CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-821/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19-821/S-001

Food and Drug Administration
Rockville MD 20857

Hoffmann-La Roche Inc.
Attention: Betty C. Holland
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

MAY - 5 1997

Dear Ms. Holland:

Please refer to your April 29, 1997, supplemental new drug application (NDA), received April 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Soriatane (acitretin capsules), Capsules 10 and 25 mg.

We acknowledge receipt of your submissions dated May 1, 2, and 21, 1997.

The supplemental application provides for revised draft labeling for the subject NDA.

We have completed the review of the supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the ENCLOSED REVISED DRAFT LABELING. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the ENCLOSED REVISED DRAFT LABELING.

Please submit twenty 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 "FINAL PRINTED LABELING" for approved supplemental NDA 19-821/S-001. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Harold Blatt
Consumer Safety Officer
(301)827-2020

Sincerely yours,

/S/

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

CONTRAINDICATION 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, and major human fetal abnormalities have been reported with the administration of etretinate and acitretin. 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 (Tegison®), which has a 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 doses approximately 0.6, 3, and 15 times the maximum recommended therapeutic dose, respectively.

Major human fetal abnormalities associated with etretinate and/or acitretin administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactylies, 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 on x-ray.

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

- has severe psoriasis and is unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments;
- has received both oral and written warnings of the hazards of taking Soriatane during pregnancy;
- has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously both during therapy and for at least 3 years *after* discontinuation of therapy and has acknowledged in writing her understanding of these warnings and of the need for using dual contraceptive methods (unless the patient has undergone a hysterectomy or practices abstinence);
- has had a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy;
- will begin therapy only on the second or third day of the next normal menstrual period;
- is capable of complying with the mandatory contraceptive measures; and
- is reliable in understanding and carrying out instructions.

A prescription for Soriatane should not be issued by the physician until a report of a negative pregnancy test has been obtained and the patient has begun her menstrual period. Pregnancy testing and contraception counseling should be repeated on a regular basis.

To encourage compliance with this recommedation, the physician should prescribe a limited supply of the drug.

Effective contraception must be used for at least 1 month before beginning Soriatane therapy, during therapy, and for at least 3 years following discontinuation of therapy even where there has been a history of infertility, unless due to hysterectomy. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. Patients who have undergone tubal ligation should use a second form of contraception.

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 5 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.

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

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 post-therapy 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]
- An increased incidence of birth defects was estimated based on a limited number of cases which have been reported to Roche, which were identified before the outcome was known, and where pregnancy occurred during the time interval when the patient was being treated with acitretin or etretinate.

For cases identified after the outcome was known, severe birth defects have been reported where pregnancy occurred during the time interval when the patient was being treated with acitretin or etretinate.

- There have been 202 cases reported before the outcome was known where pregnancy occurred after the last dose of etretinate or acitretin. Fetal outcome remained unknown in approximately one-half of these cases, of which 67 were terminated and 11 were spontaneous abortions. Fetal outcome is known for 103 of these prospectively reported cases. Fifteen of the outcomes were abnormal: hernia, hypocalcemia, hypotonia (2), undescended testicle, laparoschisis, absent hand wrist, clubfoot, ichthyosis, apnea/anemia, placental disorder/death, and premature birth (5). Birth defects have also been reported retrospectively (ie, after the outcome was known). Among the retrospectively reported cases where pregnancy occurred more than 2 years after the last dose of etretinate or acitretin, there are 2 normal outcomes, 3 unknown outcomes, and 7 abnormal outcomes. The 7 abnormal outcomes reported are: malformation unspecified, aplasia of the forearm, stillbirth, right ventricular/aortic duct defect, heart malformation unspecified, and chromosomal disorder. For these listed reports, the relationship of the birth defects to the drug is unknown.

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the physician and patient should discuss the possible effects on the pregnancy.

Soriatane should be prescribed only by physicians 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.

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:

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

Gelatin capsule shells contain gelatin, parabens (methyl and propyl), iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, butyl paraben, carboxymethylcellulose sodium, edetate calcium disodium, potassium sorbate, and/or sodium propionate.

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 Interaction-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 eight-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 WARNINGS: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 CONTRAINDICATION 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 six 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]. It is not known whether other progestational contraceptives, such as implants and injectables, are inadequate methods of contraception during acitretin therapy.

INDICATIONS AND USAGE: Soriatane is indicated for the treatment of severe psoriasis, including the erythrodermic and generalized pustular types, in adults. Because of significant adverse effects associated with its use, Soriatane should be prescribed only by physicians knowledgeable in the systemic use of retinoids. In females of reproductive potential, Soriatane should be reserved for patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

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

CONTRAINDICATIONS: Pregnancy Category X (see Boxed CONTRAINDICATION AND WARNINGS)

WARNINGS: (See also Boxed CONTRAINDICATION 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 threefold 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 acitretin 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.

Pancreatitis: Lipid elevations occur in 25-50% of patients treated with acitretin. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported for one patient.

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.

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 Soriatane-treated patient experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation.

Hyperostosis: 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: 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 diabetes mellitus, obesity, increased alcohol intake, or a familial history of these conditions.

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.

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 10 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.

