enhance the safe and effective use of Soriatane.

  The Medication Guide for Soriatane must be distributed by the pharmacist, as required by law, to every Soriatane patient each time a Soriatane prescription is dispensed. The Medication Guide was developed in conjunction with the FDA to emphasize key safety issues that patients should know about the use of Soriatane. The Medication Guide for Soriatane summarizes, in simple language, the professional Package Insert, including the approved indication for Soriatane, information about birth defects and pregnancy avoidance, and major adverse events. The Medication Guide is a document required by the FDA for specific medications and must be available for every patient. **To reorder additional Soriatane Medication Guides, please call toll free 1-800-93-ROCHE.** Soriatane is supplied in 10 mg and 25 mg capsule strengths in bottles of 30. The Medication Guide is piggy backed onto the Package Insert which is affixed to each bottle.

- **Informational Changes made to the Soriatane Package Insert are as follows:**

  - The **boxed CONTRAINDICATIONS AND WARNINGS SECTION** has been changed as follows:

- **Emphasizes the need for two effective forms of contraception (birth control) simultaneously** . The labeling now emphasizes that effective forms of contraception include both primary (tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products) and secondary forms (diaphragms, latex condoms, and cervical caps each used with a spermicide). At least one of the two methods of birth control must be a primary form.

- Data related to **teratogenicity** when Soriatane is taken by female and male patients have been updated, clarified, and made more concise.

- Patients should be **cautioned not to self-medicate with the herbal supplement St. John's Wort** because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort.

- Instructions for patients **not to donate blood** have been clarified and now appear both in the boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections of the Package Insert: "Patients should not donate blood during Soriatane during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane".

- A **section entitled CLINICAL STUDIES** has been added. This section presents the efficacy data from the two pivotal clinical trials.

- The first sentence of the **INDICATIONS AND USAGE** section has been amended. Instead of stating "Soriatane is indicated for the treatment of severe psoriasis, including the erythrodermic and generalized pustular types, in adults", it now states "*Soriatane is indicated for the treatment of severe psoriasis in adults*". This change is consistent with the data in the CLINICAL STUDIES section.

- The **CONTRAINDICATIONS section** has been revised. Soriatane is contraindicated in patients with severely impaired liver and kidney function and in patients with chronic abnormally elevated blood lipid levels. The combined use of Soriatane and methotrexate, and Soriatane and tetracyclines is contraindicated.

- The following revisions and additions have been made to the **WARNINGS section**:
  - The internal black boxes around pancreatitis and pseudotumor cerebri have been removed, but these warnings remain in the WARNINGS section. The internal black box for hepatoxicity remains. This change does *not* reflect new safety information. It was made simply for labeling consistency with other serious adverse events.

  - Additional information has been added regarding ***Pancreatitis***. There have been rare reports of pancreatitis during Soriatane therapy in the *absence* of hypertriglyceridemia.

  - Additional instruction has been added regarding ***Hyperostosis***. Periodic radiography of patients on Soriatane treatment is warranted in the presence of symptoms or long-term use because the frequency and severity of iatrogenic bony abnormality in adults is low.

  - Additional information has been added regarding ***Lipids and Possible Cardiovascular Effects***. Although no causal relationship has been established, there have been postmarketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy.

- The following revisions and additions have been made to the **PRECAUTIONS section**:

  - The subsection "**Nursing Mothers**" has been updated to note that there is one prospective case report where actitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants.

  - **Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm** have been reported. These events, including self-injurious behavior, have been reported in patients taking other

systemically administered retinoids as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms.

- **Decreased night vision** has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored.

- **Patients should not donate blood** during Soriatane treatment and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane.

- The following language has been clarified to **differentiate between non-medical and medically supervised UV exposure**: "Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical ultraviolet exposure) because the effects are enhanced by retinoids)".

- Prescribers should **significantly lower doses of phototherapy** when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning).

- A ***Drug Interactions*** section has been reformatted for ease of reading and contains information about the interactions between Soriatane and a) ethanol ; b) glibenclamide; c) information that microdosed progestin preparations (minipills) may be an inadequate method of contraception during Soriatane therapy; d) phenytoin.

- The ***Pediatric Use*** section has been amended to include reports of **decreases in bone mineral density** in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between effect on bone and Soriatane has not been established.

- A ***Geriatric Use*** section has been added to note that clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determined whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

- The **ADVERSE REACTIONS** section which reports on the clinical trials experience has been reformatted for your convenience to list the reported events by body system in alphabetical order. *Additional* adverse events are reported in a **newly created section *Adverse Events/Postmarketing* reports**:

  - In addition to the events listed in the tables for the clinical trials, the following adverse events have been identified during post-approval use of Soriatane. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
    - **Cardiovascular** - Acute myocardial infaction, thromboembolism, (see WARNINGS)stroke
    - **Nervous System**: Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug.
    - **Psychiatric**: Aggressive feelings and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. (see PRECAUTIONS).
    - **Reproductive** - Vulvovaginitis due to *Candida albicans*
    - **Skin and appendages** – Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed.

- The **OVERDOSAGE section** has been amended to indicate that in the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. Further instructions are provided regarding pregnancy testing and counseling for all female patients of childbearing potential who have taken an overdose of Soriatane.

- The **DOSAGE AND ADMINISTRATION** section now addresses the fact that maintenance doses of 25 *to* 50 mg may be given (note: the previous Package Insert stated 25 or 50 mg). The section has been clarified to note that **maintenance doses** be given dependent upon an individual patient's response to initial treatment. This section also notes that when Soriatane is used with phototherapy, the prescriber should **decrease the phototherapy dose**, dependent on the patient's individual response.

Please refer to the enclosed complete updated product information for detailed information on Boxed Warnings, Contraindications, Warnings, Precautions, Adverse Events, Overdosage, Dosage and Administration, Informed Consent, and the Medication Guide.

If you have any questions about Soriatane, we encourage you to call the toll-free number for Roche at 1-800-526-6367. Also, if you are aware of any serious Adverse Events potentially associated with the use of Soriatane, report such information to Roche at the above number or to the Food and Drug Administration MedWatch program at 1-800-FDA-1088.

Sincerely,

[End of *Dear Professional Letter]*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

MEDICAL REVIEW(s)

Medical Officer Review
Labeling Supplement

NDA#: **19-821** Doc ID#: SLR-002 and 006 BL/BM

Stamp Date: February 12 and 28, 2003

Review Completed: March 12, 2003
Revised: March 17, 2003

Sponsor: Hoffman-LaRoche

Product: Soriatane (acitretin)

Indication: Severe recalcitrant psoriasis

Formulation: Capsule

Submission Summary:

At the Agency's request, the sponsor submitted a supplement to the Soriatane NDA to address the need for a number of revisions. A subsequent request asked the sponsor to submit the revised Patient Package Insert as a formal Medication Guide. In addition to these two submissions, the new labeling incorporates a geriatric labeling supplement submitted in 1999 (because the Geriatric supplement essentially adds no new information of use to prescribers or patients, action on that labeling amendment was postponed in anticipation of this major labeling revision). This review covers a re-submission of the 2002 labeling supplement. It received an Approvable action in November 2002 essentially because several important details were still under negotiation when the division chose to close the application with an official action (for specifics, please refer to review in DFS for Supplement #002 Geriatric labeling, #006 comprehensive labeling revisions, and the Medication Guide amendment to #006). My review of the Pregnancy Prevention Program associated with this new labeling is in DFS December 26, 2002.

This review consists of the following sections:

- Labeling: A "clean" copy of the professional package insert, the Informed Consent form for female patients, the Medication Guide, and the Pregnancy Prevention Program text (not forms; available only as PDF) as I recommend they be implemented. *To avoid re-examination of each line of this lengthy

labeling, this is based on *our* working version, not the version sent by the sponsor. This wording represents the consensus achieved via adverse event analyses from the Office of Drug Safety and the cardio-renal division, patient labeling advice from ODS, advice from DDMAC, and recommendations from the division labeling team for this product (biopharmaceutics, pharmacology, chemistry, biostatistics, and clinical - see documents in DFS under NDA 19-821: O'Connell, Bashaw, Pitts, Best J, Karwoski, Brown P, Hathaway S, and cardio-renal consult in paper file dated 7/27/99; additional advice is documented in December 2002 and January/February 2003 emails from biostatistics, Al-Osh and from DDMAC, R. Williams). This recommended wording reflects the sponsors' submitted wording whenever possible within our goals for the improved labeling. On March 12, 2003 the Sponsor agreed via teleconference with all other changes.

- A "clean" copy Dear Professional Letter as I recommend it be implemented (agreed upon with Sponsor at March 12, 2003 teleconference.
- A list of issues where the labeling differs from the version submitted here by Roche (as noted above, all agreed upon with Sponsor on March 12, 2003).
- Additional Review Comments
- Action Items
- Recommendation

Professional Package Insert

Roche

SORIATANE®
(acitretin)
CAPSULES

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS: Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment or for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected.

Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.

Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.

Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae.

Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.

Important Information for Women of Childbearing Potential:

Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.
Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity

of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.

- Must have selected and have committed to use 2 effective forms of contraception [birth control] simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly post menopausal.

- Patients must use 2 effective forms of contraception [birth control] simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed.

  Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide.

  Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception [birth control] simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[2] Microdosed "minipill" progestin preparations are not recommended for use with Soriatane. It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.

  Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the

herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.

Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:

Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.

- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,

  - greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean elimination half-life of 120 days.

  - greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168

days.

However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.[1]

- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.

  - There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred after the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.

  - There are also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia and stillbirth.

  - Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer

marketed in the U.S.; for information, call Roche at 1-800-526-6367.

Important Information For Males Taking Soriatane:

- Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

  There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome):

  NOTE to HLR: I had technical difficulties inserting the data table here that is based on your *Dermatology* 2002 paper. Please insert here exactly as in comments section of letter. Please also insert the reference for the data and adjust reference numbers that follow in the labeling accordingly)

For All Patients: A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.

DESCRIPTION: Soriatane (acitretin), a retinoid, is available in 10 mg and 25 mg gelatin capsules for oral administration. Chemically, acitretin is all-*trans*-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. It is a metabolite of etretinate and is related to both retinoic acid and retinol (vitamin A). It is a yellow to greenish-yellow powder with a molecular weight of 326.44. The structural formula is:

[[graphic: molecular structure]]

Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides).

Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

CLINICAL PHARMACOLOGY: The mechanism of action of Soriatane is unknown.

Pharmacokinetics: *Absorption:* Oral absorption of acitretin is optimal when given with food. For this reason, acitretin was given with food in all of the following studies. After administration of a single 50 mg oral dose of acitretin to 18 healthy subjects, maximum plasma concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in 2 to 5 hours (mean 2.7 hours). The oral absorption of acitretin is linear and proportional with increasing doses from 25 to 100 mg. Approximately 72% (range 47% to 109%) of the administered dose was absorbed after a single 50 mg dose of acitretin was given to 12 healthy subjects.

Distribution: Acitretin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism (see Pharmacokinetic Drug Interactions: Ethanol): Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-*cis* form (*cis*-acitretin). The formation of *cis*-acitretin relative to parent compound is not altered by dose or fed/fast conditions of oral administration of acitretin. Both parent compound and isomer are further metabolized into chain-shortened breakdown products and conjugates, which are excreted. Following multiple-dose administration of acitretin, steady-state concentrations of acitretin and *cis*-acitretin in plasma are achieved within approximately 3 weeks.

Elimination: The chain-shortened metabolites and conjugates of acitretin and *cis*-acitretin are ultimately excreted in the feces (34% to 54%) and urine (16% to 53%). The terminal elimination half-life of acitretin following multiple-dose administration is 49 hours (range 33 to 96 hours), and that of *cis*-acitretin under

the same conditions is 63 hours (range 28 to 157 hours). The accumulation ratio of the parent compound is 1.2; that of *cis*-acitretin is 6.6.

Special Populations: Psoriasis: In an 8-week study of acitretin pharmacokinetics in patients with psoriasis, mean steady-state trough concentrations of acitretin increased in a dose proportional manner with dosages ranging from 10 to 50 mg daily. Acitretin plasma concentrations were nonmeasurable (<4 ng/mL) in all patients 3 weeks after cessation of therapy.

Elderly: In a multiple-dose study in healthy young (n=6) and elderly (n=8) subjects, a two-fold increase in acitretin plasma concentrations were seen in elderly subjects, although the elimination half-life did not change.

Renal Failure: Plasma concentrations of acitretin were significantly (59.3%) lower in end-stage renal failure subjects (n=6) when compared to age-matched controls, following single 50 mg oral doses. Acitretin was not removed by hemodialysis in these subjects.

Pharmacokinetic Drug Interactions (see also boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS: *Drug Interactions*): In studies of in vivo pharmacokinetic drug interactions, no interaction was seen between acitretin and cimetidine, digoxin, phenprocoumon or glyburide.

Ethanol: Clinical evidence has shown that etretinate (a retinoid with a much longer half-life, see below) can be formed with concurrent ingestion of acitretin and ethanol. In a two-way crossover study, all 10 subjects formed etretinate with concurrent ingestion of a single 100 mg oral dose of acitretin during a 3-hour period of ethanol ingestion (total ethanol, approximately 1.4 g/kg body weight). A mean peak etretinate concentration of 59 ng/mL (range 22 to 105 ng/mL) was observed, and extrapolation of AUC values indicated that the formation of etretinate in this study was comparable to a single 5 mg oral dose of etretinate. There was no detectable formation of etretinate when a single 100 mg oral dose of acitretin was administered without concurrent ethanol ingestion, although the formation of etretinate without concurrent ethanol ingestion cannot be excluded (see boxed CONTRAINDICATIONS AND WARNINGS). Of 93 evaluable psoriatic patients on acitretin therapy in several foreign studies (10 to 80 mg/day), 16% had measurable etretinate levels (>5 ng/mL).

Etretinate has a much longer elimination half-life compared to that of acitretin. In one study the apparent mean terminal half-life after 6 months of therapy was approximately 120 days (range 84 to 168 days). In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 0.5 to 12 ng/mL) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

Progestin-only Contraceptives: It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[2] Microdosed "minipill" progestin

preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

CLINICAL STUDIES: In two double-blind placebo controlled studies, Soriatane was administered once daily to patients with severe psoriasis (ie, covering at least 10% to 20% of the body surface area). At 8 weeks (see Table 1) patients treated in Study A with 50 mg Soriatane per day showed significant improvements ($p \leq 0.05$) relative to baseline and to placebo in the physician's global evaluation and in the mean ratings of severity of psoriasis (scaling, thickness, and erythema). In study B, differences from baseline and from placebo were statistically significant ($p \leq 0.05$) for all variables at both the 25 mg and 50 mg doses; it should be noted for Study B that no statistical adjustment for multiplicity was carried out.

Table 1. Summary of the Soriatane Efficacy Results of the 8-Week Double-Blind Phase of Studies A and B

	Study A		Study B		
	Total daily dose		Total daily dose		
Efficacy Variables	**Placebo (N=29)**	**50 mg (N=29)**	**Placebo (N=72)**	**25 mg (N=74)**	**50 mg (N=71)**
Physician's Global Evaluation					
Baseline	4.62	4.55	4.43	4.37	4.49
Mean Change After 8 Weeks	-0.29	-2.00*	-0.06	-1.06*	-1.57*
Scaling					
Baseline	4.10	3.76	3.97	4.11	4.10
Mean Change After 8 Weeks	-0.22	-1.62*	-0.21	-1.50*	-1.78*
Thickness					
Baseline	4.10	4.10	4.03	4.11	4.20
Mean Change After 8 Weeks	-0.39	-2.10*	-0.18	-1.43*	-2.11*
Erythema					
Baseline	4.21	4.59	4.42	4.24	4.45
Mean Change After 8 Weeks	-0.33	-2.10*	-0.37	-1.12*	-1.65*

*Values were statistically significantly different from placebo and from baseline ($p \leq 0.05$). No adjustment for multiplicity was done for Study B.

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema, and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0=none, 1=trace, 2=mild, 3=mild-moderate, 4=moderate, 5=moderate-severe, 6=severe).

A subset of 141 patients from both pivotal studies A and B continued to receive Soriatane in an open fashion for up to 24 weeks. At the end of the treatment period, all efficacy variables, as indicated in Table 2, were significantly improved ($p \leq 0.01$) from baseline, including extent of psoriasis, mean ratings of psoriasis severity and physician's global evaluation.

Table 2. Summary of the First Course of Soriatane Therapy (24 Weeks)

Variables	Study A	Study B
Mean Total Daily Soriatane Dose (mg)	42.8	43.1
Mean Duration of Therapy (Weeks)	21.1	22.6
Physician's Global Evaluation	**N=39**	**N=98**
Baseline	4.51	4.43
Mean Change From Baseline	-2.26*	-2.60*
Scaling	**N=59**	**N=132**
Baseline	3.97	4.07
Mean Change From Baseline	-2.15 *	-2.42*
Thickness	**N=59**	**N=132**
Baseline	4.00	4.12
Mean Change From Baseline	-2.44*	-2.66*
Erythema	**N=59**	**N=132**
Baseline	4.35	4.33
Mean Change From Baseline	-2.31*	-2.29*

*Indicates that the difference from baseline was statistically significant ($p \leq 0.01$).

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema; and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0=none, 1=trace, 2=mild, 3=mild-moderate, 4=moderate, 5=moderate-severe, 6=severe).

All efficacy variables improved significantly in a subset of 55 patients from Study A treated for a second, 6-month maintenance course of therapy (for a total of 12 months of treatment); a small subset of patients (n=4) from Study A continued to improve after a third 6-month course of therapy (for a total of 18 months of treatment).

INDICATIONS AND USAGE: Soriatane is indicated for the treatment of severe psoriasis in adults. Because of significant adverse effects associated with its use, Soriatane should be prescribed only by those knowledgeable in the systemic use of retinoids. In females of reproductive potential, Soriatane should be reserved for non-pregnant patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments (see Boxed CONTRAINDICATIONS AND WARNING: Soriatane can cause severe birth defects).

Most patients experience relapse of psoriasis after discontinuing therapy. Subsequent courses, when clinically indicated, have produced efficacy results similar to the initial course of therapy.

CONTRAINDICATIONS: Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).

Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values (see boxed WARNINGS, *Hepatotoxicity*; WARNINGS, *Lipids*; and PRECAUTIONS).

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate.] Consequently, the combination of methotrexate with Soriatane is also contraindicated (see PRECAUTIONS: *Drug Interactions*).

Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see WARNINGS: *Pseudotumor Cerebri*).

Soriatane is contraindicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

WARNINGS: (See also boxed CONTRAINDICATIONS AND WARNINGS)

Hepatotoxicity: Of the 525 patients treated in US clinical trials, 2 had clinical jaundice with elevated serum bilirubin and transaminases considered related to Soriatane treatment. Liver function test results in these patients returned to normal after Soriatane was discontinued. Two of the 1289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal 2 months after Soriatane was discontinued.

The potential of Soriatane therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For 6 patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for 7 patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for 1 patient, the change was from class II to class IIIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found.

Elevations of AST (SGOT), ALT (SGPT), GGT (GGTP) or LDH have occurred in approximately 1 in 3 patients treated with Soriatane. Of the 525 patients treated in clinical trials in the US, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with Soriatane, the drug should be discontinued and the etiology further investigated.

Ten of 652 patients treated in US clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for a month or less before presenting with hepatic symptoms or signs.

Hyperostosis: In adults receiving long-term treatment with Soriatane, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see ADVERSE REACTIONS). Because the frequency and severity of iatrogenic bony abnormality in adults is low, periodic radiography is only warranted in the presence of symptoms or long term use of Soriatane. If such disorders arise, the continuation of therapy should be discussed with the patient on the basis of a careful risk/benefit analysis. In clinical trials with Soriatane, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column, knees and ankles.

Vertebral Results: Of 380 patients treated with Soriatane, 15% had preexisting abnormalities of the spine which showed new changes or progression of preexisting findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification and narrowing and destruction of a cervical disc space. De novo changes (formation of small spurs) were seen in 3 patients after 1½ to 2½ years.

Skeletal Appendicular Results: Six of 128 patients treated with Soriatane showed abnormalities in the knees and ankles before treatment that progressed during treatment. In 5, these changes involved the formation of additional spurs or enlargement of existing spurs. The sixth patient had degenerative joint disease which worsened. No patients developed spurs de novo. Clinical complaints did not predict radiographic changes.

Lipids and Possible Cardiovascular Effects: Blood lipid determinations should be performed before Soriatane is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% of patients. These effects of Soriatane were generally reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridemia included those with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions. Because of the risk of hypertriglyceridemia, serum lipids must be more closely monitored in high-risk patients and during long-term treatment.

Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. Although no causal relationship has been established, there have been post-marketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with fatal fulminant pancreatitis. Therefore, dietary modifications, reduction in Soriatane dose, or drug therapy should be employed to control significant elevations of triglycerides. If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Soriatane should be considered.

Ophthalmologic Effects: The eyes and vision of 329 patients treated with Soriatane were examined by ophthalmologists. The findings included dry eyes (23%), irritation of eyes (9%) and brow and lash loss (5%). The following were reported in less than 5% of patients: Bell's Palsy, blepharitis and/or crusting of lids, blurred vision, conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties and subepithelial corneal lesions.

Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation.

Pancreatitis: Lipid elevations occur in 25% to 50% of patients treated with Soriatane. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported. There have been rare reports of pancreatitis during Soriatane therapy in the absence of hypertrigyceridemia.

Pseudotumor Cerebri: Soriatane and other retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Some of these events involved concomitant use of isotretinoin and tetracyclines. However, the event seen in a single Soriatane patient was not associated with tetracyline use. Early signs and symptoms include papilledema, headache, nausea and vomiting and visual disturbances. Patients with these signs and symptoms should be examined for papilledema and, if present, should discontinue Soriatane immediately and be referred for neurological evaluation and care. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS).

PRECAUTIONS: ***Information for Patients*** **(see Medication Guide for all patients and Patient Agreement/Informed Consent for Female Patients at end of professional labeling):**

Patients should be instructed to read the Medication Guide supplied as required by law when Soriatane is dispensed.

Females of reproductive potential: **Soriatane can cause severe birth defects**. Female patients must not be pregnant when Soriatane therapy is initiated, they must not become pregnant while taking Soriatane, and for at least 3 years after stopping Soriatane so that the drug can be eliminated to below a blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely (see boxed CONTRAINDICATIONS AND WARNINGS).

Females of reproductive potential should also be advised that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued. This allows for elimination of the acitretin which can be converted to etretinate in the presence of alcohol.

Female patients should be advised that any method of birth control can fail, including tubal ligation, and that microdosed progestin "minipill" preparations are not recommended for use with Soriatane. Data from one patient who received a very low-dosed progestin contraceptive (levonorgestrel 0.03 mg) had a significant increase of the progesterone level after three menstrual cycles during acitretin treatment.[2]

Female patients should sign a consent form prior to beginning Soriatane therapy (see boxed CONTRAINDICATIONS AND WARNINGS).

Nursing Mothers: Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants.

All Patients:

Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms.

Patients should be advised that a transient worsening of psoriasis is sometimes seen during the initial treatment period. Patients should be advised that they may have to wait 2 to 3 months before they get the full benefit of Soriatane, although some patients may achieve significant improvements within the first 8 weeks of treatment as demonstrated in clinical trials.

Decreased night vision has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see WARNINGS and ADVERSE REACTIONS). Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period and sometimes after treatment has stopped.

Patients should not donate blood during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane.

Because of the relationship of Soriatane to vitamin A, patients should be advised against taking vitamin A supplements in excess of minimum recommended daily allowances to avoid possible additive toxic effects.

Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical UV exposure) because the effects of UV light are enhanced by retinoids.

Patients should be advised that they must not give their Soriatane capsules to any other person.

For Prescribers:

Phototherapy: Significantly lower doses of phototherapy are required when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning). (see DOSAGE AND ADMINISTRATION).

Drug Interactions:

Ethanol: Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see boxed CONTRAINDICATIONS AND WARNINGS and CLINICAL PHARMACOLOGY: *Pharmacokinetics*).

Glibenclamide: In a study of 7 healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide (a sulfonylurea similar to chlorpropamide) in 3 of the 7 subjects. Repeating the study with 6 healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with Soriatane is recommended (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

Hormonal Contraceptives: It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin "minipill" preparations. Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

Methotrexate: An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with acitretin is also contraindicated (see CONTRAINDICATIONS).

Phenytoin: If acitretin is given concurrently with phenytoin, the protein binding of phenytoin may be reduced.

Tetracyclines: Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS AND WARNINGS: *Pseudotumor Cerebri*).

Vitamin A and oral retinoids: Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis A.

Other: There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, or glyburide. Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction.

Laboratory Tests: If significant abnormal laboratory results are obtained, either dosage reduction with careful monitoring or treatment discontinuation is recommended, depending on clinical judgment.

Blood Sugar: Some patients receiving retinoids have experienced problems with blood sugar control. In addition, new cases of diabetes have been diagnosed during retinoid therapy, including diabetic ketoacidosis. In diabetics, blood-sugar levels should be monitored very carefully.

Lipids: In clinical studies, the incidence of hypertriglyceridemia was 66%, hypercholesterolemia was 33% and that of decreased HDL was 40%. Pretreatment and follow-up measurements should be obtained under fasting conditions. It is recommended that these tests be performed weekly or every other week until the lipid response to Soriatane has stabilized (see WARNINGS).

Liver Function Tests: Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. It is recommended that these tests be performed prior to initiation of Soriatane therapy, at 1- to 2-week intervals until stable and thereafter at intervals as clinically indicated (see CONTRAINDICATIONS AND boxed WARNING).

