

PRODUCT MONOGRAPH

**‘Soriatane’<sup>TM</sup>**

**(acitretin)**

**Capsules**

Keratinization Disorder Therapy

DATE OF REVISION:

January 13, 1997

## NAME OF DRUG

`Soriatane'<sup>TM</sup> (acitretin) CAPSULES

Keratinization Disorder Therapy

### ACTIONS AND CLINICAL PHARMACOLOGY

`Soriatane' (acitretin) is a retinoid, an aromatic analog of vitamin A. The mechanism of action of `Soriatane' is unknown, however, evidence exists for a wide range of actions at various cellular and subcellular levels. These include: regulation of RNA/DNA synthesis, modulation of factors which influence epidermal proliferation, modification of glycoprotein synthesis and modulation of the immune response. Whatever the exact mechanism of action, the most prominent effect of acitretin is a modulation of cellular differentiation in the epidermis, which re-establishes a more normal pattern of cell growth.

Use of acitretin in psoriatic patients results in improvement manifested by a decrease in scale, erythema, and thickness of lesions, and decreased inflammation in the epidermis and dermis.

Oral absorption of `Soriatane' was optimal when given with food. Following administration of a single oral dose of 50 mg `Soriatane' to healthy volunteers, maximum plasma acitretin concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in two to five hours (mean 2.7 hours). Following multiple doses, acitretin plasma concentrations reached steady-state conditions within two weeks. In psoriatic patients who received `Soriatane' (10 to 50 mg/day) for eight weeks, mean steady-state trough concentrations of acitretin ranged between 6 and 25 ng/mL in a dose-dependent manner. In patients administered multiple oral doses of `Soriatane' for up to nine months, the range of elimination half-life (t<sub>1/2</sub>) values observed was 33-92 hours for acitretin (harmonic mean = 48 hours) and 28-123 hours for cis - acitretin (harmonic mean = 64 hours).

In a multiple-dose study in healthy young and elderly subjects, increased acitretin plasma concentrations were seen in elderly subjects. The range of terminal elimination half-lives observed for acitretin were 37-96 hours (harmonic mean = 54 hours) in elderly and 39-70 hours (harmonic mean = 53 hours) in young subjects.

Following oral absorption, acitretin undergoes metabolism and interconversion by simple isomerization to its 13-cis form. Both acitretin and its 13-cis isomer are eliminated from the body primarily by metabolism to chain-shortened breakdown products and conjugates. Acitretin is more than 98% bound to plasma proteins, primarily albumin.

Measurable levels of etretinate (`Tegison'), of which acitretin is the active metabolite, have been detected in plasma samples of patients administered `Soriatane'. The use of alcohol may have been a factor contributing to the presence of etretinate in these patients. In a two-way crossover study in healthy volunteers, all 10 subjects formed etretinate following the ingestion of a single 100 mg oral dose of acitretin in the presence of alcohol (1.4 g/kg ethanol over approximately 3 hours). Peak concentrations of etretinate measured in these subjects ranged from 22 ng/mL to 105 ng/mL (mean: 55 ng/mL). When acitretin was administered in the absence of ethanol in this study, etretinate was not measurable. However, the formation of etretinate from acitretin in the absence of ethanol cannot be excluded. Etretinate has a long elimination phase. When

etretinate has been used as primary therapy, etretinate has been found in the blood of some patients up to 2.9 years after discontinuation of treatment. Of 240 evaluated psoriatic patients who received treatment with `Soriatane' (5-60 mg/day) with no restrictions on alcohol use, 7.5% were found to have measurable concentrations of etretinate (range: 5-62 ng/mL) and a further 27% had a trace of etretinate in the plasma which was not measurable.

### INDICATIONS AND CLINICAL USE

`Soriatane' (acitretin) may be indicated for the treatment of:

- Severe psoriasis (includes erythrodermic and pustular types).
- Other disorders of keratinization.

Severe psoriasis is a condition that involves more than 10% of body surface area or is physically, occupationally or psychologically disabling.