PRECAUTIONS: ***General:*** Caution is advised in patients with severely impaired liver or kidney function (See CLINICAL PHARMACOLOGY). Soriatane should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule.

Information for Patients: Females of reproductive potential should be advised that they must not be pregnant when Soriatane therapy is initiated and that they should use effective contraception for at least 1 month prior to Soriatane therapy, and while taking Soriatane. Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformation 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 post-therapy 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]
- An increased incidence of birth defects was estimated based on a limited number of cases which have been reported to Roche, which were identified before the outcome was known, and where pregnancy occurred during the time interval when the patient was being treated with acitretin or etretinate. For cases identified after the outcome was known, severe birth defects have been reported where pregnancy occurred during the time interval when the patient was being treated with acitretin or etretinate

- There have been 202 cases reported before the outcome was known where pregnancy occurred after the last dose of etretinate or acitretin. Fetal outcome remained unknown in approximately one-half of these cases, of which 67 were terminated and 11 were spontaneous abortions. Fetal outcome is known for 113 of these prospectively reported cases. Fifteen of the outcomes were abnormal: hernia, hypocalcemia, hypotonia (2), undescended testicle, laparoschisis, absent hand/wrist, clubfoot, ichthyosis, apnea/anemia, placental disorder/death, and premature birth (5). Birth defects have also been reported retrospectively (ie, after the outcome was known). Among retrospectively reported cases where pregnancy occurred more than 2 years after the last dose of etretinate or acitretin, there are 2 normal outcomes, 3 unknown outcomes, and 7 abnormal outcomes. The 7 abnormal outcomes reported are: malformation unspecified, aplasia of the forearm, stillbirth, right ventricular/aortic duct defect, heart malformation unspecified, and chromosomal disorder. For these listed reports, the relationship of the birth defects to the drug is unknown.

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. They should be advised that methods of birth control can fail, including tubal ligation and microdosed progestin "minipill" preparations. 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 CONTRAINDICATION AND WARNINGS).

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 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 two or three months before they get the full benefit of Soriatane.

Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period.

It is recommended that patients not donate blood during and for 3 years following therapy.

Patients should avoid the use of sun lamps and excessive exposure to sunlight because the effects of UV light are enhanced by retinoid therapy.

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

Laboratory Tests: 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).

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.

Certain patients receiving retinoids have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during retinoid therapy, although no causal relationship has been established.

Drug Interactions:

Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see Boxed CONTRAINDICATION AND WARNINGS and *Pharmacokinetics* sections).

In a study of 7 healthy male volunteers, acitretin treatment enhanced clearance of blood glucose in the presence 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 *Pharmacokinetics* and DOSAGE AND ADMINISTRATION sections).

There may be the possibility of an increased risk of hepatotoxicity in patients treated with etretinate and methotrexate concomitantly. Consequently, the concomitant use of Soriatane and methotrexate should be avoided.

There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, phenprocoumon or glyburide.

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. *It is not known whether other progestational contraceptives,*

such as implants and injectables, may be inadequate methods of contraception during acitretin therapy.

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. A 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 5.7 to 7.1 times the maximum recommended human therapeutic dose.

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 three times the maximum recommended therapeutic dose). 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 30-50 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.[3,4,5] 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 CONTRAINDICATION AND WARNINGS).**

Effective contraception must be used by female patients of reproductive potential for at least 1 month before beginning Soriatane therapy, during therapy and for at least 3 years following discontinuation of therapy. This warning applies even where there has been a history of infertility, unless due to hysterectomy.

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.

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 5 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 one 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.

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.

Nursing Mothers: Studies on lactating rats have shown that etretinate is excreted in the milk. However, it is not known whether either etretinate or acitretin is excreted in human milk. However, nursing mothers should not receive Soriatane because of the potential for excretion in milk and serious adverse reactions in nursing infants.

Pediatric Use: No clinical studies have been conducted in pediatric patients. Therefore, safety and effectiveness in pediatric patients have not been established. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses and premature epiphyseal closure have been reported with other systemic retinoids. While it is not known that these occurrences are more severe or more frequent in children, there is concern in pediatric patients because of the implications for growth potential.

ADVERSE EVENTS: During clinical trials with acitretin, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred sixteen patients 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 has been associated with elevations in liver function test results or triglyceride levels and hepatitis. A case of fatal fulminant pancreatitis has been reported during Soriatane therapy.

Soriatane has also been associated with a case of pseudotumor cerebri (see WARNINGS section). One case of myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug.

Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, and central nervous systems. Many of the clinical adverse events reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome. The tables below list by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis.