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80 week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m^2 comparison.

Mutagenesis: Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays.

Impairment of Fertility: In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day).

No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[3-5] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[3,4]

Pregnancy: *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).**

In a study in which acitretin was administered to male rats only at a dosage of 5 mg/kg/day for 10 weeks (approximate duration of one spermatogenic cycle) prior to and during mating with untreated female rats, no teratogenic effects were observed in the progeny. (see boxed CONTRAINDICATIONS AND WARNINGS for information about male use of Soriatane.)

Nonteratogenic Effects: In rats dosed at 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison), slightly decreased pup survival and delayed incisor eruption were noted. At the next lowest dose tested, 1 mg/kg/day, no treatment-related adverse effects were observed.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses, decreases in bone mineral density, and premature epiphyseal closure have been reported in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between these effects and Soriatane has not been established. While it is not known that these occurrences are more severe or more frequent in children, there is special concern in pediatric patients because of the implications for growth potential (see WARNINGS: *Hyperostosis*).

Geriatric Use: Clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A two-fold increase in acitretin plasma concentrations was seen in healthy elderly subjects compared with young subjects, although the elimination half-life did not change (see CLINICAL PHARMACOLOGY: *Special Populations*).

ADVERSE REACTIONS: Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, neuropsychiatric, and central nervous systems. Many of the clinical adverse

reactions reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome.

***Adverse Events/Post-Marketing Reports*:** In addition to the events listed in the tables for the clinical trials, the following adverse events have been identified during post-approval use of Soriatane. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Acute myocardial infarction, thromboembolism, (see WARNINGS), stroke

Nervous System: Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug.

Psychiatric: Aggressive feelings and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane (see PRECAUTIONS).

Reproductive: Vulvo-vaginitis due to *Candida albicans*

Skin and Appendages: Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed.

Clinical Trials: During clinical trials with Soriatane, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred sixteen patients (22%) left studies prematurely, primarily because of adverse experiences involving the mucous membranes and skin. Three patients died. Two of the deaths were not drug related (pancreatic adenocarcinoma and lung cancer); the other patient died of an acute myocardial infarction, considered remotely related to drug therapy. In clinical trials, Soriatane was associated with elevations in liver function test results or triglyceride levels and hepatitis.

The tables below list by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis.

Table 3. Adverse Events Frequently Reported During Clinical Trials
Percent of Patients Reporting (N=525)

BODY SYSTEM	>75%	50% to 75%	25% to 50%	10% to 25%
CNS				Rigors
Eye Disorders				Xerophthalmia
Mucous Membranes	Cheilitis		Rhinitis	Dry mouth Epistaxis
Musculoskeletal				Arthralgia Spinal hyperostosis (progression of existing lesions)
Skin and Appendages		Alopecia Skin peeling	Dry skin Nail disorder Pruritus	Erythematous rash Hyperesthesia Paresthesia Paronychia Skin atrophy Sticky skin

Table 4. Adverse Events Less Frequently Reported During Clinical Trials
(Some of Which May Bear No Relationship to Therapy)
Percent of Patients Reporting (N=525)

BODY SYSTEM	1% to 10%	<1%
Body as a Whole	Anorexia Edema Fatigue Hot flashes Increased appetite	Alcohol intolerance Dizziness Fever Influenza-like symptoms Malaise Moniliasis Muscle weakness Weight increase
Cardiovascular	Flushing	Chest pain Cyanosis Increased bleeding time Intermittent claudication Peripheral ischemia
CNS (also see Psychiatric)	Headache Pain	Abnormal gait Migraine Neuritis Pseudotumor cerebri (intracranial hypertension)
Eye Disorders	Abnormal/blurred vision	Abnormal lacrimation

BODY SYSTEM	1% to 10%	<1%
	Blepharitis Conjunctivitis/irritation Corneal epithelial abnormality Decreased night vision/night blindness Eye abnormality Eye pain Photophobia	Chalazion Conjunctival hemorrhage Corneal ulceration Diplopia Ectropion Itchy eyes and lids Papilledema Recurrent sties Subepithelial corneal lesions
Gastrointestinal	Abdominal pain Diarrhea Nausea Tongue disorder	Constipation Dyspepsia Esophagitis Gastritis Gastroenteritis Glossitis Hemorrhoids Melena Tenesmus Tongue ulceration
Liver and Biliary		Hepatic function abnormal Hepatitis Jaundice
Mucous Membranes	Gingival bleeding Gingivitis Increased saliva Stomatitis Thirst Ulcerative stomatitis	Altered saliva Anal disorder Gum hyperplasia Hemorrhage Pharyngitis
Musculoskeletal	Arthritis Arthrosis Back pain Hypertonia Myalgia Osteodynia Peripheral joint Hyperostosis (progression of existing lesions)	Bone disorder Olecranon bursitis Spinal hyperostosis (new lesions) Tendonitis
Psychiatric	Depression Insomnia Somnolence	Anxiety Dysphonia Libido decreased Nervousness
Reproductive		Atrophic vaginitis Leukorrhea
Respiratory	Sinusitis	Coughing

BODY SYSTEM	1% to 10%	<1%
		Increased sputum Laryngitis
Skin and Appendages	Abnormal skin odor Abnormal hair texture Bullous eruption Cold/clammy skin Dermatitis Increased sweating Infection Psoriasiform rash Purpura Pyogenic granuloma Rash Seborrhea Skin fissures Skin ulceration Sunburn	Acne Breast pain Cyst Eczema Fungal infection Furunculosis Hair discoloration Herpes simplex Hyperkeratosis Hypertrichosis Hypoesthesia Impaired healing Otitis media Otitis externa Photosensitivity reaction Psoriasis aggravated Scleroderma Skin nodule Skin hypertrophy Skin disorder Skin irritation Sweat gland disorder Urticaria Verrucae
Special Senses/Other	Earache Taste perversion Tinnitus	Ceruminosis Deafness Taste loss
Urinary		Abnormal urine Dysuria Penis disorder

Laboratory: Soriatane therapy induces changes in liver function tests in a significant number of patients. Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% (see WARNINGS). Transient, usually reversible elevations of alkaline phosphatase have been observed.

Table 5 lists the laboratory abnormalities reported during clinical trials.

Table 5. Abnormal Laboratory Test Results Reported During Clinical Trials
Percent of Patients Reporting

BODY SYSTEM	50% to 75%	25% to 50%	10% to 25%	1% to 10%
Electrolytes			Increased: – Phosphorus – Potassium – Sodium Increased and decreased magnesium	Decreased: – Phosphorus – Potassium – Sodium Increased and decreased: – Calcium – Chloride
Hematologic		Increased -Reticulocytes	Decreased: – Hematocrit – Hemoglobin – WBC Increased: – Haptoglobin – Neutrophils – WBC	Increased: – Bands – Basophils – Eosinophils – Hematocrit – Hemoglobin – Lymphocytes – Monocytes Decreased: – Haptoglobin – Lymphocytes – Neutrophils – Reticulocytes Increased or decreased: – Platelets – RBC
Hepatic		Increased: – Cholesterol – LDH – SGOT – SGPT Decreased: – HDL cholesterol	Increased: – Alkaline phosphatase – Direct bilirubin – GGTP	Increased: – Globulin – Total bilirubin – Total protein Increased and decreased: – Serum albumin
Miscellaneous	Increased triglycerides	Increased: – CPK – Fasting blood sugar	Decreased: – Fasting blood sugar – High occult blood	Increased and decreased: – Iron
Renal			Increased: – Uric acid	Increased: – BUN – Creatinine
Urinary		WBC in urine	Acetonuria Hematuria RBC in urine	Glycosuria Proteinuria

			RBC in urine	

OVERDOSAGE: In the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg.

In one reported case of overdose, a 32-year-old male with Darier's disease took 21 x 25 mg capsules (525 mg single dose). He vomited several hours later but experienced no other ill effects.

All female patients of childbearing potential who have taken an overdose of Soriatane must: 1) Have a pregnancy test at the time of overdose. 2) Be counseled as per the b*oxed Contraindications and Warnings* and *Precautions* sections regarding birth defects and contraceptive use for at least 3 years duration after the overdose.

DOSAGE AND ADMINISTRATION: There is intersubject variation in the pharmacokinetics, clinical efficacy and incidence of side effects with Soriatane. A number of the more common side effects are dose related. Individualization of dosage is required to achieve sufficient therapeutic response while minimizing side effects. Soriatane therapy should be initiated at 25 to 50 mg per day, given as a single dose with the main meal. Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial treatment. Relapses may be treated as outlined for initial therapy.

When Soriatane is used with phototherapy, the prescriber should decrease the phototherapy dose, dependent on the patient's individual response (see PRECAUTIONS: *General*).

Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison.

Information for Pharmacists: A Soriatane Medication Guide must be given to the patient each time Soriatane is dispensed, as required by law.

HOW SUPPLIED: Brown and white capsules, 10 mg, imprinted SORIATANE 10 ROCHE; bottles of 30 (NDC 0004-0288-57).

Brown and yellow capsules, 25 mg, imprinted SORIATANE 25 ROCHE; bottles of 30 (NDC 0004-0289-57).

Store between 15° and 25°C (59° and 77°F). Protect from light. Avoid exposure to high temperatures and humidity after the bottle is opened.

REFERENCES:

1. Berbis Ph, et al.: *Arch Dermatol Res* (1988) 280:388-389.

2. Maier H, Honigsmann H: Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 348:1107, 1996.

3. Sigg C, et al.: Andrological investigations in patients treated with etretin. *Dermatologica* 175:48-49, 1987.

4. Parsch EM, et al.: Andrological investigation in men treated with acitretin (Ro 10-1670). *Andrologia* 22:479-482, 1990

5. Kadar L, et al.: Spermatological investigations in psoriatic patients treated with acitretin. In: Pharmacology of Retinoids in the Skin; Reichert U. et al., ed, KARGER, Basel, vol. 3, pp 253-254, 1988.

PATIENT AGREEMENT/INFORMED CONSENT for FEMALE Patients:

To be completed by the patient, her parent/guardian*and signed by her prescriber.

Read each item below and initial in the space provided to show that you understand each item and agree to follow your doctor's instructions. **Do not sign this consent and do not take Soriatane if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and initial each item before signing the consent.

_____
(Patient's Name)

1. I understand that there is a very high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Soriatane in any amount even for short periods of time. Birth defects have also happened in babies of women who became pregnant after stopping Soriatane treatment.

2. I understand that I must not take Soriatane if I am pregnant.
Initial: _____

3. I understand that I must not become pregnant while taking Soriatane and for at least 3 years after the end of my treatment with Soriatane.
Initial: _____

4. I know that I must avoid drinks, food, and medicines, including over-the-counter products, that contain alcohol. This is extremely important, because alcohol changes Soriatane in the blood into a drug that takes even longer to

leave the body. This means the risk of birth defects may last longer than 3 years if I swallow any form of alcohol during Soriatane therapy or for 2 months after I stop taking Soriatane.

5. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) **at the same time**. The only exception is if I have had surgery to remove the womb (a hysterectomy) or my prescriber has told me I have gone completely through menopause.
Initial: _____

6. I have been told by my prescriber that 2 effective forms of birth control (contraception) must be used at the same time for at least 1 month before starting Soriatane, for the entire time of Soriatane therapy, and for at least 3 years after Soriatane treatment has stopped.

7. I understand that birth control pills and injectable/implantable/insertable/topical (patch) hormonal birth control products are among the most effective forms of birth control. However, any form of birth control can fail. Therefore, I must use 2 different methods at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is birth control pills, injections, or tubal ligation (tube-tying).
Initial: _____

8. I understand that the following are considered effective forms of birth control:
Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills, injectable/implantable/insertable/topical (patch) hormonal birth control products, and an IUD (intrauterine device).
Secondary: Diaphragms, latex condoms, and cervical caps. Each must be used with a spermicide, which is a special cream or jelly that kills sperm.

I understand that at least 1 of my 2 methods of birth control must be a primary method.
Initial: _____

9. I will talk with my prescriber about any medicines or dietary supplements I plan to take during my Soriatane treatment because hormonal birth control methods (for example, birth control pills) may not work if I am taking certain medicines or herbal products (for example, St. John's Wort).
Initial: _____

10. I understand that if I have taken Tegison (etretinate), I must continue to follow the birth control (contraception) recommendations for Tegison.
Initial: _____

11. Unless I have had a hysterectomy or my prescriber says I have gone completely through menopause, I understand that I must have 2 negative pregnancy test results before I can get a prescription for Soriatane. The first pregnancy test should be done when my prescriber decides to prescribe

Soriatane. The second pregnancy test should be done during the first 5 days of my menstrual period right before starting Soriatane therapy, or as instructed by my prescriber. I will then have pregnancy tests on a regular basis as instructed by my prescriber during my Soriatane therapy.
Initial: _____

12. I understand that I should not start taking Soriatane until I am *sure* that I am not pregnant and have negative results from 2 pregnancy tests.
Initial: _____

13. I have read and understand the materials my prescriber has given to me, including the Soriatane Pregnancy Prevention Program. My prescriber gave me and asked me to watch the video about contraception (birth control). I was told about a confidential counseling line that I may call at Roche for more information about birth control (1-800-542-6900).

14. I have received information on emergency contraception (birth control).
Initial: _____

15. I understand that I may receive a free contraceptive (birth control) counseling session and pregnancy testing. My prescriber can give me a Soriatane Patient Referral Form for this free consultation.
Initial: _____

16. I understand that I should receive counseling from my prescriber, repeated on a regular basis, about contraception (birth control) and behaviors associated with an increased risk of pregnancy.
Initial: _____

17. I understand that I must stop taking Soriatane right away and call my prescriber if I get pregnant, miss my menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods during and at least 3 years after stopping Soriatane treatment.
Initial: _____

18. If I do become pregnant while on Soriatane or at any time within 3 years of stopping Soriatane, I understand that I should report my pregnancy to Roche at 1-800-526-6367 or to the Food and Drug Administration (FDA) MedWatch program at 1-800-FDA-1088. The information I share will be kept confidential (private) and will help the company and the FDA evaluate the pregnancy prevention program.
Initial: _____

My prescriber has answered all my questions about Soriatane. I understand that it is my responsibility not to get pregnant during Soriatane treatment or for at least 3 years after I stop taking Soriatane. I now authorize my prescriber _____ to begin my treatment with Soriatane.

Patient signature:_____
Date:_____
Parent/guardian signature (if under age 18):_____
Date:_____
Please print: Patient name and
address_____
_____ Telephone
_____

I have fully explained to the patient, _____, the nature and purpose of the treatment described above and the risks to females of childbearing potential. I have asked the patient if she has any questions regarding her treatment with Soriatane and have answered those questions to the best of my ability.
Prescriber signature: _____
Date:_____

Medication Guide for Patients:

Read this Medication Guide carefully before you start taking Soriatane and read it each time you get more Soriatane. There may be new information.

The first information in this Guide is about birth defects and how to avoid pregnancy. **After this section there is important safety information about possible effects for any patient taking Soriatane**. ALL patients should read this entire Medication Guide carefully.

This information does not take the place of talking with your prescriber about your medical condition or treatment.

What is the most important information I should know about Soriatane?

Soriatane can cause severe birth defects. If you are a female who can get pregnant, you should use Soriatane only if you are not pregnant now, can avoid becoming pregnant, and other medicines do not work for your severe psoriasis or you cannot use other psoriasis medicines. Information about effects on unborn babies and about how to avoid pregnancy is found in the next section: "What are the important warnings and instructions for females taking Soriatane?".

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

What are the important warnings and instructions for females taking Soriatane?

- **Before you receive your Soriatane prescription, you should have discussed and signed a Patient Information/Consent form with your prescriber. This is to help make sure you understand the risk of birth defects and how to avoid getting pregnant. If you did not talk to your prescriber about this and sign the Form, contact your prescriber.**

- **You must not take Soriatane if you are pregnant or might become pregnant during treatment or at any time for at least 3 years after you stop treatment because Soriatane can cause severe birth defects.**
- **During Soriatane treatment and for 2 months after you stop Soriatane treatment, you must avoid drinks, foods, and all medicines that contain alcohol. This includes over-the-counter products that contain alcohol.** Avoiding alcohol is very important, because alcohol changes Soriatane into a drug that may take longer than 3 years to leave your body. The chance of birth defects may last longer than 3 years if you swallow any form of alcohol during Soriatane therapy and for 2 months after you stop taking Soriatane.

- **You and your prescriber must be sure you are not pregnant before you start Soriatane therapy. You must** have **negative** results from **2 pregnancy tests.** A negative result shows you are not pregnant. Because it takes a few days after pregnancy begins for a test to show that you are pregnant, the first negative test may not ensure you are not pregnant. Do not take Soriatane until you have negative results from **2** pregnancy tests.
  - The **first pregnancy test** will be done at the time you and your prescriber decide if Soriatane might be right for you.
  - The **second pregnancy test** will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane. Your prescriber may suggest another time.

- **Discuss effective birth control (contraception) with your prescriber. You must use 2 effective forms of birth control (contraception) at the same time during all of the following:**
  - for at least 1 month before beginning Soriatane treatment
  - during treatment with Soriatane
  - for at least 3 years after stopping Soriatane treatment

- **You must use 2 effective forms of birth control (contraception) at the same time even if you think you cannot become pregnant, unless 1 of the following is true for you:**
  - You had your womb (uterus) removed during an operation (a hysterectomy).
  - Your prescriber said you have gone completely through menopause (the "change of life").
  - You choose a method called "abstinence". This means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during, and for at least 3 years after Soriatane treatment.

- **You can get a free birth control counseling session and pregnancy testing from a prescriber or family planning expert. Your prescriber can give you a Soriatane Patient Referral Form for this free session.**

- **You must use 2 effective forms of birth control (contraception) at the same time every time you repeat Soriatane treatment. You must use birth control for at least 1 month before you start Soriatane, during treatment, and at least 3 years after you stop Soriatane treatment.**

- **The following are considered effective forms of birth control:**

  Primary Forms:
  - having your tubes tied (tubal ligation)
  - partner's vasectomy
  - IUD (intrauterine device)
  - birth control pills that contain both estrogen and progestin (combination oral contraceptives)
  - hormonal birth control products that are injected, implanted, or inserted in your body.
  - birth control patch

  Secondary Forms (use with a Primary Form):
  - diaphragms with spermicide
  - latex condoms with spermicide
  - cervical caps with spermicide

  At least 1 of your 2 methods of birth control must be a primary form.

- **If you have sex at any time without using 2 effective forms of birth control (contraception) at the same time, or if you get pregnant or miss your period, stop using Soriatane and call your prescriber right away.**

- **Consider "Emergency Contraception" (EC) if you have sex with a male without correctly using 2 effective forms of birth control (contraception)**

at the same time. EC is also called "emergency birth control" or the "morning after" pill. Contact your prescriber **as soon as possible** if you have sex without using 2 effective forms of birth control (contraception) at the same time, because EC works best if it is used within 1 or 2 days after sex. EC is not a replacement for your usual 2 effective forms of birth control (contraception) because it is not as effective as regular birth control methods.

You can get EC from private doctors or nurse practitioners, women's health centers, or hospital emergency rooms. You can get the name and phone number of EC providers nearest you by calling, the free Emergency Contraception Hotline at 1-888-NOT-2-LATE (1-888-668-2528).

- **Stop taking Soriatane right away and contact your prescriber if you get pregnant while taking Soriatane or at any time for at least 3 years after treatment has stopped. You need to discuss the possible effects on the unborn baby with your prescriber.**

- **If you do become pregnant while taking Soriatane or at any time for at least 3 years after stopping Soriatane, you should report your pregnancy to Roche at 1-800-526-6367 or directly to the Food and Drug Administration (FDA) MedWatch program (1-800-FDA-1088).** Your name will be kept in private (confidential). The information you share will help the FDA and the manufacturer evaluate pregnancy prevention program for Soriatane.

- **Do not take Soriatane if you are breast feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast feed or take Soriatane, but not both.

What should males know before taking Soriatane?

Small amounts of Soriatane are found in the semen of males taking Soriatane. Based upon available information, it appears that these small amounts of Soriatane in semen pose little, if any, risk to an unborn child while a male patient is taking the drug or after it is discontinued. Discuss any concerns you have about this with your prescriber.

All patients should read the rest of this Medication Guide

What is Soriatane?

Soriatane is a medicine used to treat severe forms of psoriasis in adults. Psoriasis is a skin disease that causes cells in the outer layer of the skin to grow faster than normal and pile up on the skin's surface. In the most common type of psoriasis, the skin becomes inflamed and produces red, thickened areas, often with silvery scales. **Because Soriatane can have serious side effects**, you

should talk with your prescriber about whether Soriatane's possible benefits outweigh its possible risks.

Soriatane may not work right away. You may have to wait 2 to 3 months before you get the full benefit of Soriatane. Psoriasis gets worse for some patients when they first start Soriatane treatment.

Soriatane has not been studied in children.

Who should not take Soriatane?

- **Do NOT take Soriatane if you can get pregnant:** Do not take Soriatane if you are pregnant or might get pregnant during Soriatane treatment or at any time for **at least 3 years** after you stop Soriatane treatment. (see "What are the important warnings and instructions for females taking Soriatane?").

- **Do NOT take Soriatane if you are breast feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast feed or take Soriatane, but not both.

- **Do NOT take Soriatane if you have severe liver or kidney disease.**

- **Do NOT take Soriatane if you have repeated high blood lipids** (fat in the blood).

- **Do NOT take Soriatane if you take these medicines:**
  - methotrexate
  - tetracyclines

  The use of these medicines with Soriatane may cause **serious** side effects.

- **Do NOT take Soriatane if you are allergic to acitretin,** the active ingredient in Soriatane, to any of the other ingredients (see the end of this Medication Guide for a list of all the ingredients in Soriatane), or to any similar drugs (ask your prescriber or pharmacist whether any drugs you are allergic to are related to Soriatane).

Tell your prescriber if you have or ever had:
- diabetes or high blood sugar
- liver problems
- kidney problems
- high cholesterol or high triglycerides (fat in the blood)
- heart disease
- depression
- alcoholism
- an allergic reaction to a medication

Your prescriber needs this information to decide if Soriatane is right for you and to know what dose is best for you.

Tell your prescriber about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines can cause **serious side effects** if taken while you also take Soriatane. Some medicines may affect how Soriatane works, or Soriatane may affect how your other medicines work. **Be especially sure to tell your prescriber if you are taking the following medicines:**

- methotrexate
- tetracyclines
- phenytoin
- vitamin A supplements
- progestin-only oral contraceptives ("mini-pills")
- Tegison® or Tigason (etretinate). Tell your prescriber if you have ever taken this medicine in the past.
- St. John's Wort herbal supplement

Tell your prescriber if you are getting phototherapy treatment. Your doses of phototherapy may need to be changed to prevent a burn.

How should I take Soriatane?

- Take Soriatane with food.
- Be sure to take your medicine as prescribed by your prescriber. The dose of Soriatane varies from patient to patient. The number of capsules you must take is chosen specially for you by your prescriber. This dose may change during treatment.
- If you miss a dose, do not double the next dose. Skip the missed dose and resume your normal schedule.
- If you take too much Soriatane (overdose), call your local poison control center or emergency room.

You should have **blood tests** for liver function, cholesterol and triglycerides before starting treatment and during treatment to check your body's response to Soriatane. Your prescriber may also do other tests.

Once you stop taking Soriatane, your psoriasis may return. Do *not* treat this new psoriasis with leftover Soriatane. It is important to see your prescriber again for treatment recommendations because your situation may have changed.

What should I avoid while taking Soriatane?

- **Avoid pregnancy.** See "What is the most important information I should know about Soriatane?", and "What are the important warnings and instructions for females taking Soriatane?".

- **Avoid breast feeding.** See "What are the important warnings and instructions for females taking Soriatane?"

- **Avoid alcohol.** Females must avoid drinks, foods, medicines, and over-the-counter products that contain alcohol The risk of birth defects may continue for longer than 3 years if you swallow any form of alcohol during Soriatane treatment and for 2 months after stopping Soriatane (see "What are the important warnings and instructions for females taking Soriatane?").

- **Avoid giving blood. Do not donate blood** while you are taking Soriatane and **for at least 3 years after stopping** Soriatane treatment. Soriatane in your blood can harm an unborn baby if your blood is given to a pregnant woman. Soriatane does not affect your ability to **receive** a blood transfusion.

- **Avoid progestin-only birth control pills ("mini-pills").** This type of birth control pill may not work while you take Soriatane. Ask your prescriber if you are not sure what type of pills you are using.

- **Avoid night driving if you develop any sudden vision problems.** Stop taking Soriatane and call your prescriber if this occurs (see Side Effects).

- **Avoid non-medical ultraviolet (UV) light.** Soriatane can make your skin more sensitive to UV light. Do not use sunlamps, and avoid sunlight as much as possible. If you are taking light treatment (phototherapy), your prescriber may need to change your light dosages to avoid burns.

- **Avoid dietary supplements containing Vitamin A.** Soriatane is related to vitamin A. Therefore, do not take supplements containing vitamin A, because they may add to the unwanted effects of Soriatane. Check with your prescriber or pharmacist if you have any questions about vitamin supplements.

- **DO NOT SHARE Soriatane with anyone else, even if they have the same symptoms**. Your medicine may harm them or their unborn child.

What are the possible side effects of Soriatane?

- **Soriatane can cause birth defects.** See "What is the most important information I should know about Soriatane?" and "What are the important warnings and instructions for females taking Soriatane?"

- Psoriasis gets worse for some patients when they first start Soriatane treatment. Some patients have more redness or itching. If this happens, tell your prescriber. These symptoms usually get better as treatment continues, but your prescriber may need to change the amount of your medicine.