Because of significant adverse effects associated with its use, `Soriatane' should be reserved for patients with the diseases listed above when these are unresponsive to or intolerant of standard treatment. `Soriatane' should only be prescribed by physicians knowledgeable in the use of systemic retinoids. It is recommended that each `Soriatane' prescription is limited to preferably a one-month supply in order to encourage patients to return for their regular appointments.

Most patients experience a relapse after discontinuing therapy. Subsequent courses, when clinically indicated, have produced similar therapeutic results.

### CONTRAINDICATIONS

`Soriatane' (acitretin) is contraindicated in pregnancy. Retinoids are known to cause severe birth defects in a very high percentage of infants exposed to them in utero (see WARNINGS - Subsection; Pregnancy, Pregnancy Testing, Contraception).

Females must not become pregnant while taking `Soriatane' and effective contraception must be practised for an undetermined period of time of at least two years following discontinuation of `Soriatane'. Thereafter, the patient and physician should assess the risks and desirability of discontinuing effective contraception, based on the most current information available. Measurable levels of etretinate (`Tegison'), the prodrug of acitretin, have been detected in plasma samples of patients administered `Soriatane'. The use of alcohol appears to be a factor contributing to the interconversion of acitretin back to etretinate. Ethanol must not be ingested during treatment with `Soriatane' as clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and alcohol. Ethanol should be avoided for two months after cessation of therapy. The length of time necessary to wait after termination of `Soriatane' treatment to ensure that no etretinate will be detectable in the blood has not been determined. Etretinate has a long elimination phase. When etretinate has been used as primary therapy, etretinate has been found in the blood of some patients up to 2.9 years after discontinuation of treatment.

`Soriatane' is contraindicated in females of childbearing potential unless all of the following conditions apply:

1. The patient has severe psoriasis or other severe disorders of keratinization.
2. The patient is reliable in understanding and carrying out instructions.

3. The patient is able to comply with mandatory contraceptive measures.
4. The patient has received, and acknowledged understanding of, a careful oral and printed explanation of the hazards of fetal exposure to `Soriatane' and the risk of possible contraception failure. This explanation may include showing a line drawing to the patient of an infant with the characteristic external deformities resulting from retinoid exposure during pregnancy.
5. The patient has had a serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL with a negative result, performed in a licensed laboratory, within two weeks prior to initiating therapy. The patient has had two or three days of the next normal menstrual period before `Soriatane' therapy is initiated.

(Regarding items 2 to 5, see WARNINGS - Subsection; Pregnancy, Pregnancy Testing, Contraception.)

`Soriatane' is also contraindicated in patients with severely impaired hepatic or renal function, intractable hyperlipidemia, hypervitaminosis A or hypersensitivity to vitamin A or its metabolites.

## WARNINGS

### Pregnancy, Pregnancy Testing and Contraception

The use of systemic retinoids in humans has been associated with congenital abnormalities. There is an extremely high risk that major human fetal abnormalities will occur if pregnancy occurs during treatment with `Soriatane'. Potentially any exposed fetus can be affected. Major fetal abnormalities associated with retinoid administration during pregnancy have been reported; including meningocele, meningoencephalocele, multiple synostosis, facial dysmorphism, anophthalmia, syndactyly, absences of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume and alterations of the skull and cervical vertebrae on X-ray.

Female patients of childbearing potential must not be given `Soriatane' until pregnancy is excluded. A serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL must be performed within two weeks prior to starting `Soriatane' treatment. `Soriatane' treatment should start on the second or third day of the next normal menstrual period following this negative pregnancy test.

Effective contraception must be used for at least one month before starting `Soriatane' treatment, during treatment and for an undetermined period of time of at least two years duration after discontinuation of treatment (see CONTRAINDICATIONS). Thereafter, the patient and physician should assess the risks and desirability of discontinuing effective contraception, based on the most current information available. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method.