Table 1. 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%
Mucous Membranes	Cheilitis		Rhinitis	Dry mouth Epistaxis

Skin and Appendages	Alopecia Skin peeling	Dry skin Nail disorder Pruritus	Erythematous rash Hyperesthesia Paresthesia Paronychia Skin atrophy Sticky skin
Eye Disorders			Xerophthalmia
Musculoskeletal			Arthralgia Spinal hyperostosis (progression of existing lesions)
CNS			Rigors

Table 2. 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%
Mucous Membranes	Gingival bleeding	Altered saliva
	Gingivitis	Anal disorder
	Increased saliva	Gum hyperplasia
	Stomatitis	Hemorrhage
	Thirst	Pharyngitis
	Ulcerative stomatitis	
Skin and Appendages	Abnormal skin odor	Acne
	Abnormal hair texture	Breast pain
	Bullous eruption	Cyst
	Cold/clammy skin	Eczema
	Dermatitis	Fungal infection
	Increased sweating	Furunculosis
	Infection	Hair discoloration
	Psoriasiform rash	Herpes simplex
	Purpura	Hyperkeratosis
	Pyogenic granuloma	Hypertrichosis
	Rash	Hypoesthesia
	Seborrhea	Impaired healing
	Skin fissures	Otitis media
	Skin ulceration	Otitis externa
	Sunburn	Photosensitivity reaction
		Psoriasis aggravated
		Scleroderma
		Skin nodule
		Skin hypertrophy
		Skin disorder
		Skin irritation
		Sweat gland disorder
		Urticaria
		Verrucae
Eye Disorders	Abnormal/blurred vision	Abnormal lacrimation
	Blepharitis	Chalazion
	Conjunctivitis/irritation	Conjunctival hemorrhage
	Corneal epithelial abnormality	Corneal ulceration
	Decreased night vision/ night blindness	Diplopia
		Ectropion
	Eye abnormality	Itchy eyes and lids
	Eye pain	Papilledema
	Photophobia	Recurrent sties
		Subepithelial corneal lesions

Table 2 (cont.) 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%
Musculoskeletal	Arthritis Arthrosis Back pain Hypertonia Myalgia Osteodynia Peripheral joint hyperostosis (progression of existing lesions)	Bone disorder Olecranon bursitis Spinal hyperostosis (new lesions) Tendinitis
CNS	Headache Pain	Abnormal gait Migraine Neuritis Pseudotumor cerebri (intracranial hypertension)
Gastrointestinal	Abdominal pain Diarrhea Nausea Tongue disorder	Constipation Dyspepsia Esophagitis Gastritis Gastroenteritis Glossitis Hemorrhoids Melena Tenesmus Tongue ulceration
Special Senses Other	Earache Taste perversion Tinnitus	Ceruminosis Deafness Taste loss
Psychiatric	Depression Insomnia Somnolence	Anxiety Dysphonia Libido decreased Nervousness
Respiratory	Sinusitis	Coughing Increased sputum Laryngitis
Urinary		Abnormal urine Dysuria Penis disorder

Reproductive	Atrophic vaginitis Leukorrhea

Table 2 (cont.) 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%
Cardiovascular	Flushing	Chest pain Cyanosis Increased bleeding time Intermittent claudication Peripheral ischemia
Body as a Whole	Anorexia Edema Fatigue Hot flashes Increased appetite	Alcohol tolerance Dizziness Fever Influenza-like symptoms Malaise Moniliasis Muscle weakness Weight increase
Liver and Biliary		Hepatic function abnormal Hepatitis Jaundice

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 section).

Table 3 lists the laboratory abnormalities reported during clinical trials.

Table 3. Laboratory Abnormalities Reported During Clinical Trials
Percent of Patients Reporting

BODY SYSTEM	50% to 75%	25% to 50%	10% to 25%	1% to 10%
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
Electrolytes			Increased: - Phosphorus - Potassium - Sodium Increased and decreased magnesium	Decreased: - Phosphorus - Potassium - Sodium Increased and decreased: - Calcium - Chloride
Renal			Increased uric acid	Increased: - BUN - Creatinine
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
Urinary		WBC in urine	Acetonuria Hematuria RBC in urine	Glycosuria Proteinuria

Miscellaneous	Increased triglycerides	Increased: - CPK - Fasting blood sugar	Decreased fasting blood sugar High occult blood	Increased and decreased iron

OVERDOSAGE: One overdose case has been reported. A 32-year-old mentally handicapped 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. His therapeutic treatment was continued. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg.

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 maximum therapeutic response while minimizing side effects. Soriatane therapy should be initiated at 25 or 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 after initial response to treatment; although, in general, therapy should be terminated when lesions have resolved sufficiently. Relapses may be treated as outlined for initial therapy.

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

HOW SUPPLIED: Brown and white capsules, 10 mg, imprinted SORIATANE 10 ROCHE; Prescription Paks of 30 (NDC 0004-0213-57).

Brown and yellow capsules, 25 mg, imprinted SORIATANE 25 ROCHE; Prescription Paks of 30 (NDC 0004-0214-57).

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.

REFERENCE:

[1]Maier H, Honigsmann H: Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. Lancet 348:1107, 1996.
[2]Berbis Ph, et al.: Arch Dermatol Res (1988) 280:388-389.
[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 INFORMATION/CONSENT:

IMPORTANT INFORMATION AND WARNING FOR *ALL* PATIENTS:

Small amounts of Soriatane have been detected in the ejaculate of males taking Soriatane. The amount of Soriatane detected corresponds to less than 1/200,000 of a 25 mg dose. You should discuss any questions you have about this information with your physician.

Alcohol intake can cause Soriatane to be changed into a related drug, etretinate, which may not leave the body for many years.

In addition, you must not donate blood during your treatment with Soriatane and for 3 years after you stop taking Soriatane.