- **Serious side effects.** These do not happen often, but they can lead to permanent harm, or rarely, to death. Stop taking Soriatane and call your prescriber right away if you get the following signs or symptoms:

  - **Bad headaches, nausea, vomiting, blurred vision**. These symptoms can be signs of increased brain pressure that can lead to blindness or even death.

  - **Decreased vision in the dark** (night blindness). Since this can start suddenly, you should be very careful when driving at night. This problem usually goes away when Soriatane treatment stops. If you develop **any** vision problems or eye pain stop taking Soriatane and call your prescriber.

  - **Depression.** There have been some reports of patients developing mental problems including a depressed mood, aggressive feelings, or thoughts of ending their own life (suicide). These events, including suicidal behavior, have been reported in patients taking other drugs similar to Soriatane as well as in patients taking Soriatane. Since other things may have contributed to these problems, it is not known if they are related to Soriatane. It is very important to stop taking Soriatane and call your prescriber right away if you develop such problems.

  - **Yellowing of your skin or the whites of your eyes, nausea and vomiting, loss of appetite, or dark urine**. These can be signs of serious liver damage.

  - **Aches or pains in your bones, joints, muscles, or back; trouble moving; loss of feeling in your hands or feet.** These can be signs of abnormal changes to your bones or muscles.

  - **Frequent urination, great thirst or hunger.** Soriatane can affect blood sugar control, even if you do not already have diabetes. These are some of the signs of high blood sugar.

  - **Shortness of breath, dizziness, nausea, chest pain, weakness, trouble speaking, or swelling of a leg. These may be signs of a heart attack, blood clots, or stroke**. Soriatane can cause serious changes in blood fats (lipids). It is possible for these changes to cause blood vessel blockages that lead to heart attacks, strokes, or blood clots.

Common side effects. If you develop any of these side effects or any unusual reaction, check with your prescriber to find out if you need to change the amount of Soriatane you take. These side effects usually get better if the Soriatane dose is reduced or Soriatane is stopped.

- **Chapped lips; peeling fingertips, palms, and soles; itching; scaly skin all over; weak nails; sticky or fragile (weak) skin; runny or dry nose, or nose bleeds**. Your prescriber or pharmacist can recommend a lotion or cream to help treat drying or chapping.

- **Dry mouth**
- **Joint pain**
- **Tight muscles**
- **Hair loss.** Most patients have some hair loss, but this condition varies among patients. No one can tell if you will lose hair, how much hair you may lose or if and when it may grow back.
- **Dry, eyes.** Soriatane may dry your eyes. Wearing **contact lenses** may be uncomfortable during and after treatment with Soriatane because of the dry feeling in your eyes. If this happens, remove your contact lenses and call your prescriber. Also read the section about vision under "Serious side effects".
- **Rise in blood fats (lipids).** Soriatane can cause your blood fats (lipids) to rise. Most of the time this is not serious. But sometimes the increase can become a serious problem. (See information under "Serious side effects."). You should have blood tests as directed by your prescriber.

These are not all the possible side effects of Soriatane. For more information, ask your prescriber or pharmacist.

How should I store Soriatane?

Keep Soriatane away from sunlight, high temperature, and humidity. **Keep Soriatane away from children.**

What are the ingredients in Soriatane?

Active ingredient: acitretin

Inactive ingredients: microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

General information about the safe and effective use of Soriatane

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Soriatane for a condition for which it was not prescribed. Do not give Soriatane to other people, even if they have the same symptoms that you have.

This Medication Guide summarizes the most important information about Soriatane. If you would like more information, talk with your prescriber. You can ask your pharmacist or prescriber for information about Soriatane that is written for health professionals.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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R_x only

Roche Pharmaceuticals

Roche Laboratories Inc.
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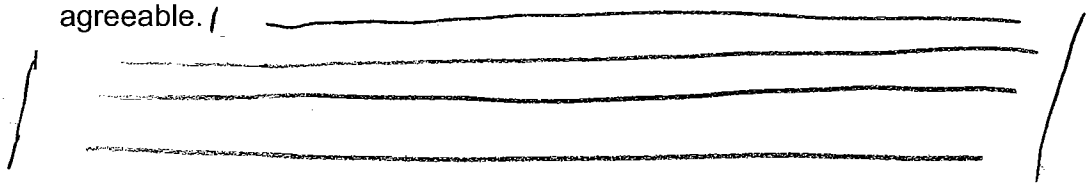
27898424

Revised: March 2003

End of Professional Labeling

Pregnancy Prevention Program (PPP) Booklet

- The Pregnancy Prevention Program booklet forms are not available in Word format and so the following Comments were sent to sponsor and were agreeable.



  - This first comment regards the Introduction for the self-assessment test. This is a suggestion; it can stand as is at your discretion. Use of the word "test" may discourage some patients from cooperating with this voluntary program. Perhaps you could re-phrase the instructions to say: "Answer the patient self-evaluation questions". On the "test" form itself, it might also intimidate some patients that they are asked to sign and date the completed "test" for the medical record with wrong answers noted. Is this really necessary given that they will already be signing a Consent Form? Also, consider instructing the patient to mark "unsures" and wrong answers with a "X" instead of a checkmark. The reason is that a busy prescriber is apt to misinterpret the checkmark as "OK", whereas a "X" is likely more universally recognized as a problem that needs further counseling.

- Page 26 of the self-assessment tool states that "Soriatane is a very powerful medicine used to treat severe psoriasis that did not get better with other treatments". This should be deleted. Instead, insert:: "Soriatane can have serious side effects. For that reason, it is used to treat only severe psoriasis. It should NEVER be taken by a pregnant woman".
- It appears that there is plenty of space in the mock up section for females, so please increase the "white space" between bullets for readability.
- The automated phone line has a title "what should I do if I think I am pregnant", but this important information should be included as well immediately before the emergency contraception section: insert "What should I do if I think I am pregnant or if I have trouble with my birth control" (answer: STOP taking Soriatane and call prescriber immediately if you suspect you might be pregnant; if problems with birth control, STOP Soriatane, call prescriber immediately, and re-read the next section on emergency contraception").
- On page 13 of the booklet please delete the words "The facts in this booklet about Soriatane treatment are very important to your health and well-being". Insert instead these words: "It is very important that you understand all of the facts in this booklet because Soriatane can have serious side effects".

The booklet recommended for approval is as submitted by the sponsor below ***with*** *the changes noted above, including wording changes to match the Medication Guide and Informed Consent*

Soriatane® (acitretin) Pregnancy Prevention Program

((PPP Logo))

Pages

CONTENTS

Back Pocket

INTRODUCTION
Please read this booklet carefully before taking Soriatane (soh-RYE-uh-tane). This booklet provides important facts about Soriatane, but it does not contain all the information about this medication. When you pick up your Soriatane prescription at the pharmacy, you will receive a copy of the Soriatane Medication Guide. If there's anything else you want to know, or if you have any questions or concerns, talk with your prescriber.

Please follow these simple steps to using this booklet:
1. Read the Patient Product Information
• Read this section carefully for important information about this medication. The information presented here is taken from the Soriatane Medication Guide.
2. Next, read the section Preventing Pregnancy: A Guide to Contraception
• Read this section for important information about primary and secondary contraception methods, free contraception counseling, and how to use the Confidential Contraception Counseling Line.
• Talk to your prescriber about getting a referral for contraception counseling. If counseling is desired, your prescriber should complete the Soriatane Patient Referral Form (located in the back pocket of this booklet); you will need to bring this form to your appointment for contraception counseling.
3. Take the patient self-evaluation test
• Test yourself using the self-evaluation form (enclosed in the back pocket of this booklet) to make sure you fully understand the information and to help you and your prescriber decide whether you are ready to start taking Soriatane.
4. Sign the Patient Agreement/Informed Consent for Female Patients form if you and your prescriber have decided that Soriatane treatment is right for you.
• Discuss and complete the Patient Agreement/Informed Consent for Female Patients form with your prescriber.

YOUR PERSONAL RECORD

Name:

_____

You MUST have negative results from 2 pregnancy tests done by your prescriber that show you are NOT pregnant before starting Soriatane therapy.

First test will be done at the time you and your prescriber decide if Soriatane might be right for you.

TEST DATE: _____TEST

RESULT:_____

Second test will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane, but your prescriber may suggest another time.

START OF MENSTRUAL PERIOD: _____
TEST DATE: _____TEST RESULT: _____

DATE SORIATANE THERAPY STARTED: _____

FOLLOW-UP APPOINTMENTS
DATE _____TIME _____
DATE _____TIME _____
DATE _____TIME _____
DATE _____TIME _____
DATE _____TIME _____
DATE _____TIME _____

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SORIATANE?

Soriatane can cause severe birth defects. If you are a female who can get pregnant, you should use Soriatane only if you are not pregnant now, can avoid becoming pregnant, and other medicines do not work for your severe psoriasis or you cannot use other psoriasis medicines. Females should read "What are the important warnings and instructions for females taking Soriatane?" on page 3 and "What should males know before taking Soriatane?" on page 6. Everyone should read this entire booklet carefully.

IMPORTANT INFORMATION FOR FEMALE PATIENTS

What are the important warnings and instructions for females taking Soriatane?

- **Before you received your Soriatane prescription, you should have discussed**

and signed a Patient Agreement/Informed Consent for Female Patients form with your prescriber. This is to help make sure you understand the risk of birth defects and how to avoid getting pregnant. If you did not talk to your prescriber about this and sign the form, contact your prescriber.

• **You must not take Soriatane if you are pregnant or might become pregnant during treatment or at any time for at least 3 years after you stop treatment because Soriatane can cause severe birth defects.**

• **During Soriatane treatment and for 2 months after you stop Soriatane treatment, you must avoid drinks, food and all medicines that contain alcohol. This includes over-the-counter products that contain alcohol.** Avoiding alcohol is very important, because alcohol changes Soriatane into a drug that may take longer than 3 years to leave your body. The chance of birth defects may last longer than 3 years if you swallow any form of alcohol during Soriatane therapy and for 2 months after you stop taking Soriatane.

• **You and your prescriber must be sure you are not pregnant before you start Soriatane therapy. You must** have **negative** results from **2 pregnancy tests.** A negative result shows you are not pregnant. Because it takes a few days after pregnancy begins for a test to show that you are pregnant, the first negative test may not ensure you are not pregnant. Do not take Soriatane until you have negative results from **2** pregnancy tests.

- The **first pregnancy test** will be done at the time you and your prescriber decide if Soriatane might be right for you.

- The **second pregnancy test** will usually be done during the first 5 days of your menstrual period, right before you plan to start Soriatane. Your prescriber may suggest another time.

• Discuss effective **birth control** (contraception) with your prescriber. You must use **2 effective forms of birth control (contraception) at the same time during all of the following:**

- **For at least 1 month before beginning Soriatane treatment**
- **During treatment with Soriatane**
- **For at least 3 years after stopping Soriatane treatment**

• You must use 2 effective forms of birth control (contraception) at the same time even if you think you cannot become pregnant, unless 1 of the following is true for you:

- You have had your womb (uterus) removed during an operation (a hysterectomy).
- Your prescriber said you have gone completely through menopause (the "change of life").
- You choose a method called "abstinence." This means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during and for at least 3 years after Soriatane treatment.

• You can get a free birth control counseling session and pregnancy testing from a prescriber or family planning expert. Your prescriber can give you a Soriatane Patient Referral Form for this free session.
• The following are considered effective forms of birth control:

Primary Forms
- having your tubes tied (tubal ligation)
- partner's vasectomy
- IUD (intrauterine device)
- birth control pills that contain both estrogen and progestin (combination oral contraceptives)
- hormonal birth control products that are injected, implanted or inserted in your body
- birth control patch

Secondary Forms (use with a Primary Form)
- diaphragms with spermicide
- latex condoms with spermicide
- cervical caps with spermicide

At least 1 of your 2 methods of birth control must be a primary form.
• You must use 2 effective forms of birth control (contraception) at the same time every time you repeat Soriatane treatment. You must use birth control for at least 1 month before you start Soriatane, during treatment and for at least 3 years after you stop Soriatane treatment.
• **If you have sex at any time without using 2 effective forms of birth control (contraception) at the same time, or if you get pregnant or miss your period, stop using Soriatane and call your prescriber right away.**
• Consider **"Emergency Contraception (EC)"** if you have sex with a male without correctly using 2 effective forms of birth control (contraception) at the same time. EC is also called "emergency birth control" or the "morning after" pill. Contact your prescriber **as soon as possible** if you have sex without using 2 effective forms of birth control (contraception) at the same time, because EC works best if it is used within 1 or 2 days after sex. EC is not a replacement for your usual 2 effective forms of birth control (contraception) because it is not as effective as regular birth control methods.

You can get EC from: **private doctors or nurse practitioners, women's health centers or hospital emergency rooms. You can get the name and phone number of EC providers nearest you by calling the free Emergency Contraception Hotline at 1-888-NOT-2-LATE (1-888-668-2528).**
• **Stop taking Soriatane right away and contact your prescriber if you get pregnant while taking Soriatane or at any time for at least 3 years after treatment has stopped. You need to discuss the possible effects on the unborn baby with your prescriber.**
• **If you do become pregnant while taking Soriatane or at any time for at least**

3 years after stopping Soriatane, you should report your pregnancy to Roche at 1-800-526-6367 or directly to the Food and Drug Administration (FDA) MedWatch program (1-800-FDA-1088).
Your name will be kept in private (confidential). The information you share may help the FDA and the manufacturer support the pregnancy prevention program for Soriatane.

- **Do not take Soriatane if you are breast-feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast-feed or take Soriatane but not both.

IMPORTANT INFORMATION
FOR MALE PATIENTS

What should <u>males</u> know before taking Soriatane?
Small amounts of Soriatane are found in the semen of males taking Soriatane. Based upon available information both during and after the treatment, small amounts of Soriatane in semen do not seem to harm the baby. It is not known for sure that there is a risk. It appears that any small remaining amount of Soriatane in semen poses little, if any, risk to an unborn child while a male patient is taking the drug or after it is discontinued. Discuss any concerns you have about this with your prescriber.

IMPORTANT INFORMATION
FOR <u>ALL</u> PATIENTS

What is Soriatane (acitretin)?
Soriatane is a medicine used to treat severe forms of psoriasis in adults. Psoriasis is a skin disease that causes cells in the outer layer of the skin to grow faster than normal and pile up on the skin's surface. In the most common type of psoriasis, the skin becomes inflamed and produces red, thickened areas, often with silvery scales. **Because Soriatane can have serious side effects,** you should talk with your prescriber about whether Soriatane's possible benefits outweigh its possible risks.

Soriatane may not work right away. You may have to wait 2 to 3 months before you get the full benefit of Soriatane. Psoriasis gets worse for some patients when they first start Soriatane treatment.

Soriatane has not been studied in children.

Who should not take Soriatane?
- **Do NOT take Soriatane if you can get pregnant:** Do not take Soriatane if you are pregnant or might get pregnant during Soriatane treatment or at any time for **at least 3 years** after you stop Soriatane treatment (see "What are the important

warnings and instructions for females taking Soriatane?" on page 3).
• **Do NOT take Soriatane if you are breast-feeding.** Soriatane can pass into your milk and may harm your baby. You will need to choose either to breast-feed or take Soriatane, but not both.
• **Do NOT take Soriatane if you have severe liver or kidney disease.**
• **Do NOT take Soriatane if you have repeated high blood lipids over time** (fat in the blood).
• **Do NOT take Soriatane if you take the medicines:**
- methotrexate - tetracyclines

The use of these medicines with Soriatane may cause **serious** side effects.

• **Do NOT take Soriatane if you are allergic to acitretin,** the active ingredient in Soriatane, or to any of the other ingredients. (See the end of this section for a list of all the ingredients in Soriatane).

Tell your prescriber if you have or ever had:
• Diabetes or high blood sugar
• Liver problems
• Kidney problems
• High cholesterol or high triglycerides (fat in the blood)
• Heart disease
• Depression
• Alcoholism

Your prescriber needs this information to decide if Soriatane is right for you and to know what dose is best for you.

Tell your prescriber about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines can cause **serious side effects** if taken while you also take Soriatane. Some medicines may affect how Soriatane works, or Soriatane may affect how your other medicines work. **Be especially sure to tell your prescriber if you are taking the following medicines:**
• methotrexate
• tetracyclines
• phenytoin
• vitamin A supplements
• progestin-only oral contraceptives ("mini-pills")
• Tegison® or Tigason® (etretinate). Tell your prescriber if you have ever taken this medicine in the past.
• St. John's Wort herbal supplement

Tell your prescriber if you are getting phototherapy treatment. Your doses of phototherapy may need to be changed to prevent a burn.

How should I take Soriatane?

- Take Soriatane with food.
- Be sure to take your medicine as prescribed by your prescriber. The dose of Soriatane varies from patient to patient. The number of capsules you must take is chosen specially for you by your prescriber. This dose may change during treatment.
- If you miss a dose, do not double the next dose. Skip the missed dose, and resume your normal schedule.
- If you take too much Soriatane (overdose), call your local poison control center or emergency room.

You should have **blood tests** for liver function, cholesterol and triglycerides before starting treatment and during treatment to check your body's response to Soriatane. Your prescriber may also do other tests.

Once you stop taking Soriatane, your psoriasis may return. Do not treat this new psoriasis with leftover Soriatane. It is important to see your prescriber again for treatment recommendations because your situation may have changed.

What should I avoid while taking Soriatane?

- **Avoid pregnancy.** See "What is the most important information I should know about Soriatane?" on page 2, "What are the important warnings and instructions for females taking Soriatane?" on page 3, and "What should males know before taking Soriatane?" on page 6.
- **Avoid breast-feeding.** See "What are the important warnings and instructions for females taking Soriatane?"
- **Avoid alcohol.** Females must avoid drinks, foods, medicines and over-the-counter products that contain alcohol. The risk of birth defects may continue for longer than 3 years if you swallow any form of alcohol during Soriatane treatment or for 2 months after stopping Soriatane (see "What are the important warnings and instructions for females taking Soriatane?" on page 3).
- **Avoid giving blood. Do not donate blood** while you are taking Soriatane and **for at least 3 years after stopping** Soriatane treatment. Soriatane in your blood can harm an unborn baby if your blood is given to a pregnant woman. Soriatane does not affect your ability to **receive** a blood transfusion.
- **Avoid progestin-only birth control pills ("mini-pills").** They may not work while you take Soriatane. Ask your prescriber if you are not sure what type of pills you are using.
- **Avoid night driving if you develop any sudden vision problems.** Stop taking

Soriatane and call your prescriber if this occurs (see the Serious side effects section on the next page).

• **Avoid nonmedical ultraviolet (UV) light.** Soriatane can make your skin more sensitive to UV light. Do not use sunlamps, and avoid sunlight as much as possible. If you are taking light treatment (phototherapy), your prescriber may need to change your light dosages to avoid burns.

• **Avoid dietary supplements containing Vitamin A.** Soriatane is related to vitamin A. Therefore, do not take supplements containing vitamin A, because they may add to the unwanted effects of Soriatane. Check with your prescriber or pharmacist if you have any questions about vitamin supplements.

• **DO NOT SHARE Soriatane with anyone else, even if they have the same symptoms.**

What are the possible side effects of Soriatane?

Soriatane can cause birth defects. See "What is the most important information I should know about Soriatane?" on page 2 and "What are the important warnings and instructions for females taking Soriatane?" on page 3.

Psoriasis gets worse for some patients when they first start Soriatane treatment. Some patients have more redness or itching. If this happens, tell your prescriber. These symptoms usually get better as treatment continues, but your prescriber may need to change the amount of your medicine.

Serious side effects

These do not happen often, but they can lead to permanent harm, or rarely, to death. Stop taking Soriatane and call your prescriber right away if you get the following signs or symptoms:

• **Bad headaches, nausea, vomiting, blurred vision.** These symptoms can be signs of increased brain pressure that can lead to blindness or even death.

• **Decreased vision in the dark** (night blindness). Since this can start suddenly, you should be very careful when driving at night. This problem usually goes away when Soriatane treatment stops. If you develop **any** vision problems or eye pain, stop taking Soriatane and call your prescriber.

• **Depression.** There have been some reports of patients who have taken oral retinoids like Soriatane and have developed mental problems including a depressed mood, aggressive feelings or thoughts of self-harm. Since other factors may have contributed to such events, it is not known if they are related to Soriatane. It is very important to stop taking Soriatane and call your prescriber right away if you experience any of these.

• **Yellowing of your skin or the whites of your eyes, nausea and vomiting, loss of appetite or dark urine.** These can be signs of serious liver damage.

• **Aches or pains in your bones, joints, muscles or back; trouble moving; loss of feeling in your hands or feet.** These can be signs of abnormal changes to your bones or muscles.

• **Frequent urination, great thirst or hunger.** Soriatane can affect blood sugar control, even if you do not already have diabetes. These are some of the signs of high blood sugar.
• **Shortness of breath, dizziness, nausea, chest pain, weakness, trouble speaking or swelling of a leg. These may be signs of a heart attack, blood clots or stroke.** Soriatane can cause serious changes in blood fats (lipids). It is possible for these changes to cause blood vessel blockages that lead to heart attacks, strokes or blood clots.

Common side effects

If you develop any of these side effects or any unusual reaction, check with your prescriber to find out if you need to change the amount of Soriatane you take. These side effects usually get better if you reduce your dose or stop taking Soriatane:

• **Chapped lips; peeling fingertips, palms and soles; itching; scaly skin all over; weak nails;**
sticky or fragile (weak) skin; runny or dry nose or nose bleeds. Your prescriber or pharmacist can recommend a lotion or cream to help treat drying or chapping.
• **Dry mouth**
• **Joint pain**
• **Tight muscles**
• **Hair loss.** Most patients have some hair loss, but this condition varies among patients. No one
can tell if you will lose hair, how much hair you may lose or if and when it may grow back.
• **Dry eyes.** Soriatane may dry your eyes. Wearing **contact lenses** may be uncomfortable during and after treatment with Soriatane because of the dry feeling in your eyes. If this happens, remove your contact lenses and call your prescriber. Also read about decreased vision in the Serious side effects section on the previous page.

• **Rise in blood fats (lipids).** Soriatane can cause your blood fats (lipids) to rise. Most of the time, this is not serious. But sometimes, the increase can become a serious problem. (See information in the Serious side effects section on the previous page.) You should have blood tests as directed by your prescriber.

These are not all the possible side effects of Soriatane. For more information, ask your prescriber or pharmacist.

How should I store Soriatane?
Keep Soriatane away from sunlight, high temperature and humidity. **Keep Soriatane away from children.**

What are the ingredients in Soriatane?

Active ingredient: acitretin
Inactive ingredients: microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black and red) and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

General information about the safe and effective use of Soriatane
Medicines are sometimes prescribed for purposes other than those listed here. Do not use Soriatane for a condition for which it was not prescribed. Do not give Soriatane to other people, even if they have the same symptoms that you have.

This section of this booklet summarizes the most important information about Soriatane. If you would like more information, talk with your prescriber. You can ask your pharmacist or prescriber for information about Soriatane that is written for health professionals.

PREVENTING PREGNANCY:
A GUIDE TO CONTRACEPTION

Why is this information very important to me?
Your dermatologist may prescribe Soriatane (acitretin) to be used in your treatment. Soriatane is used to treat severe psoriasis in adults. In females of reproductive potential, Soriatane should be reserved for nonpregnant patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Soriatane can cause severe birth defects. Soriatane is indicated only for females who are **not** pregnant. This booklet contains very important facts about Soriatane that **you must know and understand before you can begin treatment with Soriatane.**

This section of the booklet explains the birth control (contraception) steps you must take before
you can start taking Soriatane; what you must do during Soriatane treatment; and what you must do for at least 3 years after you stop your Soriatane treatment.

To help you avoid becoming pregnant while taking Soriatane, a special Contraception Counseling Referral Program is available through your prescriber that will pay for you to go to another healthcare professional to receive contraception counseling and pregnancy testing. Details of this program are given in the section called *Contraception Counseling Referral Program,* on page 14.

Emergency Contraception (EC), or emergency birth control, is used to prevent pregnancy following unprotected intercourse or sex. Details on emergency birth control are provided in the section called *Emergency Contraception,* on page 24.

Also, it is *extremely* important that your sexual partner understand that you must use 2 effective forms of birth control (contraception) at the same time for at least 1 month before beginning Soriatane treatment, during treatment with Soriatane and for at least 3 years after stopping Soriatane treatment. It is very important that your sexual partner understand you must not become pregnant and the special precautions that must be taken during Soriatane treatment and for at least 3 years after you completely stop taking Soriatane. The section called *Your sexual partner,* on page 26, is provided to help you as you talk to your sexual partner about his important role in your Soriatane treatment.

Because you need to understand all the facts in this booklet, read it all the way through. Do **NOT** skip any section of the booklet. After you have read through the booklet once, read it through again. As you read through the second time, write down a list of questions for your prescriber to answer. Do not worry if you think the question is silly or may be unimportant. You have to understand all the facts in this booklet. Your prescriber wants you to understand everything in this booklet and everything that he or she tells you about Soriatane treatment. The facts in this booklet about Soriatane treatment are very important to your health and well-being.

Why must I use 2 effective forms of birth control (contraception)?

You must use 2 effective forms of birth control (contraception) at the same time for at least 1 month before beginning Soriatane treatment, during treatment with Soriatane and for at least 3 years after stopping Soriatane treatment to prevent pregnancy, because any birth control method can fail and your baby could be born with severe birth defects if you are taking Soriatane while you are pregnant.

