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.

<u>Important Information For Males Taking Soriatane</u>:

♦ 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 07110-1

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 <u>for at least 3 years</u> 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 <u>all</u> 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.

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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]*