It is recommended that you and your doctor schedule appointments regularly to check your body's response to Soriatane. For your health and well-being, be sure to keep your appointments as scheduled.

Do not give your Soriatane capsules to any other person.

IMPORTANT INFORMATION AND WARNING FOR *FEMALE* PATIENTS:

Soriatane must not be used by females who are pregnant or who may become pregnant while undergoing treatment or at any time for at least 3 years after treatment is discontinued.

If you do become pregnant during Soriatane therapy, or at any time for at least three years after you stop taking Soriatane, you should discuss with your physician the possible effects on the pregnancy.

Soriatane can cause severe birth defects if it is taken when a female is pregnant. In addition, birth defects have occurred in babies of females who become pregnant after stopping Soriatane treatment. Therefore:

- you must not be pregnant when you start taking Soriatane.
- you must not become pregnant while you are taking Soriatane.
- you must wait at least 3 years after you stop taking Soriatane before becoming pregnant.

Alcohol must be avoided during the entire Soriatane treatment course and for 2 months after you stop taking Soriatane. This is because alcohol intake can cause Soriatane to be changed into a related drug, etretinate. Etretinate may not leave the body for many years and, like Soriatane, can cause severe birth defects. It is recommended that you and your doctor schedule appointments regularly to repeat the pregnancy test and check your body's response to Soriatane. For your health and well-being, be sure to keep your appointments as scheduled.

In addition, you must not donate blood during your treatment with Soriatane and for 3 years after you stop taking Soriatane.

Do not give your Soriatane capsules to any other person.

THE CONSENT FOR *FEMALE* PATIENTS:

My treatment with Soriatane has been personally explained to me by Dr._____.
The following points of information, among others, have been specifically discussed and made clear:

1. I, _____
(Patient's Name)
understand that Soriatane is used to treat severe psoriasis that is unresponsive to other therapies.
Initials ____

2. I understand that severe birth defects related to treatment with Soriatane have occurred in babies of women who have taken Soriatane during pregnancy. In addition, birth defects have occurred in babies of women who became pregnant after stopping Soriatane treatment.
Initials ____

3. I understand that I must not be pregnant when I start taking Soriatane.
Initials ____

4. I understand that I must not become pregnant while I am taking Soriatane.
Initials ____

5. I understand that I must wait at least 3 years after I stop taking Soriatane before becoming pregnant.
Initials ____

6. I have been told by my doctor that effective birth control (contraception) must be used for at least 1 month before starting Soriatane, for the entire duration of Soriatane therapy and for at least 3 years after Soriatane treatment has stopped. My doctor has told me that I must either abstain from sexual intercourse or use two reliable kinds of birth control at the same time. I have also been told that any method of birth control can fail, including tubal ligation or microdosed progestin "minipill" preparations. I must use two forms of reliable birth control simultaneously, even if I think I cannot become pregnant, unless I abstain from sexual intercourse or have had a hysterectomy.
Initials_____

7. I understand that if I have taken Tegison (etretinate), I must continue to follow the birth control (contraception) recommendations for Tegison.
Initials ____

8. I know that I must have a blood or urine test done by my doctor that shows I am not pregnant within 1 week before starting Soriatane. I understand that I must wait until the second or third day of my next normal menstrual period before starting Soriatane.
Initials ____

9. My doctor has told me that I can participate in the "Patient Referral" program for an initial free pregnancy test and birth control counseling session by a consulting physician.
Initials ____

10. I know that I must immediately stop taking Soriatane if I become pregnant and immediately contact my doctor to discuss possible effects on the pregnancy. I also know that I must

immediately contact my doctor if I become pregnant at any time for at least 3 years after stopping Soriatane.

Initials ____

11. I have carefully read the Soriatane patient brochure, "Important information concerning your treatment with Soriatane," given to me by my doctor. I understand all of its contents and have talked over any questions I have with my doctor.

Initials ____

12. I am not now pregnant, nor do I plan to become pregnant while taking Soriatane and for at least 3 years after I have completely finished taking Soriatane.

Initials ____

13. I know that I must avoid ingesting any beverage or product that contains alcohol during the entire Soriatane treatment course and for 2 months after I have completely finished taking Soriatane.

Initials ____

14 I understand that if I consume any beverage or product that contains alcohol during my treatment with Soriatane or during the two months after I stop taking Soriatane, the risk of birth defects will persist for a longer period of time.

Initials ____

15. I have been told not to donate blood during my treatment with Soriatane and for 3 years after I have completely finished taking Soriatane.

Initials ____

I now authorize Dr. _____ to begin my treatment with Soriatane.

_____

Patient signature, Parent or Guardian signature if patient is a minor Date

_____

Address

_____

_____

Telephone Number

I have fully explained to the patient, _____, the nature and purpose of the treatment described above and the teratogenic risk. I have asked the patient if there are any questions regarding treatment with Soriatane and have answered those questions to the best of my ability.