There is an **extremely high risk** that a deformed baby can result if you become pregnant while taking Soriatane in any amount, even for short periods of time. When an unborn baby is exposed to Soriatane, there is a higher risk of deformities or a miscarriage. This explains the need for the precautions that must be taken at least 1 month before, during and for at least 3 years after stopping Soriatane use. **Remember, not 1 but 2 effective forms of birth control are required while you are taking Soriatane.**

CONTRACEPTION COUNSELING
REFERRAL PROGRAM
Be sure to ask your prescriber about the Contraception Counseling Referral Program

Before you can start taking Soriatane (acitretin), you and your prescriber must be sure that you are not pregnant and that you understand how to avoid becoming pregnant. Because it is so very important that you understand how to avoid

becoming pregnant while taking Soriatane, a special Contraception Counseling Referral Program has been established by the manufacturer of Soriatane.

You or your prescriber can arrange for you to see a contraception counselor who specializes in the female reproductive system. This healthcare professional will provide you with expert counseling about birth control and may even do a pregnancy test.

Even if you feel that you know about birth control, and even if you are not having sex or do not plan to have sex, this counseling is very important in planning your treatment with Soriatane. You will not be required to pay for the counseling or any pregnancy testing that they may do. **Be sure to ask your prescriber about the Contraception Counseling Referral Program.**

What is abstinence?
Abstinence means that you are absolutely certain (100% sure) you will not have sex with a male partner for at least 1 month before, during, and for at least 3 years after Soriatane treatment.
Abstinence is not considered a method of birth control.

Using abstinence
If you are not currently having sexual intercourse with a male partner, it is extremely important that you ask yourself:

Will I definitely remain abstinent for at least 1 month before, during and for at least 3 years after
Soriatane treatment?

If your answer is no, talk to your prescriber immediately.

How can I avoid becoming pregnant?
Any method of birth control can fail. Even if you use one of the most effective birth control methods correctly, there is still a risk of getting pregnant.

Therefore, 2 effective forms of birth control must always be used together at the same time by female patients starting at least 1 month before, during and at least 3 years after Soriatane treatment.

CONTRACEPTION METHODS[1]
Primary (most effective) methods of birth control

At least 1 of the 2 effective forms of birth control must be a primary method of birth control.

This information does not contain all available information about contraception. As always, you should discuss this and any other medical question with your

prescriber or contraception counselor.

THE PILL (oral contraception)
Two kinds of birth control pills are available and they work in different ways.

Combination pills, which contain 2 hormones, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. In addition, combination pills prevent eggs from being released. Your healthcare professional will discuss the different types of pills and help you decide which one is right for you.

Mini-pills, which contain only 1 type of hormone, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. Mini-pills are not recommended for birth control during Soriatane (acitretin) use.

With the Pill method of birth control, 1 pill is taken once a day until the package is completed.
The Pill is usually started the first Sunday after a normal menstrual period or as instructed by your healthcare professional. One package is completed every menstrual cycle. Not all pills provide protection from the start; you can become pregnant during the first 4 weeks after you start taking the Pill. Pills should be taken at the same time every day, and it may be helpful to use a calendar. Strike an "X" for the first day of a new package of pills, and check each day thereafter.

With **perfect use** (correctly and consistently), about 1 woman in 1000 becomes pregnant.
For **typical use** (not always correctly or consistently), the rate is 5 in 100.

The Pill can have a variety of side effects; most are considered minor. Some rare, but serious, health risks do exist, including blood clots, heart attack and stroke. Women who are older than 35 years, who smoke or who are greatly overweight are at greater risk for these side effects, so it is important to discuss these issues with your prescriber.

If a dose of the combination pill is missed, you can take one when you realize it and then continue taking the others at their regular time. **If you miss an entire day, it may be okay to take 2 pills together if necessary; however, you should consult the patient information included in your birth control package and contact your healthcare professional. If you miss taking your pills more than 2 days in a row, you can become pregnant. Do not have sexual intercourse at this time. If you miss more than 2 days, you should call your healthcare professional as soon as you realize it. You are at greatest risk for pregnancy if you start a package late or miss taking pills during the first week of each package.**

Remember: If the Pill is your primary method, you must still use a secondary method at the same time.

THE PATCH (topical contraceptive)
The 2 hormones in the contraceptive patch are absorbed through the skin and released into the bloodstream while the patch is worn. The hormones in the contraceptive patch thicken vaginal mucus to keep the sperm from joining the egg and may prevent a fertilized egg from attaching to the womb. They also prevent eggs from being released.

With the 4-week patch method of birth control, 1 patch is used per week for 3 weeks; then, no patch is worn for the fourth week. The first patch may be applied on the first day of a woman's menstrual period (First Day Start) OR on the first Sunday after the woman's menstrual period starts (Sunday Start). If Sunday Start is selected, or the patch is applied on any other day except the first day of the menstrual period, a woman may become pregnant during the first week of her cycle. The patch should be changed on the same day each week.

The effectiveness of the patch is considered to be similar to combination contraceptive pills if used as directed. However, the patch may be less effective for a woman who weighs more than 198 lb (90 kg). Your healthcare professional should discuss your individual needs with you if your weight is more than 198 lb.

The patch may have similar side effects to combination contraceptive pills. Most side effects are considered minor. However, some rare but serious side effects include blood clots, heart attack and stroke. Women who are older than 35 years, who smoke or who are significantly overweight are at greater risk for these side effects.

If the patch falls off or is partially detached for less than 24 hours, a new patch should be put on immediately, and this patch should be changed on the usual change day. If the patch is detached for more than 1 day, a new cycle with a new change day should be started by applying a new patch. Should this occur, you may not be protected from pregnancy for the first week. Do not have sexual intercourse at this time.

If you forget to apply a patch on the first day of your cycle or forget to change a patch for more than 2 days in the middle of the cycle, you should apply a new patch immediately and begin a new 4-week cycle with a new change day. You may not be protected from pregnancy for the next week. It is very important that no more than 7 days elapse during the patch-free week of treatment. Do not have sexual intercourse at this time. Consult your healthcare professional if you forget to follow the instructions in the patient information

included with your patch.

Remember: If the patch is your primary method, you must still use a secondary method at the same time.

IMPLANTABLE HORMONES—This method of birth control is no longer available to new patients.

With this birth control method, your healthcare professional puts 6 small rod-shaped capsules under the skin of your upper arm. The procedure is simple and can be done during an office visit. The capsules release small amounts of hormone that stop eggs from being released and thicken vaginal mucus to keep sperm from joining the egg. The capsules remain effective for a number of years, and they can be removed by your healthcare professional at any time.

Generally, the side effects are similar to those that occur if you take the Pill. There is only a small chance of an irritation at the spot where the capsules are implanted. The contraceptive effectiveness of these hormones begins 3 days after being implanted.

With **perfect use,** about 5 women in 10,000 become pregnant.
For **typical use,** the rate is also 5 in 10,000.

Remember: If implantable hormones are your primary method, you must still use a secondary method at the same time.

INJECTABLE HORMONES
This method of birth control is a shot or needle injection of a hormone in your arm or buttocks, given to you by your healthcare professional at specific intervals every 4 to 12 weeks. The hormone shot stops eggs from being released, thickens vaginal mucus to keep the sperm from joining the egg and keeps a fertilized egg from attaching to the womb.

Generally, the side effects are similar to those that occur if you take the Pill. This form of birth control is reversible, but it may take several months after stopping the shots before you can become pregnant.

With **perfect use,** about 2-3 women in 1000 become pregnant.
For **typical use,** the rate is also 2-3 in 1000.

Injectable hormones can take up to 1 week to be fully effective; you can become pregnant during this week. Patients who have certain illnesses, or a family history of some illnesses, may not be suited for this type of birth control, so it is important to discuss these issues with your healthcare professional.

Remember: If injectable hormones are your primary method, you must still use a secondary method at the same time.

THE INTRAUTERINE DEVICE (IUD)

The intrauterine device, which is called the IUD, is a plastic device that contains either copper or hormones. Your healthcare professional puts the small plastic IUD in your womb. The copper or hormones in the IUD keep the sperm from joining the egg and prevent a fertilized egg from attaching to the womb.

IUDs that contain hormones can be left in place for between 1 and 5 years. The copper-containing IUDs can be left in place for up to 10 years. Side effects of all types of IUDs may include increased cramps and heavier and longer periods. Women with new sex partners, women with more than one partner or women whose partners have other partners have an increased chance of tubal infection (which may lead to sterility). These risks should be discussed with your healthcare professional. He or she will also explain how to check the IUD for proper position by feeling for a "tail" or string in the vagina. If the string cannot be felt, the IUD may have been expelled or dislodged from its proper position and a healthcare professional should be consulted. This method is not recommended for women who have not had a child.

With **perfect use,** about 1.5 women in 100 become pregnant.
For **typical use,** the rate is 2 in 100.

Remember: If an IUD is your primary method, you must still use a secondary method at the same time.

INSERTABLE HORMONES

The hormonal vaginal contraceptive ring is inserted by you into your vagina and contains a combination of hormones similar to the Pill. After the ring is inserted, it releases a continuous low dose of hormones into your body. The hormones stop the release of an egg and alter cervical mucus to keep sperm from entering the womb. You leave it in for 3 weeks, and then you remove it for 1 week. During this time, your menstrual period will begin. For your first cycle, the ring should be inserted between day 1 and day 5 of your menstrual period. It may take up to 1 week to become fully effective in the first cycle.

Generally, the side effects are similar to those of the Pill. Other side effects may include vaginal discharge or irritation. Like the Pill, the hormonal vaginal contraceptive ring may increase the risk of blood clots, heart attack and stroke, especially in women who smoke. It should not be used by women with certain types of cancer or other medical conditions, so it is important to discuss these issues with your prescriber.

With **perfect use,** about 7-8 women in 1000 become pregnant.

For **typical use,** the rate is 1-2 in 100.

Remember: If the hormonal vaginal contraceptive ring is your primary method, you must still use a secondary method at the same time. You cannot use the diaphragm as a secondary method because the vaginal contraceptive ring may interfere with correct placement and position of a diaphragm.

STERILIZATION: TUBAL LIGATION AND VASECTOMY
Sterilization of either a man or woman requires an operation. A tubal tying (ligation) is intended to permanently block a woman's tubes where the sperm joins with the egg. A vasectomy is intended to permanently block a man's semen duct that carries sperm. However, it takes 15 to 20 ejaculations after sterilization to clear sperm from the man's semen.

You may become pregnant if your male partner has not had 2 consecutive counts that show there are no sperm in the seminal fluid.

There are no lasting side effects and sterilization has no effect on sexual pleasure. Mild bleeding or infection may occur right after the procedure. Sterilization is intended to be permanent; reversing the operation is very difficult and cannot be guaranteed.

With **perfect use,** about 5 women in 1000 (using female sterilization) or 1 woman in 1000 (using male sterilization) become pregnant.
For **typical use,** the rates are 5 in 1000 (female) and 1.5 in 1000 (male).

Remember: If sterilization is your primary method, you must still use a secondary method at the same time.

Secondary (moderately effective) forms of birth control

CONDOM, DIAPHRAGM OR CERVICAL CAP
Each of these is called a "barrier" method of birth control. They are used with a special gel called a spermicide. A spermicide is a substance that kills sperm. By itself, it is NOT an adequate birth control method for Soriatane (acitretin) users. Spermicides come in several forms—creams, jellies, foams and suppositories, which should be applied with your barrier method 10 to 30 minutes before each intercourse.

Spermicide must be applied each time you have sexual intercourse. Your contraception counselor should explain to you exactly how to use the spermicide with the "barrier" method you choose. The barrier method, plus the spermicide, only count as ONE of the 2 forms of effective birth control you must choose before starting Soriatane. The diaphragm or cervical cap must be left in place for 6 hours after your last sexual act, and a woman should not douche or rinse the vagina during this time.

You should understand exactly how to and how not to use barrier methods of birth control. You need to be aware of common mistakes in their use that may result in pregnancy. These barrier methods of birth control are considered less reliable than the other methods discussed earlier.

CONDOM

The condom, also called a "rubber," is a thin sheath that traps the sperm. Condoms are made of latex, plastic or animal tissue (natural skin). Condoms, when used properly and consistently, and with a spermicide, can be effective in preventing pregnancy. It is also believed that latex condoms reduce the spread of some STDs (sexually transmitted diseases), including HIV. Synthetic and natural skin condoms, or those made from the skin of lamb's intestines, are equally effective at preventing pregnancy. However, natural skin condoms do not protect against STDs.

Proper use of a condom means several things. If you choose this method, it is important to have your contraception counselor explain exactly how to follow these directions. The condom has to have been stored in a cool, dry place and not exposed to heat or pressure. It should be rolled onto the erect penis before any contact with the woman's genitals. The rolled rim should always remain on the outside of the condom. If the condom has been rolled incorrectly (backward), it should be discarded and replaced with a new one. A 1/2 inch of empty space should be left at the tip, but no air should be trapped. Air at the tip could cause the condom to break.

The condom should be removed immediately after intercourse to prevent spillage of semen. A condom can be used only once. Oil-based lubricants, like petroleum jelly and baby oil, should not be used with a condom. Water-based lubricants are safe to use and will not destroy the condom. However, since it is necessary to use a spermicide with a condom, this can be used as a lubricant. Care should be taken to avoid ripping, tearing or slipping off during sexual activity.

With **perfect use**, about 3 women in 100 become pregnant.
For **typical use**, the rate is 14 in 100.

Remember: Condoms should never be used alone without a primary birth control method.

DIAPHRAGM

The diaphragm is a shallow latex cup. Its purpose is to cover the cervix and prevent sperm from passing up into the womb. Because the size around the cervix varies from woman to woman, a diaphragm has to be custom fit by a healthcare professional. The fit needs to be checked at least once every 2 years, if

a weight gain or loss of 10 or more pounds occurs, or after pregnancy or an abortion.

The diaphragm can be inserted into the vagina up to 6 hours before sexual intercourse. Spermicide jelly or cream is placed in the diaphragm and around the rim before insertion. Fresh spermicide should be applied with each sexual intercourse or if 6 hours have elapsed before sexual intercourse occurs. The diaphragm should not be removed when spermicide is reapplied. The diaphragm must be left in place for at least 6 hours after the last sexual intercourse; it should not be left in place for longer than a total of 24 hours because of the risk of serious infection (toxic shock syndrome). Once fitted, the diaphragm is inserted into the vagina so that the dome covers the cervix and the rim fits snugly on the vaginal walls.

With **perfect use** (with spermicide), about 6 women in 100 become pregnant.
For **typical use** (with spermicide), the rate is 20 in 100.

Remember: A diaphragm should always be used with spermicide and only as a secondary method. A separate primary method must always be used.

CERVICAL CAP
The cervical cap is a barrier method that must be individually fitted and prescribed by a healthcare provider. The cervical cap is inserted by the female before each sexual intercourse and must be used in combination with a spermicide to be considered moderately effective as a birth control method. The cervical cap is made of latex and should never be used with an oil-based lubricant, such as petroleum jelly, as this will destroy the cap.

The cervical cap actually fits over the cervix. The cap should be left in place for at least 6 hours after the last sexual intercourse, but not longer than 48 hours because of the risk of toxic shock syndrome. Spermicide is placed in the cap before insertion, but it is best to add more spermicide with each intercourse while the cap is still in place. The cervical cap should not be removed while the spermicide is being reapplied. Inserting and removing the cervical cap can be somewhat more difficult than inserting and removing the diaphragm. However, with sufficient instruction and practice, insertion and removal can usually be accomplished.

With **perfect use,** about 9 women in 100 become pregnant.
For **typical use,** the rate is 20 in 100.

Remember: A cervical cap should always be used with a spermicide and only as a secondary method. A separate primary method must always be used.

Other contraception methods

Do not use less effective methods of birth control such as birth control pills without estrogen, natural family planning, fertility awareness or withdrawal while taking Soriatane (acitretin), a medication that can cause birth defects to your unborn child. Ask your healthcare professional about other contraception methods that you may use or have heard about.

Reference: 1. Trussell J, Card JJ, Rowland Hogue CJ. Adolescent sexual behavior, pregnancy, and childbearing. In: Hatcher RA, Trussell J, Stewart F, et al, eds. *Contraceptive Technology.* 17th ed. New York, NY: Ardent Media, Inc.; 1998:701-744.

[end of PPP booklet]

Dear Prescriber/Pharmacist letter:

Dear Prescriber/Pharmacist:

Please be advised of the following **important changes to the Soriatane (acitretin) labeling**.

The Soriatane Package Insert has been updated to provide additional information collected during the time the product has been marketed. It has also been revised for ease of use. It is important to note the new Medication Guide for all patients taking Soriatane, as well as changes to the informed consent form for female patients.

Prescribers and pharmacists are advised to read the entire Package Insert (enclosed) after reviewing the "Synopsis of Informational Changes" below.

Synopsis of Informational Changes

- The Soriatane **"Patient Agreement/Informed Consent for Female Patients"** has been revised for consistency with the changes made in the Package Insert. After the prescriber has determined that a female patient may be a candidate for Soriatane, and has explained the proper use of this medication, the patient should initial each of the 18 items and sign and date the entire informed consent. This is an important component of the Pregnancy Prevention Program and is included as part of the professional Package Insert.

- To improve the communication regarding Soriatane to all healthcare providers, pharmacists and patients, Roche Laboratories Inc. will be releasing a FDA approved **Medication Guide (MedGuide) for Soriatane**. This

document will be sent to prescribers' offices and to all pharmacies in the United States to enhance the safe and effective use of Soriatane.

The Medication Guide for Soriatane must be distributed by the pharmacist, as required by law, to every Soriatane patient each time a Soriatane prescription is dispensed. The Medication Guide was developed in conjunction with the FDA to emphasize key safety issues that patients should know about the use of Soriatane. The Medication Guide for Soriatane summarizes, in simple language, the professional Package Insert, including the approved indication for Soriatane, information about birth defects and pregnancy avoidance, and major adverse events. The Medication Guide is a document required by the FDA for specific medications and must be available for every patient. **To reorder additional Soriatane Medication Guides, please call toll free 1-800-93-ROCHE.** Soriatane is supplied in 10 mg and 25 mg capsule strengths in bottles of 30. The Medication Guide is piggy backed onto the Package Insert which is affixed to each bottle.

- **Informational Changes made to the Soriatane Package Insert are as follows:**

  - The **boxed CONTRAINDICATIONS AND WARNINGS SECTION** has been changed as follows:

    - **Emphasizes the need for two effective forms of contraception (birth control) simultaneously** . The labeling now emphasizes that effective forms of contraception include both primary (tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products) and secondary forms (diaphragms, latex condoms, and cervical caps each used with a spermicide). At least one of the two methods of birth control must be a primary form.

    - Data related to **teratogenicity** when Soriatane is taken by female and male patients have been updated, clarified, and made more concise.

    - Patients should be **cautioned not to self-medicate with the herbal supplement St. John's Wort** because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort.

    - Instructions for patients **not to donate blood** have been clarified and now appear both in the boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections of the Package Insert: "Patients should not donate blood during Soriatane during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane".

- A **section entitled CLINICAL STUDIES** has been added. This section presents the efficacy data from the two pivotal clinical trials.

- The first sentence of the **INDICATIONS AND USAGE** section has been amended. Instead of stating "Soriatane is indicated for the treatment of severe psoriasis, including the erythrodermic and generalized pustular types, in adults", it now states "*Soriatane is indicated for the treatment of severe psoriasis in adults*". This change is consistent with the data in the CLINICAL STUDIES section.

- The **CONTRAINDICATIONS section** has been revised. Soriatane is contraindicated in patients with severely impaired liver and kidney function and in patients with chronic abnormally elevated blood lipid levels. The combined use of Soriatane and methotrexate, and Soriatane and tetracyclines is contraindicated.

- The following revisions and additions have been made to the **WARNINGS section**:
  - The internal black boxes around pancreatitis and pseudotumor cerebri have been removed, but these warnings remain in the WARNINGS section. The internal black box for hepatoxicity remains. This change does *not* reflect new safety information. It was made simply for labeling consistency with other serious adverse events.

  - Additional information has been added regarding ***Pancreatitis***. There have been rare reports of pancreatitis during Soriatane therapy in the *absence* of hypertriglyceridemia.

  - Additional instruction has been added regarding ***Hyperostosis***. Periodic radiography of patients on Soriatane treatment is warranted in the presence of symptoms or long-term use because the frequency and severity of iatrogenic bony abnormality in adults is low.

  - Additional information has been added regarding ***Lipids and Possible Cardiovascular Effects***. Although no causal relationship has been established, there have been postmarketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy.

- The following revisions and additions have been made to the **PRECAUTIONS section**:

  - The subsection "**Nursing Mothers**" has been updated to note that there is one prospective case report where actitretin is reported to be excreted in human milk. Therefore, nursing mothers should not

receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants.

- **Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm** have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms.

- **Decreased night vision** has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored.

- **Patients should not donate blood** during Soriatane treatment and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane.

- The following language has been clarified to **differentiate between non-medical and medically supervised UV exposure**: "Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical ultraviolet exposure) because the effects are enhanced by retinoids)".

- Prescribers should **significantly lower doses of phototherapy** when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning).

- A ***Drug Interactions*** section has been reformatted for ease of reading and contains information about the interactions between Soriatane and a) ethanol ; b) glibenclamide; c) information that microdosed progestin preparations (minipills) may be an inadequate method of contraception during Soriatane therapy; d) phenytoin.

- The ***Pediatric Use*** section has been amended to include reports of **decreases in bone mineral density** in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between effect on bone and Soriatane has not been established.

- A ***Geriatric Use*** section has been added to note that clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determined whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

- The **ADVERSE REACTIONS** section which reports on the clinical trials experience has been reformatted for your convenience to list the reported events by body system in alphabetical order. *Additional* adverse events are reported in a **newly created section *Adverse Events/Postmarketing* reports**:

  - In addition to the events listed in the tables for the clinical trials, the following adverse events have been identified during post-approval use of Soriatane. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
    - **Cardiovascular** - Acute myocardial infaction, thromboembolism, (see WARNINGS)stroke
    - **Nervous System**: Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug.
    - **Psychiatric**: Aggressive feelings and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. (see PRECAUTIONS).
    - **Reproductive** - Vulvovaginitis due to *Candida albicans*
    - **Skin and appendages** – Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed.

- The **OVERDOSAGE section** has been amended to indicate that in the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. Further instructions are provided regarding pregnancy testing and counseling for all female patients of childbearing potential who have taken an overdose of Soriatane.

- The **DOSAGE AND ADMINISTRATION** section now addresses the fact that maintenance doses of 25 *to* 50 mg may be given (note: the previous Package Insert stated 25 or 50 mg). The section has been clarified to note that **maintenance doses** be given dependent upon an individual patient's response to initial treatment. This section also notes that when Soriatane is used with phototherapy, the prescriber should **decrease the phototherapy dose**, dependent on the patient's individual response.

Please refer to the enclosed complete updated product information for detailed information on Boxed Warnings, Contraindications, Warnings, Precautions,

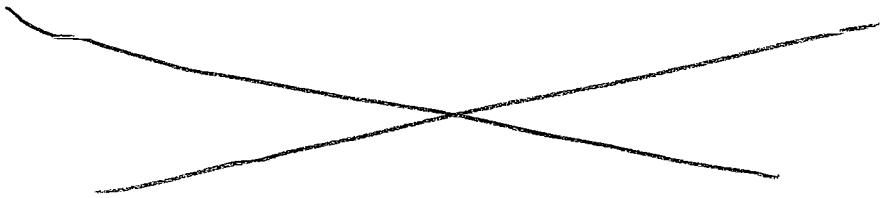
Adverse Events, Overdosage, Dosage and Administration, Informed Consent, and the Medication Guide.

If you have any questions about Soriatane, we encourage you to call the toll-free number for Roche at 1-800-526-6367. Also, if you are aware of any serious Adverse Events potentially associated with the use of Soriatane, report such information to Roche at the above number or to the Food and Drug Administration MedWatch program at 1-800-FDA-1088.

Sincerely,

[End of *Dear Professional Letter]*

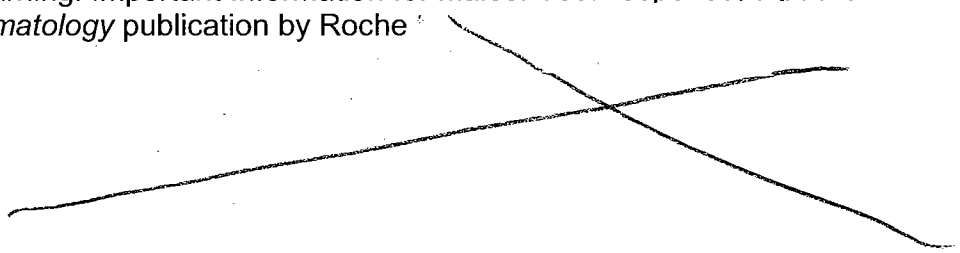
List of additional issues where the labeling differs from the version submitted by Roche (conveyed to Sponsor and agreed upon prior to approval of labeling; there is no need to convey again with Action Letter)



- Boxed Warning for teratogenicity regarding etiology of reported birth defects: added "The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not".

- Boxed Warning (and all other relevant sections) for teratogenicity regarding microdosed progestin preparations: added "Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane".

- Boxed Warning: Important Information for Males: Your response, a published 2002 *Dermatology* publication by Roche



Timing of paternal acitretin treatment relative to conception	Delivery of healthy	Spontaneous abortion	Induced abortion	Total

	neonate			
At time of conception	5*	5	1	11
Discontinued ~ 4 weeks prior	0	0	1**	1
Discontinued ~ 6-8 months prior	0	1	0	1

* Four of 5 cases were prospective

**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)

- Clinical Trial Efficacy
The number of subjects is given and should stand on its own.