_____

Physician signature Date

(Roche Hexagon)

Roche Laboratories
A Member of the Roche Group

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

24907009-0497C

Issued: April 1997

Printed in USA

Revised: June 4, 1997

APPEARS THIS WAY
ON ORIGINAL

Soriatane (acitretin, Ro 10-1670) Capsules

Patient Brochure/Bottle Label
Things you should know about
SORIATANE®
acitretin
CAPSULES
((Roche hex))

Please carefully read the following **WARNINGS TO FEMALE PATIENTS** and **INSTRUCTIONS FOR PATIENTS** for before, during and after your treatment with Soriatane.

APPEARS THIS WAY
ON ORIGINAL

WARNINGS TO FEMALE PATIENTS ((Avoid Pregnancy Symbol))

YOU MUST NOT TAKE SORIATANE IF YOU ARE PREGNANT OR MAY BECOME PREGNANT DURING SORIATANE THERAPY OR AT ANY TIME FOR AT LEAST 3 YEARS FOLLOWING DISCONTINUATION OF SORIATANE THERAPY. Soriatane can cause severe birth defects if it is taken during pregnancy. In addition, birth defects have occurred when conception happened after stopping Soriatane treatment. The possibility that you may be pregnant must be ruled out by you and your doctor before you start Soriatane therapy. Wait until the second or third day of your next normal menstrual period before beginning Soriatane therapy.

Effective contraception (birth control) should be discussed with your doctor. Two forms of reliable contraception must be used simultaneously for at least 1 month before beginning therapy and during therapy, and must be continued for at least 3 years after Soriatane treatment has stopped. It is recommended that you either abstain from sexual intercourse or use two reliable kinds of birth control at the same time. Birth control must be used even if you think you cannot become pregnant, unless you have had a hysterectomy. Immediately stop taking Soriatane if you become pregnant while you are taking the drug. If you become pregnant while on Soriatane therapy or at any time for at least 3 years after treatment has stopped, immediately contact your physician to discuss the possible effects on the pregnancy.

YOU MUST AVOID CONSUMING ANY BEVERAGE OR PRODUCT THAT CONTAINS ALCOHOL DURING THE ENTIRE SORIATANE TREATMENT COURSE AND FOR 2 MONTHS AFTER SORIATANE TREATMENT HAS STOPPED.

This brochure provides important facts about Soriatane (acitretin), but it does not contain all information about this medication. If there is anything else you want to know or if you have any questions, talk to your doctor.

Soriatane is a medicine used to treat severe forms of psoriasis in adults. Soriatane treatment generally results in improvement in most patients. Some patients, in fact, have obtained complete clearing of their disease after receiving Soriatane for up to 24 weeks. You should keep in mind, however, that because some degree of relapse commonly occurs after therapy is discontinued, most patients require long-term therapy with Soriatane. Also, because each patient's dosage regimen may vary, you should discuss your course of therapy with your doctor. *Do not give your Soriatane capsules to any other person.*

Before you decide to take Soriatane, you must have talked with your doctor about the types of deformed babies that can occur if you are pregnant or may become pregnant while taking Soriatane or at any time for at least 3 years after stopping Soriatane treatment. It is recommended that you and your doctor schedule appointments regularly to repeat the pregnancy test and check your body's response to Soriatane. For your health and well-being, be sure to keep your appointments as scheduled. Please read the following information carefully and be certain that you understand what your doctor told you.

INSTRUCTIONS FOR PATIENTS

Before Your Treatment Begins ((Avoid Pregnancy Symbol))

For Female Patients

- You must read, understand, and sign a consent form before you take Soriatane (acitretin); contact your doctor if you have not signed this form.
- You must not take Soriatane until you are sure you are not pregnant (please see **WARNINGS TO FEMALE PATIENTS**).
- You must use effective contraception (birth control) for at least 1 month before beginning Soriatane therapy.
- You must have a blood or urine test done by your doctor that shows you are NOT pregnant within 1 week before beginning Soriatane therapy.
- You must wait until the second or third day of your next normal menstrual period before beginning Soriatane therapy.
- You must not take Soriatane, if you cannot avoid pregnancy.
- You should not take Soriatane, if you are a nursing mother.

For All Patients

- Blood tests will be necessary before and periodically during treatment to check your body's response to Soriatane (acitretin).
- If you have a family or personal history of medical conditions such as diabetes, liver disease, heart disease, depression, alcoholism or obesity, please inform your doctor.
- Soriatane is related to Vitamin A. Therefore, you should avoid taking vitamin supplements containing vitamin A, because they may add to the unwanted effects of Soriatane. Check with your doctor or pharmacist if you have any questions about vitamin supplements.
- Tell your doctor if you are allergic to parabens, since they are used in Soriatane capsules.

During Your Treatment ((Avoid Pregnancy Symbol))

For Female Patients

- You must continue to use effective contraception (birth control) while taking Soriatane (acitretin) (please see **WARNINGS TO FEMALE PATIENTS**).
- It is recommended that you return to your doctor regularly for a pregnancy test.
- If your menstrual period is delayed, stop taking Soriatane and call your doctor.
- Additionally, beverages or products that contain alcohol must not be consumed while you are taking Soriatane and for 2 months after you stop taking Soriatane. This is because alcohol intake can cause Soriatane to be changed within your body into a related drug, etretinate, which may not leave the body for many years and which, like Soriatane, can cause birth defects. It is recommended that you and your doctor schedule appointments regularly to repeat the pregnancy test and check your body's response to Soriatane. For your health and well-being, be sure to keep your appointments as scheduled.