- Precautions ophthalmologic: Added "See WARNINGS".

- Precautions psychiatric and all other locations with same wording
"as well as in patients taking...".

- In the text preceding safety data tables from trials, added percentage (22%) of patients who discontinued due to adverse event

- In Table 4 alcohol "tolerance" was changed to "intolerance". The rationale is that this was an obvious error

- Medication Guide:

"Read this Medication Guide carefully before you start taking Soriatane and read it each time you get more Soriatane. There may be new information. The first information in this Guide is about birth defects and how to avoid pregnancy. **After this section there is important safety information about possible effects for any patient taking Soriatane**. ALL patients should read this entire Medication Guide carefully. This information does not take the place of talking with your prescriber about your medical condition or treatment".

-

"...or to any similar drugs (ask your prescriber or pharmacist whether any drugs you are allergic to are related to Soriatane)".

•

End of Additional Comments to Sponsor (already sent)

Additional Review Comments:

1) Male Information in Boxed Warning Regarding Teratogenicity

The wording I am recommending is as follows:

- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

  There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome):

Timing of paternal acitretin treatment relative to conception	Delivery of healthy neonate	Spontaneous abortion	Induced abortion	Total
At time of conception	5*	5	1	11
Discontinued ~ 4 weeks prior	0	0	1**	1
Discontinued ~ 6-8 months prior	0	1	0	1

* Four of 5 cases were prospective

**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)

The currently approved wording states:

"It is not known whether residual acitretin in seminal fluid poses risk to a fetus while a male patient is taking the drug or after it is discontinued. There have been five pregnancies reported in which the male partner was undergoing Soriatane treatment. One pregnancy resulted in a normal infant. Two pregnancies ended in spontaneous abortions. In another case, the fetus had bilateral cystic hygromas and multiple cardiopulmonary malformations. The relationship of these malformations to the drug is unknown. The outcome of the fifth case is unknown.

Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL.

Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule.

The new wording and format are clearly more informative and were prompted by a December 2002 publication by Roche in *Dermatology* (Geiger JM, Walker M. Is There a Reproductive Safety Risk in Male Patients Treated with Acitretin (Neotigason/Soriatane)? Dermatology 2002; 205:105-107).

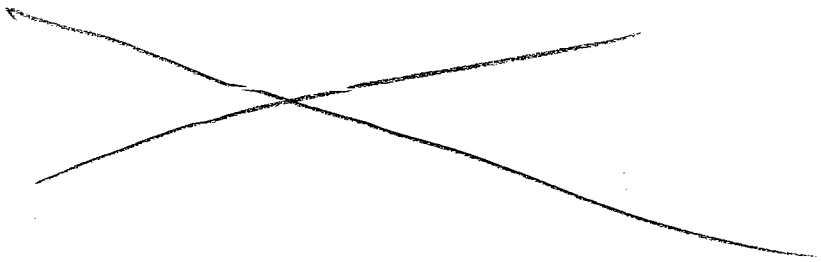
The reason for this reviewer's comment is to state the rationale for recommending labeling approval of the footnote: "**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)".

While I do not agree with all of the reasoning in the Roche publication, I do agree that the above statement is factually correct: the reported defects in the noted case do not follow the recognized *pattern* of retinoid embryopathy, which involves prominent effects on craniofacial and central nervous system development in addition to heart defects. Heart defects are not uncommon serious congenital abnormalities and there is nothing about this case to suggest it is not background. A PubMed literature search revealed no reference to cystic hygroma or cavernous lymphangioma in association with retinoid exposure. Instead, this defect is most commonly associated with chromosomal abnormalities.

Any possible fetal exposure in this case would have to have been extremely low (4 weeks after the father stopped the drug; even if the father had consumed alcohol during treatment, etretinate compartmentalizes to semen *less than* acitretin). While it is certainly possible that very low-level teratogen exposure might cause more subtle defects than the classic patterns, the cardiac defects reported were clearly not subtle, and I am aware of no evidence to suggest that retinoid-induced cardiovascular defects occur at lower levels of exposure than craniofacial and CNS defects.

I think it is appropriate to put this case into perspective in the labeling so that prescribers and patients can make rational decisions about risk to pregnancy in partners of male patients using this drug.

2) Sponsor's submitted plan for implementing new labeling and Medication Guide into marketplace



Action Items:

1) Convey that the Sponsor's submitted plan for implementing new labeling and Medication Guide into the marketplace is acceptable, but every effort should be made to exchange patient materials and package inserts in prescribers' offices at next marketing representative call.

2) Include in Action letter a reminder that FDA expects the post-marketing agreement in the original 1997 approval action to be completed as agreed upon at that time.

3) FDA considers the patient brochure (including Pregnancy Prevention Program [PPP] booklet), like the Informed Consent Form and the Medication Guide on which it is based, part of the approved labeling for Soriatane. As such, they should ensure that the FPL for the PPP booklet reflects the revisions in the approved Informed Consent Form and the approved wording for the Medication Guide.

Recommendation: **Approval as per this document**

Kathryn O'Connell, MD PhD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine OConnell
3/17/03 04:46:32 PM
MEDICAL OFFICER

Jonathan Wilkin
3/17/03 04:52:09 PM
MEDICAL OFFICER

Medical Officer Review
Revised Pregnancy Prevention Program for Soriatane

NDA#:	**19-821**
Stamp Dates:	desk copy letter date December 19, 2002
Review Date:	December 26, 2002
Sponsor:	Hoffman-LaRoche
Product:	Soriatane (acitretin)
Indication:	Severe recalcitrant psoriasis
Formulation:	Capsule

Submission Summary:

At the Agency's request, the sponsor has submitted a revised Pregnancy Prevention Program (PPP) for Soriatane in accordance with the labeling revisions underway, which include a new Medication Guide. This draft was concurrently submitted to DDMAC.

Recommendation for Project Management Action:

1) The draft PPP booklet should be sent to Dr. Furlong in Reproductive Health to confirm my impression that the information on new developments in contraceptive technology is correct and appropriately presented for patients. The section on Emergency Contraception appears to be consistent with the information in the Accutane SMART booklet, which has already been reviewed by Dr. Furlong, but this should also be confirmed. It is *not* necessary to send all of the parts of the submission; Dr. Furlong's opinion is needed as soon as possible, so please send over only the PPP booklet.

2) The following comments should be sent to HLR as soon as possible; please mark *draft*:

   - These comments pertain to your December 19, 2002 submission and are from Dr. O'Connell; a few additional (compatible) comments may be forthcoming from DDMAC and/or Reproductive Health.

- It is very helpful that you reproduced in this submission the draft professional labeling/Medication Guide that we sent to you most recently. The pregnant lady logo appears to have survived our electronic transmission, but this time 3 sides of the hepatotoxicity "box" are missing (only the bottom survived). Please retain the Boxed Warning for hepatotoxicity as previously discussed
- [redacted]
- On page 25 of the submission (Medication Guide)

  [redacted]

  . "The first information in this Guide is about birth defects. After this section there is important safety information about possible effects of patients taking Soriatane. **ALL patients should read this entire Medication Guide carefully."**

- <u>PPP booklet:</u>
  - I have a suggestion for the Introduction regarding the "test"; this is only a suggestion; it can stand as is at your discretion. Use of the word "test" may discourage some patients from cooperating with this voluntary program. Perhaps you could re-phrase the instructions to say: "Answer the patient self-evaluation questions". On the "test" form itself, it might also intimidate some patients that they are asked to sign and date the completed "test" for the medical record with wrong answers noted. Is this really necessary given that they will already be signing a Consent Form? Also, consider instructing the patient to mark "unsures" and wrong answers with a "X" instead of a checkmark. The reason is that a busy prescriber is apt to misinterpret the checkmark as "OK", whereas a "X" is likely more universally recognized as a problem that needs further counseling.
  - It appears that there is plenty of space in the mock up section for females, so it would be helpful to increase the "white space" between bullets for readability.

    [redacted]

  - I noted that the automated phone line has a title "what should I do if I think I am pregnant", but I don't see this important section title in the booklet. Suggestion: immediately before the EC section, insert "What should I do if I think I am pregnant or if I have trouble with my birth control" (answer: STOP taking Soriatane and call prescriber

immediately if suspect pregnancy; if problems with birth control, STOP Soriatane, call prescriber immediately, and re-read the next section on emergency contraception).

- Informed Consent: Please be sure final version is identical to the version we finally agree to for the professional package insert.

Addendum January 13, 2003: Comments from DDMAC have been received. I made some revisions following discussion with R. Williams and agree with the following additional items to be conveyed to sponsor:

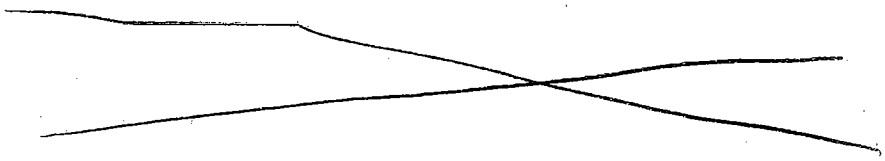
DDMAC Comments on Draft Pregnancy Prevention Program Materials

Note: The materials are very similar to the approved Accutane patient education materials. Therefore, my comments are only on items that are unique to the Soriatane materials. Furthermore, I cannot provide final comments on the draft materials acceptability without viewing them in their final format.

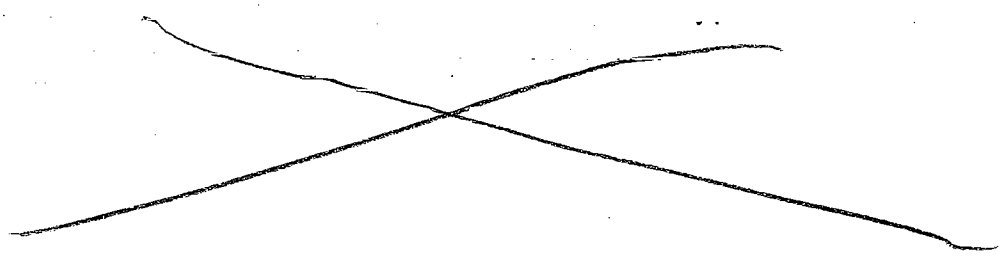
1. The name of at least one specific dosage form and quantitative ingredient information should be presented in direct conjunction with the tradename and established name (i.e., 10mg and 25 mg capsules).

2. "The facts in this booklet about Soriatane treatment are very important to your health and well-being (page 13)." This should be deleted and substituted with "It is very important that you understand all of the facts in this booklet because Soriatane can have serious side effects".

3. "Mini-pills are not recommended for birth control (acitretin) use (page 16)." Patients may be interested in why they are not recommended for use. I would recommend adding a sentence explaining that there is an interaction with Soriatane which interferes with the effectiveness of the mini-pill.

4 

Soriatane Patient Self-Evaluation

1. 

Kathryn O'Connell, M.D. Ph.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Katherine OConnell
1/13/03 03:24:03 PM
MEDICAL OFFICER

the comments for sponsor were emailed earlier to PM
in draft to expedite getting to sponsor

Jonathan Wilkin
1/13/03 04:35:49 PM
MEDICAL OFFICER

Medical Officer Review
Labeling Supplement

NDA#: **19-821** Doc ID#: SLR-002 & 006

Stamp Dates: August 18, 1999 (002)
May 21, 2002

Review Date: November 14, 2002

Sponsor: Hoffman-LaRoche

Product: Soriatane (acitretin)

Indication: Severe recalcitrant psoriasis

Formulation: Capsule

Submission Summary:

At the Agency's request, the sponsor submitted a supplement to the Soriatane NDA to address the need for a number of revisions. A subsequent request asked the sponsor to submit the revised Patient Package Insert as a formal Medication Guide. In addition to these two submissions, this new labeling incorporates a geriatric labeling supplement submitted in 1999 (because the Geriatric supplement essentially adds no new information of use to prescribers or patients, action on that labeling amendment was postponed in anticipation of this major labeling revision). This review covers Supplement #002 (Geriatric labeling), #006 (comprehensive labeling revisions), and the Medication Guide amendment to #006.

This review consists of the following sections:

- The principle points of the labeling revision.
- The sponsor's version emailed to us on November 8, 2002 after several rounds of revisions and discussions. Unfortunately, some of the issues remain unresolved. I have inserted "Reviewer Comment" in italic font highlighted in yellow into the relevant sections if the sponsor's changes are anything other than acceptable editorial/wording changes. Only those sections identified by the sponsor as different from the last version we sent to them are so noted (see next bullet*).
- The wording that I recommend for the professional package insert, the Informed Consent form for female patients, and the Medication Guide. *To

avoid re-examination of each line of this lengthy labeling, this is based on *our* working version, not the version sent by the sponsor. This wording represents the consensus achieved via adverse event analyses from the Office of Drug Safety, the Cardiorenal division, patient labeling advice from ODS in consultation with DDMAC, and a formal labeling day attended by reviewers from biopharmaceutics, pharmacology, chemistry, biostatistics, ODS, and clinical (see documents in DFS under NDA 19-821: O'Connell, Bashaw, Pitts, Best J, Karwoski, Brown P, Hathaway S, and Cardiorenal consult in paper file dated 7/27/99). This recommended wording also reflects the sponsors' suggested wording whenever possible within our goals for the improved labeling.

- Issues where concurrence with the sponsor was not achieved are listed at the end and can be shared with them as part of an Approvable action or for continued negotiation (an administrative decision).
- Action Items
- Recommendation

Principle points of the labeling revision:

- The Boxed warning regarding teratogenicity has been revised for consistency with the Accutane S.M.A.R.T. program where appropriate.
- The reproductive outcome data in the Boxed Warning has been updated and streamlined to provide only that data needed to help clinicians and patients make risk aware choices in the event of conception after the 3 year waiting period.
- The Informed Consent form for females has been updated to conform where appropriate to the new S.M.A.R.T program.
- Changes to second Boxed Warning for consistency with current database and with Accutane labeling.
- Important new Contradindications.
- Add acute myocardial infarction to Warnings section.
- Add suicidal behavior to Precaution section.
- Add events to Adverse Reactions based on post-marketing reports.
- Add drug interactions.
- Add Geriatric labeling.
- Add overdose information related to teratogenicity.
- Add Medication Guide for patients.

73 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 19821
5002/5000

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Tegison® is a registered trademark of Hoffmann-La Roche Inc.

R_X only

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Comments for Sponsor on Unresolved Issues/ Major Revisions (please note that the labeling to follow was prepared from FDA's working version, not from the sponsor's revision; there may be other changes to the sponsor's last revision that are NOT the subject of comment below:

- Since the September 2002 HLR version, there appear to be about 28 new prospective pregnancy cases where exposure occurred after the last dose of retinoid. There is also an apparent deletion of fetal outcomes for retrospective cases occurring 2 or more years after the last dose (craniofacial/cardiac malformations). Please clarify this difference and the source of the new cases.

- Regarding males taking Soriatane: It is a fact that it is *not* known if residual acitretin poses any risk. especially given the fact that there is no formal registry and that spontaneous reports are unreliable for an event such as this. However, it is also true that residual acitretin is very unlikely to pose risk because the amounts are very low and there is no evidence of which we are aware that any drug has ever

caused human birth defects when taken by the father. Over-warning is not in best interest of patients, since some may abort an otherwise wanted fetus. The statement is followed by available outcome data so that prescribers and patients can decide on condom use and make risk aware choices. For these reasons,

(the Medication Guide was also revised accordingly).

- Our statistician has expressed concern that the efficacy data for Study B from the NDA many years ago does not appear to have been analyzed by today's standards for multiple comparisons. We had asked for, if possible, only a summary statement regarding patients who were cleared or almost cleared, since the submitted data are not particularly helpful and the labeling is already very long. There are, however, valid concerns about post-hoc analysis, since the data were not collected or analyzed that way in the NDA

This information is not crucial to safe use of the product, but other revisions needed for safety are being delayed by this unresolved issue. Thus, we are postponing efficacy data for consideration in a future labeling amendment.

- The Sponsor removed the boxed Warning for non-teratogenicty related adverse events. This is consistent with Accutane labeling, which shares the same events NOT in a black box, and with the safety database, including published literature, at the time of the Division's labeling meeting about this amendment. (The issue of multiple Boxed warnings was discussed for Accutane at the 2000 DODAC meeting in the context of having a second lengthy Boxed Warning distract from the teratogenicity Boxed Warning). If the Soriatane box is removed here, the product will remain under the regulations for Boxed Warnings, since the pregnancy information will remain Boxed.

  When this review was begun, our concern was that this change might be interpreted as the result of new "improved" safety data, when that is not the case. The sponsor has assured us they will not use such a promotion. HOWEVER, FDA has just received a new Soriatane post-marketing report of liver transplant. It is unclear from the submitted information whether the transplant is related in any way to Soriatane treatment, but the fact that the case was reported is itself cause for caution. Due to this new concern, we are

recommending that the Boxed Warning be retained for hepatotoxicity in this revision. If the case can be ruled out as evidence of acitretin-induced hepatic failure, a future supplement can be submitted for review based on the database at that time. Of course, if the new case is found to be causally related, that information should be added to the boxed Warning. (Pancreatitis and pseudotumor cerebri have been left out of the Box in this revision; note that the statement from the current adverse reactions section about fatal pancreatitis has been moved to this Warnings section).

- Regarding psychiatric labeling: Our post-marketing safety analysis did not reveal a large number of cases of self-injurious or aggressive behavior, but we think that these reports may be significant because some of them include positive dechallenge/rechallenge, these events are associated with other systemically administered retinoids, and there are published reports of aggressive/depressive mood changes with the drug's metabolite, etretinate. In addition, [redacted] We recommend the wording we suggested previously for the Adverse Reactions section and the following alternative in the Precautions section: "**Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience [redacted] psychiatric symptoms**. [redacted] (We did receive the desk copy of the new issue work-up; this recommendation reflects the Division's review of that information).

- Regarding pediatric labeling: This section should acknowledge that "other retinoids" includes etretinate, a metabolite of Soriatane. It should also reference the Warning section.

- Regarding Adverse Reactions section: The list of additional events should be moved to the beginning of this section and integrated with the other events not included in the tables; see final recommended labeling.

- Regarding Informed consent Item #4: The prohibition on ethanol is based on the fact that it can enhance formation of etretinate, which was labeled when marketed for an indefinitely long post-therapy contraceptive period due to its extremely long half-life. The labeling for Soriatane states "at least 3 years" in the context of NO ethanol. In presence of ethanol, it is indefinite, due to the probability of etretinate formation. Although not tracked as such in the electronic version I received, the above wording adds "at least 3 years" to the statement as we sent it to the sponsor. It is simply incorrect and the error is potentially dangerous.

- Medication Guide:

  - [redacted]

- [redacted] is a statement that is not necessary for patient safety (the goal of the Medication Guide).
- [redacted]
  - Please see corresponding comments re: professional package insert issues.
  - Please incorporate as much appropriately placed white space into the Medication Guide as space will allow.
- A Dear Doctor letter should be submitted for review.
- The Pregnancy Prevention Program and marketing materials should be sent for review concurrently to the NDA and to DDMAC.
- All current safety reporting requirements should be maintained.

Project Management Action Item:

- The eventual approval letter should reiterate the original post-marketing agreement in the 1997 Soriatane approval letter to study acitretin and etretinate levels in 100 women (see Dr. Bashaw's memorandum in DFS).

Recommendation: Assuming there are no CMC issues, I recommend Approval AS REVISED by FDA. This can be accomplished either by continued negotiation on this supplement or by a re-submission of a new supplement after an Approvable action on this one. Either way, the sponsor should be strongly encouraged to quickly finalize the updated labeling for this product, since several of the issues are of importance to safe, risk-aware use of the drug.

Kathryn O'Connell, M.D. Ph.D.

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/s/

Katherine OConnell
11/18/02 05:56:42 PM
MEDICAL OFFICER

Jonathan Wilkin
11/21/02 04:39:51 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

PHARMACOLOGY REVIEW

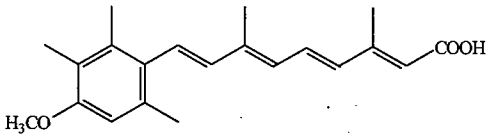
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 19-821
Sequence number/date/type of submission: S002/S006 / 11 February 2003 / Response to AE
Information to sponsor: No
Sponsor and/or agent: Hoffmann-La Roche Inc.

Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: March 18, 2003

Drug:

Trade name: Soriatane
Generic name: acitretin
Code name: Ro 10-1670
Chemical name: all trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid
CAS registry number: 55079-83-9
Molecular formula/molecular weight: $C_{21}H_{26}O_3$ / MW=326.44
Structure:



Relevant INDs/NDAs/DMFs: IND 25,782;

Drug class: retinoid

Indication: severe psoriasis

Clinical formulation: 10 mg and 25 mg gelatin capsules. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

Route of administration: oral

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction:
This submission contains sponsor proposed wording for the package insert and the patient package insert. This submission is in response to wording proposed by the Division in an approvable letter sent to the sponsor on 21 November 2002.

Nonclinical studies reviewed in this submission:
None

Executive Summary

I. Recommendations

A. Recommendation on Approvability
The labeling submitted by the sponsor is approvable from a pharm/tox perspective.
B. Recommendation for Nonclinical Studies
None
C. Recommendations on Labeling
None

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No new nonclinical findings were presented in the current submission.
B. Pharmacologic Activity
No new findings on the pharmacologic activity of acitretin were presented in the current submission.
C. Nonclinical Safety Issues Relevant to Clinical Use
No new nonclinical safety issues relevant to clinical use were identified in the current submission.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/Sup./Jacobs
HFD-540/MO/O'Connell
HFD-540/Chem/Turujman
HFD-540/PM/Bhatt
HFD-540/Div. Dir./Wilkin

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology conclusions:

No new pharmacology information was submitted at this time.

II. SAFETY PHARMACOLOGY:

Safety pharmacology conclusions:

No new safety pharmacology information was submitted at this time.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK conclusions:

No new pk/tk information was submitted at this time.

IV. GENERAL TOXICOLOGY:

Toxicology conclusions:

No new toxicology information was submitted at this time.

V. GENETIC TOXICOLOGY:

Genetic toxicology conclusions:

No new genetic toxicology information was submitted at this time.

VI. CARCINOGENICITY:

Carcinogenicity conclusions:

No new carcinogenicity information was submitted at this time.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology conclusions:

No new reproductive and developmental toxicology information was submitted at this time.

VIII. SPECIAL TOXICOLOGY STUDIES:

Conclusions:

No new special toxicology information was submitted at this time.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Labeling with basis for findings:

The nonclinical information in the label submitted by the sponsor in the current submission is the same as that determined to be acceptable in the previous review of labeling supplement S006.

Conclusions and recommendations: The labeling supplement remains approvable from a pharm/tox perspective.

X. APPENDIX/ATTACHMENTS:

None

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/s/

Paul Brown
3/18/03 09:26:38 AM
PHARMACOLOGIST

Abby Jacobs
3/18/03 10:20:47 AM
PHARMACOLOGIST

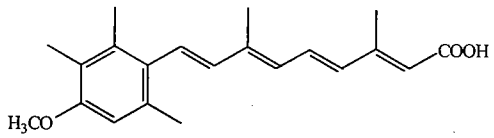
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 19-821
Sequence number/date/type of submission: SLR-006 / 17 May 2002 / labeling supplement
Information to sponsor: No
Sponsor and/or agent: Hoffmann-La Roche Inc.

Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: February 3, 2003

Drug:

Trade name: Soriatane
Generic name: acitretin
Code name: Ro 10-1670
Chemical name: all trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenois acid
CAS registry number: 55079-83-9
Molecular formula/molecular weight: $C_{21}H_{26}O_3$ / MW=326.44
Structure:



Relevant INDs/NDAs/DMFs: IND 25,782; [redacted]

Drug class: retinoid

Indication: severe psoriasis

Clinical formulation: 10 mg and 25 mg gelatin capsules. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

Route of administration: oral

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction:
This submission contains sponsor proposed wording for the package insert and the patient package insert. The purpose of these changes is to incorporate updated pregnancy and birth defect data, other safety data and a clinical studies section.

Nonclinical studies reviewed in this submission:
None

Executive Summary

I. Recommendations

A. Recommendation on Approvability
This labeling supplement is approvable with the labeling changes suggested.
B. Recommendation for Nonclinical Studies
None
C. Recommendations on Labeling

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No new nonclinical findings were presented in the current submission.
B. Pharmacologic Activity
No new findings on the pharmacologic activity of acitretin were presented in the current submission.
C. Nonclinical Safety Issues Relevant to Clinical Use
No new nonclinical safety issues relevant to clinical use were identified in the current submission.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/Sup./Jacobs
HFD-540/MO/O'Connell
HFD-540/Chem/Turujman
HFD-540/PM/Cross
HFD-540/Div. Dir./Wilkin

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

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I. PHARMACOLOGY:

Pharmacology conclusions:

No new pharmacology information was submitted at this time.

II. SAFETY PHARMACOLOGY:

Safety pharmacology conclusions:

No new safety pharmacology information was submitted at this time.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK conclusions:

No new pk/tk information was submitted at this time.

IV. GENERAL TOXICOLOGY:

Toxicology conclusions:

No new toxicology information was submitted at this time.

V. GENETIC TOXICOLOGY:

Genetic toxicology conclusions:

No new genetic toxicology information was submitted at this time.

VI. CARCINOGENICITY:

Carcinogenicity conclusions:

No new carcinogenicity information was submitted at this time.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology conclusions:

No new reproductive and developmental toxicology information was submitted at this time.

VIII. SPECIAL TOXICOLOGY STUDIES:

Conclusions:

No new special toxicology information was submitted at this time.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Labeling with basis for findings:

The boxed Contraindications and Warnings section of the label contains the following paragraph.

> Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at doses approximately 0.6, 3 and 15 times the maximum recommended therapeutic dose, respectively.

Comment:

This information appears to be accurate. Current CDER practice is to include the mk/kg dose and

calculate the animal to human dose ratios using doses expressed on a mg/m^2 basis

The Warnings section of the label proposed by the sponsor contains the following two paragraphs which were also included in previous versions of the label.

Animal Studies: Subchronic and chronic toxicity studies in rats and dogs revealed dose-related, reversible signs of intolerance typical of retinoids. In rats, decreased body weight gain and increases in serum cholesterol, triglycerides, lipoproteins and alkaline phosphatase were observed; fractures and evidence of healed fractures were also noted. In dogs, signs of intolerance included erythema, skin hypertrophy/hyperplasia and testicular changes. In dogs, the dosages studied were as much as ten times the recommended human dosage; in rats, one to two times. Most of the side effects were readily reversible after cessation of treatment, except for epiphyseal ossification.

Acitretin shares with vitamin A and other retinoids the potential to cause malformations in the offspring of various species, including mouse, rat and rabbit, even at dosage levels recommended for humans. Since acitretin is teratogenic in animals at human dosage levels, females of reproductive potential must not be treated if pregnancy cannot be excluded.

Comment:
The medical officer, Dr. Kathryn O'Connell, has suggested that these paragraphs can be deleted. It is acceptable from a pharm/tox perspective to delete these paragraphs at this time since there is now human data that will be included in the label that supersedes the animal data.

The wording proposed by the sponsor for the Carcinogenesis, Mutagenesis and Impairment of Fertility and Pregnancy sections of the label are reproduced below.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenesis: A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. / , in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately

Mutagenesis: Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and

human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays.

Impairment of Fertility: In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day. Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day).

No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[3-5] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[3,4]

Pregnancy: *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).**

In a study in which acitretin was administered to male rats only at a dosage of 5 mg/kg/day for 10 weeks (approximate duration of one spermatogenic cycle) prior to and during mating with untreated female rats, no teratogenic effects were observed in the progeny.

Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been

assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule.

Nonteratogenic Effects: In rats dosed at 3 mg/kg/day (approximately three times the maximum recommended therapeutic dose), slightly decreased pup survival and delayed incisor eruption were noted. At the next lowest dose tested, 1 mg/kg/day, no treatment-related adverse effects were observed.

Comments:
The Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label appears to be unchanged from the previous Soriatane label. Several changes are appropriate at this time. As noted with other sections of the label,

The study conducted and so it is recommended that this be noted in the label.

The last paragraph of the Carcinogenesis, Mutagenesis and Impairment of Fertility section describes data from studies in male humans. The superscripts in this paragraph are no longer correct since reference number 2 (Berbis et al., Arch. Dermatol. Res. 1988; 280(6)388-389) has been removed from the References section of the package insert by the sponsor. Removal of this reference may have been inadvertent since this reference appears to be still cited in the Clinical Pharmacology section of the label. The sponsor should confirm which references are correct and assign superscripts accordingly.

This is acceptable from a pharm/tox perspective. This would leave the pregnancy section with one paragraph about the study in male rats and one paragraph about nonteratogenic effects in rats.

Recommended labeling:

With [redacted] the paragraph of animal data that appears in the boxed Contraindications and Warning section would appear as shown below.

Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.

With [redacted] the Carcinogenesis, Mutagenesis and Impairment of Fertility and Pregnancy sections of the label would appear as shown below. (Superscripts need to be confirmed by sponsor.)

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Carcinogenesis: A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80 week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m^2 comparison.

Mutagenesis: Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays.

Impairment of Fertility: In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day).

No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[3-5] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[3,4]

The Pregnancy section of the label would appear as shown below ...

Pregnancy: *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).**

Nonteratogenic Effects: In rats dosed at 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison), slightly decreased pup survival and delayed incisor eruption were noted. At the next lowest dose tested, 1 mg/kg/day, no treatment-related adverse effects were observed.

Conclusions and recommendations:
The labeling supplement is approvable from a pharm/tox perspective with the label changes suggested above. It is recommended that these changes be incorporated into the draft label. The sponsor should review the references cited in the label to make sure that all citations are correct.

Note: The suggested changes were incorporated into the draft label and this was sent to the sponsor. The sponsor was also asked to check that all of the references were correct. The ... An approvable letter dated 11/21/02 incorporating these changes was sent to the sponsor. Because of these communications with the sponsor, no additional pharm/tox recommendations need to be conveyed to the sponsor at this time.

X. APPENDIX/ATTACHMENTS:

Calculation of animal to human dose ratios based on mg/m^2
Teratogenicity:
The maximum recommended human dose is 50 mg/day. This is equal to a dose of 0.8 mg/kg in a 60 kg individual. Using a Km of 37, this dose is equal to 30.8 mg/m^2.

The table below shows the doses at which the teratogenicity of acitretin was observed in the various animal models. The table shows equivalent mg/m^2 doses and the animal to human dose ratios calculated using the human dose of 30.8 mg/m^2.

Species	Teratogenic dose (mg/kg)	Km	Teratogenic dose (mg/m^2)	Animal/ human ratio
Rabbit	0.6	12	7.2	0.2
Mice	3	3	9	0.3
Rats	15	6	90	3

Carcinogenicity:

In the 80 week mouse carcinogenicity study, increased hemangiomas and hemangiosarcomas were observed in the high dose group which was treated with 5 mg/kg for 26 weeks and then treatment was suspended for 4 weeks followed by treatment with 4 mg/kg for the remainder of the study. Doses of 4 and 5 mg/kg in the mouse are equal to 12 and 15 mg/m^2, respectively. These doses are 0.4 and 0.5 times the maximum recommended human dose of 30.8 mg/m^2. Therefore, the hemangiomas and hemangiosarcomas were observed at doses that were approximately one-half the maximum recommended human therapeutic dose.

Fertility and segment III reproductive toxicity:
A dose of 3 mg/kg in rats is equal to 18 mg/m^2, which is 0.6 or about one-half of the maximum recommended human therapeutic dose of 30.8 mg/m^2.

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/s/

Paul Brown
2/3/03 01:35:00 PM
PHARMACOLOGIST

Abby Jacobs
2/3/03 03:54:57 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-821/S-002
NDA 19-821/S-006

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 2002

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Vickey Lutwak, Regulatory Health ProjectManager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Medication Guide for Soriatane® (acitretin) Capsules, NDA 19-821/S-006.

The labeling that follows is the revised Medication Guide for Soriatane® (acitretin) Capsules, NDA 19-821/S-006. It has been reviewed by our office and by DDMAC. We have simplified wording, made it consistent with the PI, removed promotional language and other unnecessary information and put it in the format that that is outlined in 21 CFR § 208.20, *Content and Format of a Medication Guide*. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Outstanding questions or comments for the review division appear in the text and are bolded, italicized, and underlined. Please let us know if you have any questions.

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S002/S006

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/s/

Jeanine Best
10/29/02 03:25:16 PM
CSO

Anne Trontell
10/29/02 04:48:03 PM
MEDICAL OFFICER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/9/02

TO: Jonathan Wilkin, M.D., Director
HFD-540

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: DSRCS Patient Package Insert Review for Soriatane
NDA 19-821

The labeling that follows is a revised Patient Package Insert for Soriatane. It has been reviewed by our office and by DDMAC. We have simplified wording, made it consistent with the PI, removed promotional language and other unnecessary information, and put it in the format we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Outstanding questions or comments for the review division appear in brackets or parentheses in the text.

Please let us know if you have any questions.

{See appended electronic signature page}

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/s/

Karen Lechter
8/9/02 03:25:28 PM
UNKNOWN

Toni Piazza Hepp
8/9/02 03:36:09 PM
PHARMACIST
for Anne Trontell

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

O *(Division/Office)*:
PSS/DSRCS
nne Trontell
eslie Stephens

FROM: HFD-540 Vickey Lutwak

ATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
ctober 21, 2002		NDA 19-821	MedGuide for SLR 006	September 27, 2002

AME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
oriatane(acitretin) capsules			

offmann-La Roche, Inc.

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
PROGRESS REPORT
NEW CORRESPONDENCE
DRUG ADVERTISING
ADVERSE REACTION REPORT
MANUFACTURING CHANGE/ADDITION
MEETING PLANNED BY

☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐~~NN~~ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

ATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

DISSOLUTION
BIOAVAILABILTY STUDIES
PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC REACTIONS (List below)
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

~~NN~~ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
~~NN~~ SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

OMMENTS/SPECIAL INSTRUCTIONS:

ease review and comment on the DRAFT MedGuide. The revisions are suggested by the sponsor, their comments to our draft. raft MedGuide and label attached to this consult form.

lso, as soon as the "formal" Med Guide comes in, we need to send a NEW consult to Anne Trontell's group to rmalize the MedGuide process here. It is just a formality, but to avoid confusion, please BE SURE to write on that "the language has already been recommended by Karen Lechter **when we changed format of PPI...please ee her consult dated July 26, 2002.**

ank you.

ie medical office is Kathryn O'Connell
ie project manager is Vickey Lutwak

NATURE OF REQUESTER key Lutwak, PM, HFD 540 7-2073	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
NATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Victoria Lutwak
10/2/02 08:52:09 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Office of Drug Safety
Karen Lecther for PPI

FROM: HFD-540 Vickey Lutwak

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 26, 2002		NDA 19-821	PPI for SLR 006	July 24, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Soriatane(acitretin) capsules			

Hoffmann-La Roche, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ ~~NN~~ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
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☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
~~NN~~ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
~~NN~~ SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and comment.
Thank you.
The medical office is Kathryn O'Connell
The project manager is Vickey Lutwak

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Vickey Lutwak, PM, HFD 540 7-2073	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Withheld Track Number: Administrative- 19-821
S002/S006

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/s/

Victoria Lutwak
7/25/02 03:48:17 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 26, 2002

FROM: Joyce Weaver, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

TO: Jonathan Wilkin, M.D., Director
Division of Dermatological and Dental Drug Products, HFD-540

SUBJECT: Office of Drug Safety Postmarketing Safety Review (PID # D020224)
Drug—Acitretin (Soriatane NDA 19-821)
Reaction: Cardiovascular and cerebrovascular events, congenital anomalies, pneumonitis, and psychiatric events

INTRODUCTION/ EXECUTIVE SUMMARY

A labeling supplement was submitted recently by the sponsor for acitretin. To assist in the review of this labeling supplement, the Division of Dermatological and Dental Drug Products requested a review of the adverse event experience with acitretin. We were asked to focus on cardiovascular, cerebrovascular, and psychiatric events, as well as reports of teratogenicity and pneumonitis.

In 2000 we reviewed cardiovascular events and suicide events occurring in association with etretinate and acitretin. This previous review is attached (Attachment 1).

For this consult, we searched the AERS database and the published medical literature using PubMed for cardiovascular, cerebrovascular, and psychiatric events, as well as reports of teratogenicity and pneumonitis. One case report of teratogenicity was found in the medical literature, but no cases were found in the literature for the other events. Therefore, except for teratogenicity, our review consists only of AERS cases.

Overall, AERS contains 463 reports for acitretin. The most frequently reported events are worsening of the skin condition, exfoliation, pruritus, headache, and abnormal liver function tests. These events are all expected events and are included in the labeling for acitretin.

We reviewed 72 cardiovascular and cerebrovascular cases, 7 cases of congenital anomalies, 2 cases of pneumonitis, and 46 psychiatric cases. The cardiovascular and cerebrovascular cases include dyslipidemias, ischemic heart disease, thromboembolic events, and two cases of valve disorders. The psychiatric cases included cases of depression, suicide-related events, and aggression. Our recommendations regarding these events are included in the table below.

Event	ODS recommendation
Dyslipidemias	No additional information needed in the labeling; topic for Patient information (Med Guide or Patient Package Insert [PPI])
Ischemic heart disease and thromboembolic events (including cerebrovascular events)	Add to *Adverse reactions* section; topic for patient information (Med Guide or PPI)
Cardiac valvulopathy	No information needed in the labeling
Congenital anomalies	Additional reporting of pregnancy exposures; topic for Patient information (Med Guide or PPI)
Pneumonitis	No information needed in the labeling
Depression, suicide-related events, aggression	Add to *Precautions* section; topic for Patient information (Med Guide or PPI)

DRUG INFORMATION/LABELING

Acitretin was approved 10/28/96 for the treatment of severe psoriasis, including erythrodermic and generalized pustular types, in adults. In females of reproductive potential, acitretin labeling states that acitretin should be reserved for patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

The labeling for acitretin contains a "black-box" warning regarding the teratogenic potential of acitretin. The "black-box" warning states that women of childbearing potential need to use two reliable forms of contraception simultaneously both during therapy and for at least 3 years *after* discontinuation of therapy.

The *Warnings* section of the labeling states the following regarding dyslipidemias (portions the sponsor proposes adding to the labeling are marked with underlining):

> ***Lipids:*** Blood lipid determinations should be performed before Soriatane is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40%. These effects of Soriatane were generally reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridemia included those with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions. Because of the risk of hypertriglyceridemia, serum lipids must be in high-risk patients and during long-term treatment.

Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with fatal fulminant pancreatitis. Therefore, dietary modifications, reduction in Soriatane dose, or drug therapy should be employed to control significant elevations of triglycerides. If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Soriatane should be considered.

The *Adverse events* section of the labeling for acitretin states that during clinical trials increased triglycerides occurred in 66% of patients and 33% of patients experienced increased cholesterol. Ischemic cardiac events, coronary artery disease, valvulopathy, and cerebrovascular accidents are not mentioned in the current labeling.

The *Adverse events* section of the labeling states that depression occurred in 1 to 10% of patients during clinical trials. Suicide-related events are not mentioned in the labeling.

Pneumonitis is not mentioned in the labeling.

DRUG USE

The following table shows the total projected acitretin prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S. from 1997 through 2001.[1]

Year	2001	2000	1999	1998	1997
Total SORIATANE prescriptions					

contains information about the patterns and treatment of disease mentioned during patient visits to office-based medical practitioners in the continental United States. of age have been prescribed approximately of the total prescriptions for acitretin since its approval.[2]

processed prescription claims for acit of the patients for whom processed claims during this period of time were female patients

See Attachments 2 and 3 for detailed information from [redacted]

OVERVIEW OF EVENTS

AERS contains a total of 463 cases of adverse events reported for acitretin. The most frequently reported events are listed below.

Condition aggravated-35	Pain Nos-15
Psoriasis aggravated-29	Pyrexia-15
Localized exfoliation-23	Dyspnea Nos-14
Pruritus Nos -22	Lip dry-14
Headache Nos -17	Blood triglycerides increased-12
Liver function tests abnormal-17	Dermatitis exfoliative Nos-12
Fatigue-16	Skin disorder Nos-12
Arthralgia-15	Blood creatinine increased-11
Depression-15	Psoriasis-11
Dry skin-15	Weight decreased-11
Nausea-15	

The most frequently reported events were worsening of the patient's skin condition, exfoliation, pruritus, headache, and abnormal liver function tests. Most of the cases in AERS originate in the United States (272). After the United States, cases were received most often from France (81), the United Kingdom (55), and Australia (11). Most cases report adverse events occurring in adults. As compared to female patients, a larger proportion of the adverse events in men occurred in patients 17 to 50 years of age. About 24% of reports for women occurred in patients 17 to 50 years of age compared to about 36% of reports for men occurred in patients 17 to 50 years of age. The following table shows the gender and age breakdown of the patients for whom adverse events have been reported for acitretin (information on age and gender are not available in all cases).

Age	Female	Male
0 to 16 years	5	7
17 to 50 years	49	89
> 50 years	118	109
Age unk	29	40

CARDIOVASCULAR and CEREBROVASCULAR EVENTS

Selection of Case Series

On June 3, 2002, we searched the AERS database for cases of cardiovascular and cerebrovascular adverse events reported for acitretin. The cases were identified using the system organ class (SOC) terms *Cardiac Disorders* and *Vascular Disorders,* and the

higher level group (HLGT) terms *Central Nervous System Vascular Disorders, Lipid Analysis,* and *Lipid Metabolism Disorders.*

AERS contained 144 cases. We excluded duplicate cases (8), and cases in which there was no cardiovascular or cerebrovascular adverse event (64). Ultimately, we included 72 cases in this case series.

Summary of Cases

Demographic data, outcomes, and summary information from the 72 cases are provided below.

Table 1. Demographic Data and General Summary Information—Cardiovascular and Cerebrovascular Cases	
Age in years (n=61)	Mean-54.1, median-53, range 7-83
Gender	Male-43; Female-28 total, female 15 to 45 years of age-6; Unknown-1
Indication	Psoriasis (type not stated in most cases)-49 Pityriasis rubra pilaris-3, Ichthyosis-2 Darier's Disease-1 Psoriatic arthropathy-1 Other or not stated-16
Time to onset (n=51)	Median- 97 days (range, 0 days to 10 years)
Event* (partial list-see Attachment 4 for a complete list of cardiovascular and cerebrovascular events)	Dyslipidemia –28 Ischemic heart disease/CAD-12 Pulmonary embolism-9 Cerebrovascular events-5 Congestive heart failure-4 Deep vein thrombosis-4
Daily dose (n=47)	Mean-27.5 mg; median-25 mg (range, 10 to 75 mg)
Report type	Periodic-19; Expedited-53
Reporting country	US-44 France-14 UK-8 Canada-2 Other non-domestic-4
Dechallenge	Positive dechallenge-11 Negative dechallenge-2 No dechallenge (acitretin continued despite development of adverse event)-12 Positive rechallenge-3
Serious Outcomes*	Death-8; disability-3; hospitalization-25; life-threatening-5

*more than 1/case possible

Cardiovascular or cerebrovascular adverse events were reported in 72 cases. Dyslipidemias, ischemic heart disease, embolic events, and cerebrovascular disease were the most commonly reported events. A valve disorder (unspecified type) was reported in one case, and mitral valve regurgitation was reported in another case. The patients averaged about 54 years of age and ranged from 7 to 83 years of age. The average daily dose of acitretin was 27.5 mg. The median time to onset was about 3 months, but the onset ranged widely from one dose (a case of paroxysmal atrial contractions) to 10 years (a case of hypertension, hypercholesterolemia, and hypertriglyceridemia) after starting therapy with acitretin. In 21 cases the patient had a diagnosis of a cardiovascular condition or diabetes before starting therapy with acitretin.

Eight patients died. One patient with necrotizing scleritis died after experiencing an unknown cardiac event. A second patient with congestive heart failure died from an unknown cause. The remaining patients died due to hepatic cirrhosis, multiple organ failure (2), myocardial infarction (2), and stroke.

Summary evaluations of the more common events are provided below. A complete listing of the cardiovascular events reported in the cases is included in Attachment 4.

1. Dyslipidemia

Twenty-eight patients experienced hypercholesterolemia (10), hypertriglyceridemia (12), or both hypercholesterolemia and hypertriglyceridemia (6). The median time to onset was 104 days. The highest serum triglyceride level reported was 1300 mg/dL, and the highest serum cholesterol reported was 261 mg/dL. Coronary artery disease was reported in two cases, both patients had hypertriglyceridemia.

Possible confounding factors in about half of the cases included increased hepatic transaminase levels (4), diabetes or hyperglycemia (3), pre-existing hypercholesterolemia or hypertriglyceridemia (3), hypothyroidism (2), nephrotic syndrome (1), and anti-rejection therapy for a transplanted heart (1).

In three cases, the reporter judged the event to be life-threatening, and in two additional cases the patients were hospitalized. One patient required coronary artery bypass grafting. Positive dechallenge was reported in six cases, and positive rechallenge was reported in three cases.

A case from the series is presented below.

AERS 3410494-6-00, MFR 210846 ✓, 1999
A 48-year-old woman with a prior history of diabetes was prescribed acitretin 40 mg daily for psoriasis. After about 2.5 months of therapy with acitretin, laboratory testing showed increased serum triglyceride levels of 356 mg/dL (normal 20-190) and increased blood glucose of 215 mg/dL. Acitretin was discontinued, and the serum triglyceride levels decreased (value not provided). Two months later acitretin was started again, and

the patient again experienced increased serum triglyceride levels (262 mg/dL) and increased serum cholesterol level (264 mg/dL). The degree of glucose control the patient had at the time of the positive rechallenge was not stated.

2. Ischemic heart disease/coronary artery disease

Twelve patients experienced ischemic heart disease or coronary artery disease. Possible confounding factors identified in the cases included a prior medical history of coronary artery disease (3), cigarette smoking (3), and a prior medical history of hypertension (1). Seven patients had myocardial infarctions after receiving acitretin for about 1 month to about 27 months. Five of the 7 patients experiencing myocardial infarction had risk factors for myocardial infarction other than the use of acitretin. Three of the patients died (2-myocardial infarction, 1-hepatic cirrhosis).

A case from the series is presented below.

AERS 3913784-3-00, MFR 312606, [redacted], 2001
A 44-year-old woman with a family history of heart disease and a 20-year history of cigarette smoking was prescribed acitretin 25 mg daily for psoriasis. This dose was later decreased to 25 mg three times weekly. After about 2 years of therapy with acitretin, laboratory testing showed increased serum cholesterol levels of 270 (units not stated), and the patient complained of shortness of breath, jaw "tightness," and decreased endurance. Diagnostic work-up established multiple-vessel coronary artery disease, and the patient had quadruple bypass surgery. Acitretin was discontinued.

3. Pulmonary embolism/deep vein thrombosis

Nine patients had pulmonary embolism (5) or lower extremity deep vein thrombosis and pulmonary embolism (4) while receiving acitretin. The median time to onset was about 3 months, but the time to onset ranged widely from about 5 days to over 3 years. Most (7) of the patients were men. One patient was on warfarin for an unknown reason. A second patient had a prior medical history of atrial fibrillation. A third patient was receiving low molecular weight heparin for a leg fracture at the time he experienced the pulmonary embolism. The patients were hospitalized and recovered. No patient in this case series died.

A case from the series is presented below.

AERS 3447030-0-00, MFR 225310, UK, 2000
A 29-year-old man was prescribed acitretin 25 mg daily for psoriasis. He was receiving acetaminophen, methoxsalen, nizatidine, propoxyphene, and sumatriptan concomitantly. After receiving acitretin for 55 days, he experienced multiple pulmonary emboli. He was admitted to the hospital and acitretin was discontinued. After receiving unspecified treatment, the pulmonary emboli resolved.

4. Cerebrovascular events

Five patients had cerebrovascular events. These events included three cerebrovascular accidents, a transient ischemic attack, and a cerebral bleed. Three women 52, 71, and 73 years of age experienced cerebrovascular accidents, a man of unknown age experienced a transient ischemic attack, and a 14-year-old girl experienced cerebral bleeding while receiving acitretin. Two of the women who experienced cerebrovascular accidents had significant prior medical histories (diabetes and arteritis in one patient and thrombocytosis in the second patient). Time to onset of CVA was reported in only one case (113 days).

A case from the series is presented below.

AERS 3640179-2-00, MFR PHRM2000FR01917, France, 2000
A 52-year-old woman was prescribed acitretin at an unknown dose for an unknown indication. She was receiving anafranil (co-suspect) concomitantly. After receiving acitretin for an unknown period of time, she experienced a CVA in the left posterior inferior cerebellar artery. She was admitted to the hospital and acitretin was discontinued. After receiving unspecified treatment, the patient recovered.

CONGENITAL ANOMALIES

Selection of Case Series

On June 3, 2002, we searched the AERS database for cases of congenital anomalies reported for acitretin. The cases were identified using the SOC terms *Congenital, Familial and Genetic Disorders*, and *Pregnancy, Puerperium and Perinatal Conditions*, the HLGT terms *Congenital Ear Disorders (Excl Deafness)*, *Musculoskeletal and Connective Tissue Disorders Congenital*, *Congenital Cardiac Disorders*, *Congenital Eye Disorders (Excl Glaucoma)*, *Congenital and Peripartum Neurological Conditions*, and *Congenital Respiratory Tract Disorders*, and the higher level term (HLT) *Congenital Gastrointestinal Malformations*. AERS contained 15 cases. We excluded duplicate cases (4) and cases in which there was no congenital anomaly (5). Additionally, we included a case found in the published medical literature that was not in AERS. Ultimately, we included 7 cases in this case series.

Summary of Cases

In a case in the published medical literature, a 34-year-old woman was treated with 50 mg acitretin daily for 9.5 weeks for palmoplantar epidermolytic keratoderma. Prior to beginning acitretin she had a negative urinary pregnancy test; however, it was later learned that she had conceived about 10 days prior to starting acitretin. An elective abortion was performed. The fetus had severe congenital anomalies, including severe symmetric anomalies of the upper and lower limbs, and craniofacial anomalies. Both arms were short with pterygium formation in the elbows. The thumbs and little fingers were short, and they did not contain nails. The lower extremities had contractures in the groin and knees. The feet were shaped into points and had only two small toes without

nails. The maxilla and mandibula were underdeveloped. The external ears were abnormal, with low-set ears, and there was agenesis of the external ear canals.[4]

Similar to the case in the published literature, two of the cases in AERS had abnormalities of the extremities and craniofacial abnormalities (cases 1 and 2, below). Although the timing of the use of acitretin with conception was not clear in these cases, these anomalies may be attributable to acitretin.

In two of the cases in AERS, conception was 3.6 years and 2 years after acitretin was discontinued (cases 3 and 4 below). An infant who was conceived 3.6 years after acitretin was discontinued had agenesis of the toes. Because conception occurred over 3 years after the mother last took acitretin, it is not clear that the abnormality in this infant was attributable to acitretin. The other infant developed diabetes at 3 months of age (conception 2 years after acitretin was discontinued).

In the final two cases in the series, mothers experienced a spontaneous abortion and an ectopic pregnancy. The role acitretin played in these events is not clear.

The six AERS cases are presented below.

1. AERS 3071685-X-00, MFR 8-98107-041A, UK, 1998
   A 33-year-old woman was prescribed acitretin at an unknown dose for an unknown indication. The woman received acitretin, cyclosporine, loratadine, and methotrexate during her pregnancy. The timing of drug intake with conception was not stated. An ultrasound showed the fetus had bent forearms with bones missing, brachycephaly, depressed nasal bridge, short right femur, and bowing of both femurs. An elective abortion was performed at 20 weeks gestation.

2. AERS 3282258-78-00, MFR 8-99153-142A, France, 1999
   An 18-year-old woman received acitretin (dose unknown) for Darier's Disease. She was taking levonorgestrol and ethinyl estradiol oral contraceptive concomitantly. The woman experienced an unintended pregnancy. The timing of conception with her use of acitretin was not stated. An elective abortion was performed at 21 weeks of amenorrhea. The fetus was a hypertrophic female with multiple congenital anomalies including facial dysmorphism with hypertelorism, and a long philtrum, and malposition of the right foot.

3. AERS 3076965-X-00, MFR 98162, France, 1998
   A woman (age unknown) with a prior medical history of spontaneous abortion became pregnant about 3 ⅔ years after discontinuing treatment with acitretin. The dose, duration of therapy, indication for use of acitretin, and ethanol history are not known. The woman's baby was born with agenesis of the toes.

4. AERS 3176767-X-00, MFR 109444, France, 1998
   A woman (age unknown) was prescribed an unknown dose of acitretin for psoriasis unresponsive to PUVA therapy and other unspecified "local" treatment. She became

pregnant 2 years after discontinuing acitretin. She gave birth to a baby boy who developed severe diabetes at 3 months of age. The baby reportedly reoovered after receiving unknown therapy.

5. AERS 3417724-5-00, MFR 216524, France, 1999
   A woman of unknown age was prescribed acitretin 10 mg alternating with 25 mg for psoriasis. The woman was taking levonorgestrol and ethinyl estradiol oral contraceptive concomitantly. She smoked cigarettes, but she denied use of ethanol. She had a past medical history of deep vein thrombosis, and she had recently intentionally lost 15 kg of body weight over a 2-to-3 month period. She stopped taking her oral contraceptive for an unknown reason and became pregnant. She experienced a spontaneous abortion at 8 weeks of amenorrhea.

6. AERS 3652698-3-00, MFR 252851, France, 2001
   A woman of unknown age was prescribed acitretin at an unknown dose for an unknown indication. She took acitretin for about 10 years. She became pregnant 2 weeks after discontinuing acitretin. She experienced an ectopic pregnancy.

PNEUMONITIS

Two reports representing one case (MCN 95073) of pulmonary alveolitis were located in AERS using the term (HLT) *Lower respiratory tract inflammatory and immunologic conditions.* A 67-year-old male patient in France with a history of rhinitis, diabetes, hypertension, and hypercholesterolemia developed pulmonary alveolitis confirmed by computed tomography (CT) scan after taking acitretin 25 mg daily for 45 days to treat psoriasis. Acitretin was continued, and the event resolved spontaneously.

An additional case (provided by the medical officer) was coded nonspecifically in AERS with the terms *Pneumonia NOS* and *Lung disorder NOS.* The patient was a 74-year-old woman with a prior history of interstitial pneumonopathy (IP) who developed an episode of IP when she began taking acitretin. She was hospitalized and treated with systemic corticosteroids. The final outcome of the case was not reported.

PSYCHIATRIC EVENTS

Selection of Case Series

On May 23, 2002, we searched the AERS database for cases of psychiatric adverse events reported for acitretin. The cases were identified using term (SOC) *Psychiatric Disorders.* AERS contained 68 cases. We excluded duplicate cases (5), cases in which there was no psychiatric adverse event (14), cases reporting insomnia only (2), and a case in which the psychiatric signs and symptoms were likely due to severe intercurrent physical illness (1). Ultimately, we included 46 cases in this case series.

Summary of Cases

Demographic data, outcomes, and summary information from the 46 cases with psychiatric adverse events are provided below.

Table 1. Demographic Data and General Summary Information—Psychiatric Cases	
Age in years (n=39)	Mean-51.3, median-50, range 16-88
Gender	Male-19; Female-25 total, female 15 to 45 years of age-8; Unknown-2
Indication	Psoriasis (type not stated in most cases)-36 Darier's Disease-3 Ichthyosis, keratoacanthoma, keratosis, Mucha-Habermann disease, pityriasis rubra pilaris-1 case each Not stated-2
Time to onset (n=31)	Median- 64 days (range, 7 days to 8 years)
Event (partial list-see Attachment 5 for a complete list of psychiatric events)	Depression-18 Suicidal ideation, suicide attempt, completed suicide-5 Aggressive behavior-5 Confusion-5 Memory loss-4 Psychosis-3 Hallucinations-2
Daily dose (n=32)	Mean-24.7 mg; median-25 mg (range, 4.2 to 50 mg)
Report type	Periodic-15; Expedited-31
Dechallenge	Positive dechallenge-10 Negative dechallenge-1 No dechallenge (acitretin continued despite development of adverse event)-12 Adverse event developed after acitretin discontinued-4 Positive rechallenge-1
Prior psychiatric history	Positive-17; Negative-2; Unk-27
Serious Outcomes*	Death-2 (1 suicide, 1 death due to pulmonary disease); disability-3; hospitalization-8
*more than 1/case possible	

Psychiatric adverse events possibly related to the use of acitretin were reported in 46 cases. The patients averaged about 51 years of age and ranged from 16 to 88 years of age. The average daily dose of acitretin was 25 mg. The median time to onset was about 2 months, but the onset ranged widely from a week to 8 years after starting therapy with acitretin. In eight cases the patient had prior use of another retinoid drug.

The most frequently reported adverse events were depression (18) and suicide-related events (5). Aggressive behavior (5), confusion (5), memory loss (4), psychosis (3), and hallucinations (2) were reported. A complete listing of the psychiatric events reported in

the cases is included in Attachment 5. In 17 cases, the patient's prior medical history includes a psychiatric diagnosis, most often depression (13). In one case reporting confusion, a possible medical basis (anemia) for the adverse event was present.

Suicide-related events occurred in five cases. In two of the cases reporting suicide-related events, the patient had a previous psychiatric history, in two cases, a previous psychiatric history was denied, and in one case the previous psychiatric history was not stated. The five suicide-related cases are presented in Attachment 6.

Aggression was reported in five cases. Only one patient had a prior history of aggressive behavior. The manifestation of aggression was not detailed in four of the cases. One patient started fires after using acitretin for over 4 years. One case reported two positive dechallenges and a positive rechallenge.

Two cases from the psychiatric case series are presented below.

1. AERS 3213754-7-00, MCN 95797, [illegible], 1999
   A 50-year old woman with a previous history of depression with use of isotretinoin, was prescribed acitretin for Darier's Disease. She did not use ethanol. She developed severe depression after using acitretin 25 mg daily for 2.5 months. She had crying spells, and she was unable to get out of bed. The patient adjusted the dose to 12.5 mg every other day and the depression resolved.

2. AERS 3902127-7-00, MCN 307880, France, 2002
   A 52-year-old woman with no prior medical history was prescribed acitretin at an unknown dose for psoriasis. After taking acitretin for 10 days she experienced aggression (manifestation not stated). After 6 weeks of therapy, acitretin was discontinued, and the aggression resolved. Three years later the patient used acitretin again. After taking acitretin for 10 days she experienced aggression again. Acitretin was discontinued and the aggression resolved. Two years later the patient used acitretin again. After 11 days of therapy she experienced severe depression. Acitretin was discontinued and she received treatment for depression, and the depression resolved.

DISCUSSION/ CONCLUSION

Overall, AERS contains 463 reports for acitretin. The most frequently reported events are worsening of the skin condition, exfoliation, pruritus, headache, and abnormal liver function tests. These events are all expected events and are included in the labeling for acitretin.

Cardiovascular and cerebrovascular events

We reviewed 72 cases reporting cardiovascular and cerebrovascular events. Dyslipidemias, ischemic heart disease, and embolic events were the most frequently reported events. The potential to develop dyslipidemias is included in the *Warnings* section of the labeling. We believe the information in the *Warnings* section of the

labeling adequately warns the healthcare practitioner regarding dyslipidemias. However, although the *Warnings* section states that dyslipidemias may increase a patient's cardiovascular risk, the *Adverse reactions* section does not state that ischemic events have occurred with the use of acitretin. Although many of the patients in the AERS cases reporting ischemic events had cardiac risk factors in addition to the use of acitretin, we believe it is appropriate to add the postmarketing experience related to these events to the *Adverse reactions* section of the labeling. Likewise, we suggest adding thromboembolic events, including cerebrovascular events, to this section of the labeling. Finally, we suggest that dyslipidemias, ischemic heart disease, and embolic events be included in information provided to the patient (Med Guide or PPI).

AERS contains one case of an unspecified valve disorder, and one case of mitral valve regurgitation reported for acitretin. We do not believe these cases warrant inclusion of valvulopathy in the labeling.

Congenital anomalies

We attempted to match the cases in AERS with cases in the sponsor's submission; however, we were not able to match all of the cases. When comparing data from AERS with postmarketing safety data submitted by a sponsor, it should be kept in mind that usually it is not possible to match each case submitted by the sponsor with a case in the AERS database. After a drug is no longer a new molecular entity, only a subset of the reports (those with serious outcomes) submitted in the periodic safety report are entered into AERS. Secondly, the sponsor may have a waiver for submission of non-serious labeled events. Finally, only a subset of adverse events from foreign countries must be submitted to the FDA. Cases originating in foreign countries reporting labeled congenital anomalies with use of acitretin need not be submitted to AERS.

The sponsor's database contains 16 birth defects associated with maternal use of acitretin, only one of which was also contained in AERS. The AERS database contained six cases, five of which were not in the sponsor's submission. All of the cases in the sponsor's database originated in foreign countries. Only foreign cases reporting unlabeled events need to be reported to AERS. Therefore, only one of the 16 cases in the sponsor's database is contained in the AERS database. This case was the case of the baby with agenesis of the toes born to a mother who had used acitretin 3.6 years prior to conception. Apparently, this event was classified as an unlabeled event, and thus reported to AERS. Of the remaining five cases in AERS, two were reported by other pharmaceutical companies because other drugs were suspected as causing the event (methotrexate and a birth control pill). Two of the remaining three cases in AERS did not result in birth defects, but rather resulted in spontaneous abortion and ectopic pregnancy (and therefore were not included in the sponsor's submission as birth defects). Additionally, the sponsor may not have regarded the final case, a case of diabetes in an infant, as a birth defect.

We reviewed 7 cases of congenital anomalies reported for acitretin (6 AERS, 1 literature report). Three of the cases reported extremity and craniofacial abnormalities. These cases demonstrate severe anomalies that are known to occur when fetuses are exposed to acitretin. A fourth case reported agenesis of the toes. The pregnancy resulting in agenesis

of the toes occurred over 3 years after acitretin therapy had stopped. The long delay between the use of acitretin and conception makes it less likely that the anomaly resulted from exposure to acitretin. However, if this anomaly was due to the exposure to acitretin, its development long after acitretin use by the mother is concerning.

Data from [redacted] show that there is small but significant use of acitretin among women [redacted] years of age. [redacted] suggest that about [redacted] of the total use of acitretin occur in this group. [redacted] database suggest that about [redacted] of the total use of acitretin occur in this group. The sponsor has submitted information suggesting that about 15% of the use of acitretin may occur in women of childbearing potential.[5]

The labeling supplement shows that the sponsor has received 152 prospective reports of maternal exposure to acitretin from foreign countries, as compared to only six prospective reports from the United States.[6] As stated by the sponsor in the labeling supplement, "Prospective follow-up and ascertainment of pregnancy outcomes in reports of accidental or necessary pregnancy exposure is still the best method [of studying the possible effects on the offspring of maternal drug exposure during pregnancy]."[7] Because it is unlikely that all pregnancy exposures and congenital anomalies have been captured by the combined databases of the sponsor and the FDA, we believe additional work should be undertaken by the sponsor to establish the extent of US pregnancy exposures. We suggest that all pregnancy exposures be reported to the Agency on an expedited basis. Additionally we suggest that the sponsor report annually on cumulative pregnancy exposures.

Pneumonitis

AERS contains only two cases of pneumonitis reported for acitretin. We do not believe these cases warrant inclusion of pneumonitis in the labeling.

Psychiatric events

We reviewed 46 psychiatric cases. The most frequently reported adverse events were depression and suicide-related events. Five cases of aggressive behavior were reported. Depression is listed in the *Adverse Events* section of the labeling. However, this event is only listed in a table of adverse events observed in clinical trials. Suicide and aggression are not mentioned in the labeling. Psychiatric adverse events are known to occur with retinoid therapy. We suggest elevating depression to the *Precautions* section of the labeling, and including the postmarketing experience of depression, suicide, and aggression. Additionally, we suggest that information on depression, suicide, and aggression be included in information provided to the patient (Med Guide or PPI).

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3.
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7. Hoffman La Roche, Acitretin Labeling Supplement S-005, 5/2002; vol 2: 135.

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Attachment 1–2000 Review of Cardiovascular and Suicide Events for Etretinate and Acitretin

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Claudia B. Karwoski, Pharm.D.
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Division of Drug Risk Evaluation I, HFD-430

THROUGH: Peter Honig, M.D., M.P.H., Acting Director
Division of Drug Risk Evaluation I, HFD-430

TO: Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: OPDRA Postmarketing Safety Review (PID 99222)
Products: Etretinate (Tegison NDA 19-369)
Acitretin (Soriatane NDA 19-821)
Reaction: Cardiovascular and Suicide Events

EXECUTIVE SUMMARY

A review of the Adverse Event Reporting System (AERS) and the published medical literature was conducted to provide a broad overview of cardiovascular events and suicide events occurring in association with etretinate and acitretin use.

Four cases of suicide-related events were evaluated, three involving suicide attempt and one case of suicide-accomplished (acitretin-3, etretinate-1). Although the cases were temporally related to the use of either acitretin or etretinate, previous depression and concomitant isotretinoin potentially confounded one case. The remaining cases did not appear to have any confounding factors however these cases lacked clinical details of the event including the method of suicide-related events and whether the event resolved after discontinuation. Based on the small number of cases and the reasons cited above, we would recommend continued close monitoring of this event at this time.

We evaluated 74 cases involving cardiovascular events reported with the use of either etretinate (62) or acitretin (12). The major categories of events include cardiac cerebrovascular events (19), miscellaneous non-cardiac thrombotic or embolic events

(20), ischemic events (11), cardiomyopathy (4), heart failure (5), cardiac rhythm disturbances (12), and miscellaneous cardiac events (3). Causality was difficult to determine in these cases because baseline cardiac work up was not conducted prior to initiating therapy and some patients (20%) had been receiving either product for greater than one year which makes a temporal relationship questionable. Additionally, many of the patients had a past cardiac history, cardiac risk factors, or possibly underlying previously undiagnosed significant cardiovascular disease or other medical conditions that may have contributed to the cardiovascular event. For the reasons stated above, we couldn't conclude with any certainty that the cardiovascular related events were directly associated with the use of either etretinate or acitretin based on post-marketing adverse event reports.

INTRODUCTION

On July 15, 1999, Dr. Kathyrn O'Connell submitted a consult request to review the post-marketing data for all cardiovascular and suicide-related adverse event cases associated with etretinate and acitretin. This information is being requested because of a recent review of a final study report submitted by the sponsor. The events included suicide in three patients, and 22 cardiovascular related deaths.

Both products are systemic retinoids used in the treatment of severe psoriasis and manufactured by Roche Pharmaceuticals. The FDA approved Acitretin on October 28, 1996. Etretinate has been approved since September 30, 1986 but is no longer marketed. The Etretinate IND was withdrawn on November 5, 1998.

The safety of the two products is thought to be the same, except for possible increased risk of teratogenicity with etretinate due to its longer half-life. Additionally, acitretin is converted to etretinate if alcohol is consumed. Although etretinate is no longer marketed in the US, the cardiovascular and suicide related events are being reviewed in both products because of their similarity.

The current labeling for acitretin in the *warnings* section under *Lipids* states that hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. Suicide is not included in the product label. The following events are listed in the *adverse events* section:[1]

- In the cardiovascular section of the table lists flushing (1-10%), chest pain, cyanosis, increased bleeding time, intermittent claudication, and peripheral ischemia (< 1%). Edema is included in the body as a whole section of the table.
- Depression is included in the psychiatric section of the table (1-10%).

DRUG USE

The following table summarizes projected total prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S. The table is

distributed by calendar years from 1993 through 1999. This informatio

Total prescriptions (in thousands)	1999	1998	1997	1996	1995	1994	1993	Total
Acitretin								
Etretinate								

The total projected prescriptions dispensed since 1993

MEDICAL LITERATURE

A MEDLINE search of the English-language literature published from 1966 to 1999 was performed. The MESH terms *etretinate* and *acitretin* with the major qualifier adverse effects was used. This search resulted in no case reports of suicide or serious cardiovascular events. There were two case reports of severe edema associated with etretinate.

SUICIDE RELATED ADVERSE EVENTS

Selection and Summary of Suicide Cases

AERS was searched on January 4, 2000 under the higher level term (HLT) "suicidal or self-injurious behavior", reported with acitretin and etretinate. Three cases of suicide attempt and one case of suicide-accomplished were identified.

Demographics of Suicide Related Cases

Age in years:	32 and 59 years old (Unknown-2)
Gender:	Male (2), Female (2)
Outcome:	Died (1), Medically Significant (3)
Time to onset:	Range 2 to 7 months
Product:	Etretinate (1), Acitretin (3)
Year:	1996 (1), 1999 (3)
Country:	US (4)

All cases were temporally associated with the use of either etretinate or acitretin. The time to the suicide event after initiating therapy was two to seven months. However, one patient had reportedly taken etretinate intermittently for years. Previous isotretinoin use and a history of depression confounded the suicide-accomplished case. The other three cases did not report a previous history of depression. None of the patients had a reported previous history of suicide attempt or suicidal ideation. All cases are described below.

AERS 3170613-6-00, MFR 103161 \ 1998 - A 59-year-old female was prescribed acitretin 25mg daily for psoriasis. During her three-month acitretin course she experienced pruritus, cheilitis, and hair loss. She decided to discontinue therapy. One

month after discontinuing therapy she reported that she attempted suicide. The method of suicide attempt was not reported. She also voiced suicidal ideation with the intent to overdose with alprazolam. She had no reported past psychiatric history. On follow up, the patient reported additional events to include hemorrhoids, panic attacks, depression, and worsening hypercholesteremia. The report also stated that she had taken an overdose of vitamin A, however it is not known if the overdose was the suicide attempt.

AERS 3107876-9-00, MFR 102836, — 1998 - A male patient (age unknown) committed suicide approximately two months after initiating therapy with acitretin for keratoacanthoma. He had previously taken isotretinoin and possibly etretinate for the same indication however the therapy dates are unknown. His past medical history includes a depressive disorder that had not being treated and anger because of his underlying, "disfiguring" skin condition. His method of suicide was not specified.

AERS 3204458-5-00, MFR 113281, UK, 1999 - A female patient (age unknown) experienced depression, paranoia, mood swings, and attempted suicide three times within three to four months of initiating therapy with acitretin. She did not have a history of depression prior to acitretin. Her physician started her on fluoxetine which she discontinued taking after six days. At the time of the report, paranoia was persisting. It is unknown what method of suicide was attempted, whether she was hospitalized for the suicide attempts, or whether she continued acitretin.

AERS 1832445, MFR 60991, — 1996 - A 32-year-old male patient attempted suicide approximately seven months after initiating therapy with etretinate 25mg daily for Darier's disease. The attempt was described as an overdose of etretinate of 100-25mg capsules. He went to the emergency room were he was administered an unknown nausea medication. Laboratory workup included a CBC, LFTs, and urinalysis (results not provided). He was not admitted to the hospital. On another unknown date, he presented with increased anger. Approximately two weeks after the suicide attempt, he was reported to be fine. He had been prescribed etretinate intermittently for five years prior to the event. His past history includes alcoholism and drug addiction, none for six years prior to suicide attempt.

Conclusion of Suicide-related Cases

Four cases of suicide-related events were evaluated, three involving suicide attempt and one case of suicide-accomplished (acitretin-3, etretinate-1). Although the cases were temporally related to the use of either acitretin or etretinate, previous depression and concomitant isotretinoin potentially confounded one case. The remaining cases did not appear to have any confounding factors however these cases lacked clinical details of the event including the method of suicide attempt and whether the event resolved after discontinuation. Based on the small number of cases and the reasons cited above, we would recommend continued close monitoring of this event at this time.

CARDIOVASCULAR ADVERSE EVENTS

Selection of Cardiovascular Cases

As of December 23, 1999, AERS was searched to identify all cardiac and vascular thrombotic, embolic, or hemorrhagic events under the following search terms:

- SOC term "cardiac disorders"
- HLT "central nervous system vascular disorders", "central nervous system haemorrhages and cerebrovascular accident", "cardiovascular embolism, thrombosis, and stenosis, "peripheral embolism, thrombosis, and stenosis", "embolism, thromboembolism, and stenosis non-site specific", and "peripheral vascular disorders NEC"
- PT "pulmonary embolism", "thrombosis NOS", "thrombophlebitis deep", "transient ischemic attack", and "vena cava embolism"

A total of 211 reports were identified, representing 200 unduplicated cases. A total of 126 cases were excluded from further analysis for the following reasons:

Events are labeled	48
Symptoms related to non-CV event or underlying disease	23
Insufficient information to determine causality	24
Probably not related	13
Event reported was confounded by pre-existing disease	9
Not a cardiac or vascular thrombotic/embolic event	4
Cardiac disorder was part of PMH and not reported event	3
Congenital cardiac anomaly or events related to teratogenicity	2

Specific reasons or details for exclusion are provided as attachment 1.

SUMMARY OF CARDIOVASCULAR EVENTS (74)

The major categories of cardiovascular events include cerebrovascular events (19), miscellaneous vascular thrombotic or embolic events (20), cardiac ischemic events (11), cardiomyopathy (4), heart failure (5), rhythm disturbances (12), and miscellaneous cardiac events (3).

Demographics of Cardiovascular Cases

Age in years:	Range 10 to 81 years old, mean 54, median 56 < 30 (4), 30-39 (7), 40-49 (15), 50-59 (16), 60-69 (17), > 70 (13)
Gender:	Male (37), Female (36), Unknown (1)
	Outcome: Died (13), Hospitalized (43), ER Treatment (2), Disability (1), Required Intervention (19), Resolved (2), Medically significant (1), unknown (1)
Onset:	Range 1 day to many years (unknown-9)
Product:	Etretinate (62), Acitretin (12)

Year: 1981 (1), 1982 (1), 1983 (3), 1984 (3), 1985 (2), 1986 (5), 1987 (10), 1988 (11), 1989 (2), 1990 (1), 1991 (1), 1992 (5), 1993 (6), 1994 (2), 1995 (3), 1996 (2), 1997 (7), 1998 (8), 1999 (1)
Country: US (45), United Kingdom (9), France (4), Germany (3), Norway (3), Finland (2), Japan (2), Sweden (2), Switzerland (2), Australia (1), Netherlands (1)

The ages of the patients ranged from 10 to 81 years of age. Eleven patients were less than 40 years old. Overall most of the events were reported with etretinate. Many of the cases were relatively old so it wasn't feasible to attempt to follow up with the reporter. There appeared to be no consistency with respect to time to onset, which ranged from days of use to many years of use. There were 14 cases with the onset reported after greater than one year of therapy with either etretinate or acitretin.

The outcomes associated with these events were serious, however, in many of these cases causality was difficult to determine because baseline cardiac work-up was not conducted prior to initiating therapy with either etretinate or acitretin. Additionally many of the cases involved patients that had a history of cardiac risk factors or a history of cardiac disease. These cases were included in the evaluation because the role of either of these two products could not be excluded.

Of the 13 death cases, four occurred in young patients with no known cardiovascular risk factors or history of cardiovascular disease. The remaining death cases occurred in mostly older patients with significant health problems. Below is a brief summary of the four death cases.

- One case involving a 26-year-old female who had a possible history of Marfan's Syndrome. This condition may involve connective tissue changes in the cardiovascular system.[2] She died of cardiac arrest approximately six months after starting etretinate. An autopsy result however was negative for this disorder.
- A 10-year-old female was diagnosed with cardiomyopathy two weeks after a two-week course of etretinate. She died one month later. This case is also described under the cardiomyopathy section.
- Two patients died of pulmonary embolism, a 19-year-old female and a 43-year-old male. The latter case did not provide clinical details. The first case was possibly confounded by Laurence-Moon-Biedl syndrome (mental retardation, retinitis pigmentosa, hypogonadism, obesity – according to report). The reporter stated that she might have been predisposed secondary to immobilization.

The 74 cases are summarized by major category under what appeared to be the most serious disorder.

1. Cerebrovascular Events (19)

Nineteen cases were evaluated (US-9, foreign-10). All but one case was reported with etretinate. The reported events include stroke or cerebrovascular accident (10), cerebral infarction (3), cerebral insult or ischemia (2), transient ischemic attack (2), and

intracranial hemorrhage (2). The ages ranged from 34 to 77 years old with a median of 59 and a mean of 53 years old (male-7, female-12).