For Male Patients

Small amounts of Soriatane have been detected in the ejaculate (semen) of males taking Soriatane. The amount of Soriatane detected corresponds to less than 1/200,000 of a 25 mg dose. You should discuss any questions you have about this information with your physician.

For All Patients

- Like many patients, you may find your psoriasis gets worse temporarily during the early period of your treatment with Soriatane. Sometimes patients have more redness or itching. If this happens, please tell your doctor. These symptoms usually get better as treatment continues.
- You may have to wait 2 or 3 months before you get the full benefit of Soriatane.
- In the first few weeks of treatment--perhaps before you see any healing--you may begin to have some side effects. The more common side effects reported in drug trials include chapped lips; peeling of the fingertips, palms and soles; loss of hair; itching; sticky skin; or runny or dry nose. If you develop any of these side effects or any other unusual reaction, check with your doctor to determine if any change in the amount of your medication is needed. Also, ask your doctor to recommend a lotion or cream if drying or chapping develops.
- Most patients experience some degree of hair loss, but the condition varies among patients. The extent of hair loss that you will experience and whether or not your hair will return after treatment cannot be predicted.
- A few patients have experienced decreased night vision. Since the onset can be sudden, you should be particularly careful when driving or operating any vehicle at night. If you experience any visual difficulties, stop taking Soriatane (acitretin) and consult your doctor. If you wear contact lenses, you may find that you are less able to tolerate them during the treatment period. If this occurs, remove the lenses and call your doctor.
- YOU SHOULD BE AWARE THAT SORIATANE MAY CAUSE SOME MORE SERIOUS SIDE EFFECTS. BE ALERT FOR ANY OF THE FOLLOWING:
  - HEADACHES, NAUSEA, VOMITING, BLURRED VISION

- CHANGES IN MOOD
- YELLOWING OF THE SKIN OR EYES AND/OR DARK URINE
- PERSISTENT FEELING OF DRYNESS OF THE EYES
- ACHES OR PAINS IN BONES OR JOINTS, OR DIFFICULTY IN MOVING, OR LOSS OF SENSATION IN THE LIMBS.

IF YOU EXPERIENCE ANY OF THESE SYMPTOMS OR ANY OTHER UNUSUAL OR SEVERE PROBLEMS, STOP TAKING SORIATANE AND CHECK WITH YOUR DOCTOR IMMEDIATELY. THEY MAY BE THE EARLY SIGNS OF MORE SERIOUS SIDE EFFECTS WHICH, IF LEFT UNTREATED, COULD POSSIBLY RESULT IN PERMANENT ADVERSE EFFECTS.

- Bone changes have been detected by x-ray examination. The significance of these changes is not presently known.
- The dosage of Soriatane varies from patient to patient. The number of capsules you must take is determined specifically for you, by your doctor, for your particular case. Periodically during treatment your doctor may change the amount of medication you need to take. Make sure you follow the schedule you are given. If you miss a dose, do not double the next dose. If you have any questions, call your doctor. *Do not give your Soriatane capsules to any other person.*
- Do not donate blood while you are taking Soriatane and for 3 years after stopping Soriatane therapy.
- Be sure to return to your doctor as scheduled. He or she will want to check your progress with Soriatane (acitretin).

<u>After Your Treatment is Completed</u> ((Avoid Pregnancy Symbol))

For Female Patients

- You must continue using effective contraception (birth control) for at least 3 years after your treatment with Soriatane has ended (please see **WARNINGS TO FEMALE PATIENTS**).
- You must continue to avoid consuming beverages or products that contain alcohol for 2 months after treatment with Soriatane has ended, because the risk of birth defects may persist longer if you consume any form of alcohol during these 2 months.

For All Patients

- Your doctor will generally stop your treatment when your skin has sufficiently cleared. You may experience some degree of relapse within a few months after you stop your therapy. This is common. If you notice a worsening of your condition, however, contact your doctor. Additional courses of treatment will generally produce the same response as the first course.
- Do not donate blood for 3 years after stopping Soriatane therapy.

<u>General Guidelines For Taking Your Medication</u>

- Call your doctor if you have any questions or experience any severe or troubling symptoms.

- If you are allergic to any foods or medication, let your doctor know. It could be very important.
- Soriatane (acitretin) does not need to be refrigerated. However, do not expose the capsules to sunlight, and avoid exposing the capsules to high temperatures and humidity after the bottle is opened.
- Be sure to take your medication as prescribed by your doctor. Read the prescription label on the package carefully. **If there is anything you don't understand**, ask your doctor or pharmacist to explain it to you.
- Soriatane has been prescribed specifically for you--do not share it with, or give it to, others who seem to have the same symptoms as you have. Also, keep Soriatane (acitretin) and all medications out of the reach of children.
- Do not give blood while you are taking Soriatane and for 3 years after stopping Soriatane therapy.
- Take Soriatane with food.
- Avoid the use of sun lamps and excessive exposure to sunlight.

SORIATANE® (acitretin) is available in two strengths.