The time to onset ranged from one week to 56 weeks with an average of 14 weeks of product use. The doses ranged from 20 to 100mg/day for etretinate and 10mg/day for acitretin. The outcomes include five deaths, nine hospitalizations, and two patients that reportedly suffered a disability. Dechallenge information was not reported in most cases however three reported patient improvement with discontinuation and one reported improvement without discontinuation of the product.

One or more of the following predisposing factors potentially confounded eleven cases: concomitant use of oral contraceptives, smoking, hypertension, presence of pre-existing serious cardiovascular medical problems, and diabetes mellitus. In addition to other predisposing factors, two patients had documented serum cholesterol elevation. The information contained in the remaining eight cases without identifiable predisposing factors was not sufficient to determine the nature of the underlying event in most of the cases. Of the eight cases three were US cases. One case is described below for your review.

AERS 776993, MFR 910201241001 / **1991** - A 35-year-old female suffered bilateral intracranial hematomas approximately one year after initiating therapy with etretinate. She was initially receiving a dose of 100mg per day, which was decreased to 25mg per day five months prior to the event. Past medical history was only significant for peptic ulcer disease and previous systemic steroid treatment. An angiogram was performed which showed no A-V malformation. At the time of the report she was improving.

2. Miscellaneous Thrombotic and Embolic Events

Twenty cases were evaluated (US-10, foreign-10). Seventeen cases were reported with etretinate and three with acitretin. One patient was receiving both etretinate and acitretin. The reported events include pulmonary embolism (13), deep vein thrombosis (2), arterial and venous thrombosis (1), right brachial embolus (1), leg thrombosis (1), and thrombophlebitis (2). The outcomes include three deaths, 16 hospitalizations, one disability, one that required intervention, and one that whose outcome was not reported.

One reporter attributed pulmonary embolism to a possible drug interaction between acenocoumarol and etretinate. He had experienced a DVT during the course of a hospitalization for the treatment of a cerebral abscess.

One or more of the following predisposing factors potentially confounded fourteen cases: immobilization due to recent hospitalization or surgery, recent leg injury, history of DVT, restrictive lung disease, congestive cardiomyopathy, sepsis, chronic leukemia, obesity, lymphoma, artherosclerosis, arrhythmia, and Laurence-Moon-Biedl Syndrome. Two had documented serum cholesterol or triglyceride elevation. The information contained in the five of the remaining six cases without identifiable predisposing factors were not

sufficient to determine the nature of the underlying event. The best representative case is described below for your review.

AERS 2045155, MFR 76403, ~ 1997 - A 76-year-old female experienced a deep vein thrombosis approximately three weeks after starting therapy with etretinate. Past medical history was not reported except for elevated cholesterol of 208. She was admitted with leg pain and fever and anticoagulants were initiated. She remained hospitalized for approximately one month and recovered. Etretinate was not rechallenged.

3. Rhythm Disturbances (12)

A total of 12 cases were evaluated (acitretin-3, etretinate-9). The reported diagnosis includes atrial fibrillation (3), premature ventricular contractions (PVC) (4), premature atrial contraction (2), tachycardia (1), unspecified arrhythmia (1), and cardiac arrest (1). The ages ranged from 26 to 77 years old (male-3, female-9). The time to onset ranged from one day to and 25mg/day for acitretin. The outcomes include one death, three hospitalizations or emergency room visits, and nine patients requiring other medical intervention. The events resolved with discontinuation of three patients and one patient's event resolved without discontinuation.

The temporal relationship was questionable in three cases. In two cases, the rhythm disturbance continued 2 to 6 months after the discontinuation of etretinate. It is unclear if this is secondary to the long half-life of the drug or it may represent a previously undiagnosed cardiac arrhythmia unrelated to etretinate. In one case, the rhythm disturbance resolved without discontinuation of etretinate.

Five patients had either a past medical history of cardiovascular disease or possible underlying disease, which may have contributed to the event. A 26-year-old female with Marfan syndrome suffered cardiac arrest and died 4 ½ months after initiating therapy with etretinate. Four patients had possible underlying cardiovascular disease (irregular heartbeat, palpitations, previous coronary artery bypass graft, and unspecified CV disease). There were four cases that did not appear to have any underlying cardiac disease or other contributing factors. Two of these cases are described below.

AERS 533876, MFR 880200022001, >, 1987 - A 60-year-old female was placed on etretinate 25mg daily for the treatment of psoriasis. Approximately one month later, her dose was increased to 50mg per day. At about the same time she began to experience PVC's. Her past medical history was significant for elevated lipids and she was receiving no concomitant medications. The treatment was not reported, however etretinate was discontinued. On follow up the event had completely resolved.

AERS 534728, MFR 870200459001, ~, 1987 - A 38-year-old male developed a rapid heart rate diagnosed as atrial fibrillation approximately four months after initiating therapy with etretinate (0.75mg/kg/day, wt not reported). He was treated in the emergency department with digoxin and verapamil and etretinate was discontinued. He reportedly restarted etretinate and had an abnormal echocardiogram. Additionally he had

elevated liver function tests so etretinate was discontinued again. A third course was initiated several months later. The patient reportedly was maintained on verapamil and digoxin with no recurrent episodes of atrial fibrillation. His past medical history was significant for IDDM and he was only receiving insulin prior to initiating etretinate.

4. Cardiac Ischemic Events or Coronary Artery Disease (11)

A total of 11 cases were evaluated (acitretin-3, etretinate-8). The reported diagnosis includes myocardial infarction (6), angina (2), coronary disease (1), coronary occlusion (1), and coronary atheroma and heart valve disorders (1). The ages ranged from 34 to 59 years old (male-8, female-3). The time to onset ranged from 27 days to four years of etretinate or acitretin use. Sixty percent occurred in patients taking the medication for greater than one year. The doses ranged from 25-150mg/day for etretinate and 10-50mg/day for acitretin. The outcomes include two deaths and eight hospitalizations. The outcome of one patient was not specified.

Cardiac risk factors or other predisposing factors were identified in nine patients. Three patients had a smoking history, which may have put them at risk for a cardiac event. One patient had low hemoglobin and suffered a myocardial infarction. Six patients had hypercholesterolemia or hypertriglyceridemia at the time of the event that was possibly (4) or probably (2) related to either etretinate or acitretin. Normal baseline lipid levels were reported in two of the six cases. The other three did not report baseline levels so it difficult to determine if the lipid abnormalities were secondary to the etretinate. Only one of the six patients had other possible cardiac risk factors (family history of heart disease and history of ventricular tachycardia).

There were two cases with no apparent risk factors; one was a poorly documented case of a 34-year-old male who was hospitalized for angina. He was diagnosed two years prior with angina (while receiving etretinate). The other case without apparent risk factors and one case associated with hypertriglyceridemia are described below for your review.

AERS 580268, MFR 870201537001, 1987 - A 53-year-old male patient was prescribed etretinate intermittently at doses ranging from 5 to 80mg/day for about 1 1/2 years for erythroderma psoriasis. His baseline lipid profile was as follows: HDL 42 (nl 35-55), triglyceride 128 (nl 10-25), cholesterol 209 (nl 130-200). Within one month of therapy his cholesterol was increasing (261) and his triglyceride level peaked after four months of therapy (481). He suffered a MI and was hospitalized during his six month of etretinate therapy (dose unknown). At that time etretinate was discontinued for two to three weeks but then restarted. Lipids levels were closely monitored. The patient had no previous cardiac history and no apparent risk factors for heart disease. He did have a family history of diabetes (mother) and stroke (father). He apparently recovered and lipids returned to normal within three months of discontinuing etretinate.

AERS 502130, MFR 870201428001, 1987- A 49-year-old female was hospitalized for coronary occlusion approximately four weeks after initiating therapy with etretinate 50mg per day. She died six days after admission. Her past medical history was significant

for plaque psoriasis and alcoholism. Autopsy revealed bleeding esophageal varices and cirrhosis probably related to alcoholism. Cause of death was coronary occlusion.

5. Heart Failure (5)

Five cases of heart failure (HF) were evaluated (etretinate-4, acitretin-1). The reported diagnoses include congestive HF (1), HF (1), left HF (1), worsening HF (1), and cardiac decompensation (1). The ages of the patients ranged from 68 to 81 years old. The onset of heart failure ranged from five days to six months of therapy. The outcomes include one death, three hospitalizations, and one patient that required intervention.

Although all heart failure cases were temporally associated with the use of either etretinate or acitretin, the causality was particularly difficult to determine in all of these cases primarily because the patients were elderly. Two patients had a history of cardiovascular disease (heart failure-1, myocardial infarction-1). One of these was a patient with heart failure who reported that her symptoms worsened after initiating therapy with etretinate. Her diuretic dose was adjusted and she improved. A rechallenge in this patient did not result in recurrence of symptoms. Concomitant methotrexate potentially confounded one case. The patient developed interstitial pneumonitis, congestive heart failure, and cor pulmonale after five months of combination therapy (methotrexate and etretinate). He was hospitalized and both drugs were discontinued. He recovered. The remaining patients did not appear to have any predisposing risk factors. One of these cases is described below for your review.

AERS 569759, MFR 840400171001, UK, 1983 - A 77-year-old female developed chest tightness, shortness of breath with palpitations after five months of etretinate. This was treated with rest and a diuretic; etretinate was continued. These symptoms recurred one month later and the patient was diagnosed with left ventricular failure. Etretinate was discontinued and the patient recovered. She remained asymptomatic to the time this report (>1 year after last event).

6. Cardiomyopathy (4)

A total of four cases of cardiomyopathy were evaluated (etretinate-4, acitretin-0). The reported diagnoses include idiopathic cardiomyopathy (1), dilated cardiomyopathy (2), and hypertrophic cardiomyopathy (1). The ages ranged from 10 to 44 years old. The time to onset ranged from two weeks to many years of etretinate use. The outcomes include one death and three hospitalizations (one reported as life threatening).

The causality of etretinate was difficult to determine in two cases because the time to onset was years after etretinate therapy. In both of these cases the cardiomyopathy was discovered during a preoperative cardiac work up. One case with no apparent predisposing risk factors is described below.

AERS 897828, MFR 920201683001, ~, 1992 - A 10-year-old female was treated with etretinate 25mg per day for erythrodermic pustular psoriasis. Etretinate was discontinued

after two weeks because the pustules cleared but the erythroderma was still present. Approximately two weeks after discontinuing etretinate, a baseline x-ray revealed a slightly enlarged heart. The patient was started on methotrexate. Eight days later she was hospitalized and a heart biopsy revealed a chronic active fibrosis with lymphocytic infiltrates. She was diagnosed with dilated cardiomyopathy. Her clinical course deteriorated and she died two weeks later. Her past medical history included only hyperhidrotic ectodermal dysplasia.

7. Miscellaneous Events (3)

The last three cases could not be characterized in any of the above major cardiovascular categories. The reported diagnoses include abdominal aneurysm (1), cardiac aneurysm (1), and pericardial effusion (1). Both cases involving aneurysm provided no clinical details surrounding the event. The pericardial effusion case is described below.

AERS 876807, MFR 920400219001, UK, 1992 - A 60-year-old male General Practitioner received oral etretinate for the treatment of traumatic psoriasis at a dose of 35mg per day. Some time after receiving etretinate (therapy dates not reported) he was hospitalized with a pericardial effusion with dyspnea and hypertension. Laboratory values included an increase in ALT of 80 IU/L and an increase in cholesterol and triglycerides (6.4mmol/L and 2.2mmol/L, respectively). His dose was decreased to 25mg per day. The patient was on no concomitant medication and had no significant PMH. His etretinate was continued and his dose was decreased to 25mg per day. He was also treated wit atenolol and bendrofluazide. Final outcome of this event was not reported.

Conclusion of Cardiovascular Cases

We evaluated 74 cases involving cardiovascular events reported with the use of either etretinate (62) or acitretin (12). The major categories of events include cardiac cerebrovascular events (19), miscellaneous non-cardiac thrombotic or embolic events (20), ischemic events (11), cardiomyopathy (4), heart failure (5), cardiac rhythm disturbances (12), and miscellaneous cardiac events (3). Causality was difficult to determine in these cases because baseline cardiovascular work up was not conducted prior to initiating therapy and some patients (20%) had been receiving either product for greater than one year which makes a temporal relationship questionable. Additionally, many of the patients had a past cardiac history, cardiac risk factors, or possibly underlying previously undiagnosed significant cardiovascular disease or other medical conditions that may have contributed to the cardiovascular event. For the reasons stated above, we couldn't conclude with any certainty that the cardiovascular related events were directly associated with the use of either etretinate or acitretin based on post-marketing adverse event reports.

REFERENCES

1. Soriatane® product information, Roche Pharmaceuticals, August 1997.

2. Robbins SL, Cotrin R, Kumar V. Genetic Disorders. *In* Saunders (eds): Pathologic Basis of Disease. 3rd Edition, pp. 137-8.

Claudia B. Karwoski, Pharm. D.

Concur:

Min Chen, R.Ph., M.S., Team Leader

cc:
HFD-540 Division File Archival NDAs 19-369, 19-821
Wilkin/Okun/O'Connell/Lutwak
HFD-430 Honig/Trontell/Chen/Karwoski/ Guinn/Division

Attachment 1. Reasons for exclusion of 126 cases

- Events are labeled (48) - There were 43 cases of edema (peripheral or generalized edema-33, pulmonary edema-3, ascites-2, gestational-1, and inflammation or swelling of the sternum, face, and eye-4). Nineteen edema cases were the result of another non-CV reported reaction, 18 involved general or peripheral edema, three involved pulmonary edema secondary to another event or previous cardiac history, and one involved gestational edema nine months after discontinuing etretinate. There were five cases of cyanosis (acrocyanosis or peripheral ischemia). Both edema and cyanosis are labeled adverse events.
- Reported events were symptoms related to non-CV event or underlying disease (23) Twenty-three cases involved events or symptoms such dyspnea (18), hypertension (2), tachycardia (2), and heart pounding (1) that were not related to cardiovascular reported adverse events or they were related to a previous underlying cardiac condition.
- Insufficient information to determine causality (24) – Twenty-four reports did not provide sufficient information of the reported cardiovascular event such as patient age, past medical history, total length of therapy in relation to onset of symptoms of the cardiovascular event, and diagnostic information.
- Probably not related (13) – Thirteen cases involved serious cardiovascular events that did not appear to be directly related to etretinate or acitretin.
  - One patient developed arrhythmias post-operatively probably secondary to hypokalemia.
  - One patient developed transitory circulatory depression related to gastrointestinal hemorrhage.

- Two patients suffered cardiac arrest, one probably related to sepsis and the other related to complications of toxic epidermal necrolysis.
- One case involving bradycardia and second degree heart block occurred two years after a second course of etretinate was instituted. There were no reported arrhythmias during the first course of etretinate.
- One patient developed acute HF secondary to obstructive cardiomyopathy four months after discontinuing etretinate. The cardiomyopathy was probably related to chronic alcoholism.
- Two patients developed HF (and pericarditis in one patient) that appeared to be related to hepatic and renal failure.
- One patient who was on etretinate for eight years developed HF that appeared to be related to tuberculosis pneumonia.
- One patient was diagnosed with cardiomyopathy eight years after initiating etretinate therapy. She also had a past medical history of Wolff-Parkinson-White syndrome that may have contributed to the event.
- One patient developed sinus thrombosis three weeks after discontinuing therapy with etretinate. He had received etretinate for 448 days with no reported problems.
- One patient (69 yom) was on etretinate for seven years and developed cerebral infarction.
- One patient with a h/o carcinoma developed leg thrombosis one month of a hospitalization. He had been receiving etretinate for years prior to this event.

- Event reported was confounded by pre-existing disease or other concomitant disease (9) – Nine patients had a past medical history (PMH) or other medical condition that appeared to be related to the reported cardiac or vascular event.
  - One patient with a PMH of Sick Sinus Syndrome (SSS) was admitted to the hospital for syncope and SSS approximately one month after the initiating etretinate.
  - One case with a reported event of atrial fibrillation was discovered on follow up to have been present prior to the initiation of etretinate.
  - Three patients who suffered a myocardial infarction (MI) had a PMH significant for previous MI, coronary artery disease, or angina.
  - One patient was hospitalized with congestive heart failure and aortic and mitral insufficiency. She had a PMH of heart murmur and possible valve disorders prior to taking etretinate.
  - One patient with a PMH of COPD and heart failure (HF) was hospitalized and died of pneumonia and HF.
  - One patient developed thrombocytopenia and cerebral hemorrhage. He had a history of carcinoma, which was determined to be the cause of the thrombocytopenia.
  - One patient who was diagnosed with toxic epidermal necrolysis (possibly drug related) experienced complications including acute renal failure and cardiac arrest.

- Not a cardiac or vascular thrombotic/embolic event (4) – Four cases were not cardiac or vascular thrombotic/embolic events. The reported events were cerebral atrophy, ischemic extremities, retrobular neuritis, and temperature intolerance.
- Cardiac disorder was part of PMH and not reported event (3) - One case was not further analyzed because the reported event was convulsions and her past medical history included cardiac insufficiency and coronary artery disease. One patient with a history of heart transplant experienced transplant rejection while receiving acitretin. One patient was with a history of hypertensive cardiomyopathy was hospitalized for macrophage activation syndrome.
- Congenital cardiac anomaly or events related to teratogenecity (2) – Two cases involve female patients who became pregnant during or after treatment with etretinate. One patient reportedly underwent induced abortion. Post mortem indicated a ventricular septal defect. The other patient delivered a premature baby that died nine days later of brain hemorrhage.

3 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 19821

S002/S006

Attachment 4—Cardiovascular and cerebrovascular adverse events in case reports

MCN	Adverse event
237993	Angina
312606	Coronary artery disease requiring CABG, hypercholesterolemia
94767	Coronary artery disease, hypertriglyceridemia
112229	Coronary artery disease, unspecified arrhythmia
200487	Cardiac aneurysm
217192	Cerebrovascular accident
91324	Cerebrovascular accident, worsened thrombocytosis
108489	Congestive heart failure
252607	Congestive heart failure
258518	Congestive heart failure
96196	Congestive heart failure
215177	Coronary atheroma, unspecified valve disorder, hypertriglyceridemia
PHRM2000FR01917	Cerebral vascular accident
241937	Deep vein thrombosis, pulmonary embolism
246553	Deep vein thrombosis, pulmonary embolism
220438	Heart block
259324	Hypertension
206789	Hypertension, skin bleeding
217165	Hypercholesterolemia
108182	Hypercholesterolemia
111792	Hypercholesterolemia
212201	Hypercholesterolemia
100641	Hypercholesterolemia
229677	Hypercholesterolemia
220375	Hypercholesterolemia,
112478	Hypercholesterolemia, hypertriglyceridemia
223069	Hypercholesterolemia, hypertriglyceridemia
225598	Hypercholesterolemia, hypertriglyceridemia
218275	Hypercholesterolemia, hypertriglyceridemia, rejection of transplanted heart
93697	Hypertension
248714	Hypertension
246043	Hypertension
111857	Hypertension, hypercholesterolemia
255713	Hypertension, hypercholesterolemia, hypertriglyceridemia
203972	Hypertriglyceridemia
223478	Hypertriglyceridemia
97468	Hypertriglyceridemia
313936	Hypertriglyceridemia

256751	Hypertriglyceridemia
209935	Hypertriglyceridemia
200102	Hypertriglyceridemia
96644	Hypertriglyceridemia
109814	Hypertriglyceridemia
267606	Hypertriglyceridemia, cerebral vasculitis
210846	Hypertriglyceridemia, hypercholesterolemia
96721	Increased bleeding time
86963	Intracerebral hematoma
227916	Left bundle branch block
253426	Mitral valve regurgitation
250162	Myocardial infarction
312710	Myocardial infarction
226924	Myocardial infarction
104314	Myocardial infarction
263589	Myocardial infarction
255612	Myocardial infarction
100739	Premature atrial contractions
225310	Pulmonary embolism
930500952002	Pulmonary embolism, deep vein thrombosis
97214	Pulmonary embolism, deep vein thrombosis
252381	Pulmonary embolism, hypercholesterolemia
223058	Pulmonary embolism, pulmonary edema
96654	Portal vein thrombosis
242836	Possible angina; chest pain, diaphoresis
254877	Postural hypotension
303877	Pulmonary embolism
110690	Pulmonary hypertension
207759	Pulmonary thrombosis resulting in inferior vena cava thrombosis
103961	Premature ventricular contractions
233880	Retinal vein thrombosis
102985	Tachycardia
221141	Transient ischemic attacks
217321	Unspecified fatal cardiac event

Attachment 5—Psychiatric adverse events in case reports

MCN	Adverse events
238438	Abnormal behavior, amnesia
225244	Abnormal dreams, emotional lability
229595	Abnormal thinking, racing thoughts
106941	Aggression, combative behavior
259185	Aggressive behavior
257204	Aggressive behavior (setting fires)
103161	Agitation, suicide attempt
229677	Attempted suicide
92731	Auditory hallucinations
244899	Bad mood
240348	Confusion
19821	Confusion
9953436	Confusion, hallucinations, aggression
221440	Dementia
95797	Depression
111857	Depression
204117	Depression
267942	Depression
99171	Depression, anxiety, paranoia,
217725	Depression worsened
235786	Depression, agitation, confusion
206789	Depression, anxiety, nervousness
244395	Depression, attempted suicide
107159	Depression, emotional lability
110959	Depression, loss of weight, asthenia
215967	Depression, mood changes, personality changes, irritability, abnormal behavior
98095	Depression, nightmares, anxiety, insomnia, confusion
113281	Depression, paranoia, anxiety, panic attacks, attempted suicide
228124	Depression, psychosis
269505	Depression, suicidal ideation
307880	Depression, unspecified aggressiveness
110809	Depression, weight loss
308105	Disorientation, memory loss
246389	Emotional disturbance, schizophrenia, social avoidant behavior,
234235	Emotional stress
104621	Irritable
89597	Manic-depressive psychosis
254013	Memory disturbance, anxiety, somnolence
306325	Memory disturbance, asthenia
200375	Mood swings
215463	Mood swings, insomnia, anxiety

103835	Moodiness
100049	Nervousness
102836	Suicide
227128	Unspecified behavior disorder
229575	Unspecified psychiatric disorder aggravated

Attachment 6—Suicide-related adverse events in case reports

1. AERS 3170613-6-00, MFR 103161 ✓, 1998
   A 59-year-old woman was prescribed acitretin 25mg daily for psoriasis. During her three-month acitretin course she experienced pruritus, cheilitis, and hair loss. She decided to discontinue therapy. One month after discontinuing therapy she reported that she **attempted suicide**. The method of suicide attempt was not reported. She also voiced suicidal ideation with the intent to overdose with alprazolam. She had no reported past psychiatric history. On follow up, the patient reported additional events to include hemorrhoids, panic attacks, depression, and worsening hypercholesteremia. The report also stated that she had taken an overdose of vitamin A, however it is not known if the overdose was the suicide attempt.

2. AERS 3107876-9-00, MFR 102836, ✓ 1998
   A man (age unknown) **committed suicide** approximately two months after initiating therapy with acitretin for keratoacanthoma. He had previously taken isotretinoin and possibly etretinate for the same indication however the therapy dates are unknown. His past medical history includes a depressive disorder that had not being treated and anger because of his underlying, "disfiguring" skin condition. His method of suicide was not specified.

3. AERS 3204458-5-00, MFR 113281, UK, 1999
   A woman (age unknown) experienced depression, paranoia, mood swings, and **attempted suicide** three times within three to four months of initiating therapy with acitretin. She did not have a history of depression prior to acitretin. Her physician started her on fluoxetine which she discontinued taking after six days. At the time of the report, paranoia was persisting. It is unknown what method of suicide was attempted, whether she was hospitalized for the suicide attempts, or whether she continued acitretin.

4. AERS 3612734-7-00, MFR 244395 ✓ 2000*
   A 57-year-old woman with a prior medical history of depression was prescribed acitretin 50 mg daily for psoriasis. After receiving acitretin for an unknown period of time, the patient's depression worsened, she **became suicidal**, and she required partial hospitalization. The patient discontinued acitretin. Five days after discontinuing acitretin, the patient's symptoms improved, and she stopped expressing suicidal thoughts.

5. AERS 3494446-6-00, MFR 229677, ? ✓ ?2000*
   A 39-year-old man was prescribed acitretin (dose not reported) for psoriasis. Prior medical history was not reported. After about 9 months of therapy with acitretin, the patient **attempted suicide** by ingesting 750 mg of acitretin. Acitretin was discontinued, and the patient was placed under observation. The patient recovered without experiencing any lasting sequelae from the suicide attempt.

*new cases since the prior DDRE review

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/s/

Joyce Weaver
7/30/02 09:21:39 AM
PHARMACIST

Julie Beitz
7/30/02 11:29:42 AM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Office of Drug Safety
Julie Beitz for pregnancies
Marilyn Pitts for psychiatric

FROM: HFD-540 Vickey Lutwak

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 13, 2002		NDA 19-821		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Soriatane(acitretin) capsules			

Hoffmann-La Roche, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ ~~NN~~ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
~~NN~~ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
~~NN~~ SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
In addition to the previous request below, for SLR 006, letter May 17, 2002, the medical officer requests "a limited work-up" in the cases of pneumonitis, HLR claims that they have only one while the MO via MedWatch repots has many more. If there is support for this to be added to the AR section, it will be added. Please call Kathy O Connell, the reviewer, if you need additional information. Thank you

We are requesting that ODS evaluate the postmarketing spontaneous reports of AEs associated with Soriatane (acitretin), especially (but not limited to), teratogenicity and psychiatric events.
The medical office is Kathryn O'Connell
The project manager is Vickey Lutwak

SIGNATURE OF REQUESTER Vickey Lutwak, PM, HFD 540 7-2073	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Victoria Lutwak
6/13/02 11:00:23 AM