10 mg ((art of capsule))

25 mg ((art of capsule))

REMINDER: WARNINGS TO FEMALE PATIENTS

- **YOU MUST** HAVE A BLOOD OR URINE TEST DONE BY YOUR DOCTOR WHICH SHOWS YOU ARE NOT PREGNANT BEFORE YOU START TAKING SORIATANE.
- **YOU MUST** WAIT UNTIL THE 2ND OR 3RD DAY OF YOUR PERIOD TO START TAKING SORIATANE.
- **YOU MUST** USE TWO FORMS OF EFFECTIVE BIRTH CONTROL FOR AT LEAST 1 MONTH BEFORE, DURING, AND FOR AT LEAST 3 YEARS AFTER TAKING SORIATANE.
- **YOU MUST** AVOID CONSUMING BEVERAGES OR PRODUCTS CONTAINING ALCOHOL DURING THE ENTIRE SORIATANE TREATMENT COURSE AND FOR 2 MONTHS AFTER YOU HAVE FINISHED TAKING SORIATANE.

YOU MUST NOT TAKE SORIATANE IF YOU ARE PREGNANT OR MAY BECOME PREGNANT EITHER DURING TREATMENT OR AT ANY TIME FOR AT LEAST 3 YEARS AFTER TREATMENT. YOU MUST USE RELIABLE CONTRACEPTION (BIRTH CONTROL) FOR AT LEAST 1 MONTH BEFORE TREATMENT, DURING TREATMENT, AND FOR AT LEAST 3 YEARS AFTER TREATMENT. PLEASE SEE COMPLETE WARNINGS TO FEMALE PATIENTS ON PAGE ___. YOU MUST AVOID CONSUMING BEVERAGES OR PRODUCTS CONTAINING ALCOHOL DURING TREATMENT AND FOR 2 MONTHS AFTER TREATMENT.

(Roche Hexagon)

Roche Laboratories

A Member of the Roche Group
Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-821/S001

CORRESPONDENCE

ORIGINAL

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey, 07110-1199

Direct Dial (201) 562-5549
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NDA 19821 SERIAL NO. S-007
NDA SUPPL TYPE Labeling

April 29, 1997

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn.: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 30 1997
MEGA DOC RM

Dear Dr. Wilkin:

Re: NDA 19-821 -- Soriatane® (acitretin) Capsules
Supplemental New Drug Application: Revised Labeling

Submitted herewith is revised labeling for Soriatane Capsules. Reference is made to the March 24, 1997 submission of updated draft labeling for the product and to the April 17, 1997 meeting of the FDA Dermatologic and Ophthalmologic Drugs Advisory Committee at which labeling for Soriatane was discussed.

The updated draft package insert submitted on March 24, 1997 has been revised to be consistent with a post-therapy contraceptive period of at least three years, in accordance with the discussion at the Advisory Committee Meeting. Minor editorial revisions have also been made. The draft patient brochure has been updated to be consistent with the draft package insert. We now propose this revised labeling (package insert and patient brochure) for use in the launch of Soriatane.

Please contact me by telephone at 201-562-5549, by facsimile at 201-562-3700 or by e-mail at Betty.Holland@Roche.com, if you have any questions regarding the proposed labeling.

REVIEWS COMPLETED 1/SI
CSO ACTION: See letter
☐ LETTER ☐ MAIL ☐ NEVER
CSO INITIALS

Sincerely,

HOFFMANN-LA ROCHE INC.

Betty C. Holland
Program Director
Drug Regulatory Affairs

BCH
HLR No. 1997-999
Attachments

Desk Copies: Dr. H. Blatt (6), Division of Dermatologic and Dental Drug Products

BEST POSSIBLE COPY

RECORD OF TELEPHONE CONFERENCE

DATE: June 4, 1997
SPONSOR: Hoffmann LaRoche
NDA: 19,821
DRUG: Soriatane
PARTICIPANTS:

FDA: Kathryn O'Connell, MD
Medical Reviewer, HFD-540
/S/ 6/4/97
Mary Jean Kozma Fornaro
Supervisor Project Management Staff. HFD-540

SPONSOR: Betty Holland
Regulatory Affairs

Agreement reached on NDA 19,821, Soriatane revised labeling supplement submitted April 29, 1997, with further revisions submitted May 21, 1997.

All revisions submitted on May 21, 1997 were acceptable with further discussion and agreement on:

1. Physician Insert, page 4: Sponsor suggested wording changed to "For these listed reports", and duplicated where same paragraph repeated.

2. Patient Brochure, page 4: Sponsor agreed to "permanent adverse effects" instead of the FDA proposed "permanent injury".

Conversation ended amicably.

cc:

NDA 19821
HFD 540 Div File
HFD 540 Blatt
HFD 540 O'Connell

/S/ 6/4/97

ORIGINAL **BEST POSSIBLE COPY**

Roche Pharmaceuticals
A Member of the Roche Group

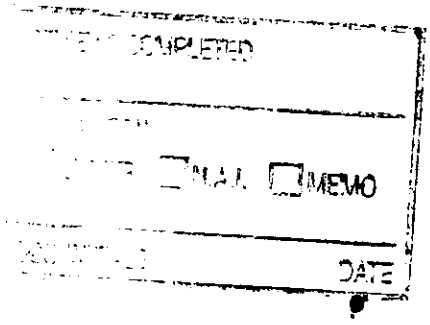
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 562-5549
Fax (201) 562-3700/3554

NEW CORRESPONDENCE

May 1, 1997

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn.: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Wilkin:

Re: NDA 19-821 -- Soriatane® (acitretin) Capsules
Response to Agency Request for Information: Revised Labeling -- Electronic Version

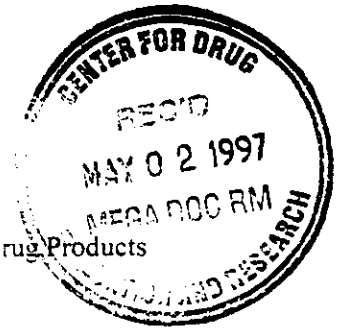
Reference is made to the Supplemental New Drug Application dated April 29, 1997, which contained revised draft labeling. As requested by Dr. H. Blatt, Project Manger, enclosed herein with the archival copy is a copy of the proposed labeling (both package insert and patient brochure) on diskette as a WordPerfect 6.1 file. Note that an additional copy of the diskette is being provided to Dr. Hal Blatt with the desk copy. Also please note that the page numbers on the electronic version do not necessarily correspond with those on the hard copy.

Please contact me by telephone at 201-562-5549, by facsimile at 201-562-3700 or by e-mail at Betty.Holland@Roche.com, if you have any questions regarding the proposed labeling.

Sincerely,

HOFFMANN-LA ROCHE INC.

Betty C. Holland
Program Director
Drug Regulatory Affairs



BCH
HLR No. 1997-1025
Attachment

Desk Copy (with electronic file): Dr. H. Blatt, Division of Dermatologic and Dental Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-821/S-001

MAY - 6 1997

Roche Pharmaceuticals
340 Kingsland Street
Nutley, NJ 07110-1199

Attention: Betty C. Holland
Program Director, Drug Regulatory Affairs

Dear Ms. Holland:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Soriatane (acitretin) Capsules

NDA Number: 19-821

Supplement Number: S-001

Date of Supplement: April 29, 1997

Date of Receipt: April 30, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ORIGINAL

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Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (973) 562-5549
Fax (973) 562-3700/3554

S-001

SUPPL NEW CORRESP

June 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 11 1997
MEGA DOCUMENT ROOM

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn.: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Wilkin:

Re: NDA 19-821/S-001 -- Soriatane® (acitretin) Capsules
Request for Information: Confirmation of Acceptance of Changes in Draft Labeling

Reference is made to the facsimile message received from the Division on May 15 with comments on labeling proposed in Supplement S-001, dated April 29, 1997, and to the amendment submitted May 21, 1997. Reference is also made to the telephone discussion I had with Dr. Kathryn O'Connell and Ms. Mary-Jean Kozmo-Fornaro this morning, June 4, 1997.

This letter is to confirm that we agree with the labeling changes from the revisions on the May 15, 1997 facsimile and May 21, 1997 amendment, per the discussion this morning. The changes are as follows.

- Correction of "undecided" to "undescended" on pages 4 and 9.
- Change of "all" these reports to these "listed" reports on pages 4 and 9.
- Change of permanent "injury" to permanent "adverse effects" on page 4 of the patient brochure.

Please contact me if you have any questions regarding this information.

Sincerely,

HOFFMANN-LA ROCHE INC.

/S/
6/10/97

Betty C. Holland
Program Director
Drug Regulatory Affairs

BCH
HLR No. 1997-1280

DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**
Center for Drug Evaluation and Research
Office of Training and Communication
Freedom of Information Staff HFD-205
5600 Fishers Lane 12 B 05
Rockville, Maryland 20857

March 10, 2000

Maria J. Wood-Armany
Tufts Center for Study of Drug Development
192 South St. STE 550
Boston, MA 02111

F98-22693

Dear Ms. Wood-Armany,

This is in response to your request of August 19, 1998, in which you requested " the approval and approvable letters for Zyrtec, NDA 20-346 (supp #2) by Pfizer, Inc.". Your request was received in the Center for Drug Evaluation and Research on August 28, 1998.

This is also in response to your request of August 19, 1998, in which you requested " the approval and approvable letters for Zyrtec, NDA 19-835 (supp #5) by Pfizer, Inc." Your request was received in the Center for Drug evaluation and Research on August 28, 1998. This information is contained within the original request for Zyrtec NDA 20-346 Supp #2 and no charge will be issued.

The documents you have requested are enclosed.

Charges of $4.90 (Search $0.00, Review $0.00, Reproduction $4.90, Computer time $0.00) will be included in a monthly invoice. **DO NOT SEND ANY PAYMENT UNTIL YOU RECEIVE AN INVOICE.**

If there are any problems with this response, please notify us in writing of your specific problem(s). Please reference the above file number.

This concludes the response for the Center for Drug Evaluation and Research.

Sincerely,

Mark Scheper

Mark Scheper DDS
Freedom of Information Officer
Office of Training and Communication
Freedom of Information Staff, HFD-205

NDA 19-835/S005
20-346/S002