Pregnancy occurring during treatment with `Soriatane' and for an undetermined period of time of at least two years duration after its discontinuation carries the risk of fetal malformation (see WARNINGS above and REPRODUCTION AND TERATOLOGY Studies). Females must be fully counseled on the serious risks to the fetus should they become pregnant whilst undergoing `Soriatane' treatment or after discontinuation of `Soriatane' treatment. If pregnancy does occur during this time the physician and patient should discuss the desirability of continuing the pregnancy.

It is strongly recommended that all female patients of childbearing potential treated with `Soriatane' have monthly pregnancy tests during treatment and at regular intervals for an undetermined period of time of at least two years duration after the discontinuation of treatment. These pregnancy tests will:

- a) Serve primarily to reinforce to the patient the necessity of avoiding pregnancy.
- b) In the event of accidental pregnancy, provide the physician and patient an immediate opportunity to discuss the serious risk to the fetus from this exposure to `Soriatane' and the desirability of continuing the pregnancy in view of the potential teratogenic effect of `Soriatane' (see WARNINGS above and REPRODUCTION AND TERATOLOGY Studies).

Women of childbearing potential who have switched from `Tegison' (etretinate) therapy to `Soriatane' must continue to follow the contraceptive recommendations for `Tegison' when on `Soriatane' therapy.

#### Nursing Mothers

Clinical data indicate that acitretin is excreted in human milk. Therefore, nursing mothers should not receive `Soriatane' because of the potential for serious adverse reactions in nursing infants. Women should not breast-feed for an undetermined period of time of at least two years following discontinuation of `Soriatane'.

#### Hyperostosis

In clinical trials with `Soriatane', patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column following six months of treatment. Of 262 patients treated with `Soriatane', 7% had pre-existing abnormalities of the spine which showed new changes or progression of pre-existing findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, and narrowing and destruction of cervical disc space. These existing abnormalities may be in some part attributable to the underlying psoriasis and/or the patient's age. During the six-month period of observation, no bone changes were seen in patients who had normal pretreatment X-rays. Other retinoids including `Tegison' (etretinate), of which `Soriatane' is the active metabolite, have been associated with the development of extraosseous calcification and/or hyperostosis. Calcification of the ligaments of the spine, tendon insertions of the arms and legs, and intraosseous membranes of the arms and legs, have been reported. Hyperostotic changes of the vertebrae, forearms, hips, acetabula, legs and calcanei have also been reported. It is not clear whether the extraosseous calcification and/or hyperostosis are progressive. Pre-treatment radiographs of the cervical, thoracic and lumbar spine may be useful when monitoring patients on long-term `Soriatane' therapy. Early recognition of musculoskeletal symptoms associated with `Soriatane' therapy may be important. There is some evidence that scintigraphic changes appear before radiographic findings. Scintigraphic changes may disappear after discontinuation of `Soriatane' treatment, however, radiographic changes may persist. Bone scintigraphy may be important in monitoring patients on `Soriatane' therapy since scintigraphic changes seem to precede radiographic changes.

In adults receiving long-term treatment with `Soriatane', appropriate examinations should be periodically performed in view of possible ossification abnormalities. If such disorders arise, the continuation of therapy should be discussed with the patient on the basis of a careful risk/benefit analysis. In one patient, spinal hyperostosis and calcification of spinal ligaments, resulting in compression of the spinal chord, appeared after several years' therapy with Tegison'.

### Hepatotoxicity

Hepatic function should be checked before starting treatment with `Soriatane' every 1-2 weeks for the first 2 months after commencement and then every 3 months during treatment. If abnormal results are obtained, weekly checks should be instituted. If hepatic function fails to return to normal or deteriorates further, `Soriatane' must be withdrawn. In such cases it is advisable to continue monitoring hepatic function for at least 3 months. Elevations of AST (SGOT), ALT (SGPT) or LDH have occurred in 20-28% of patients treated with `Soriatane'. One of the 329 patients treated in clinical trials had clinical jaundice with elevated serum bilirubin and transaminases considered possibly related to `Soriatane' treatment. Liver function test results in this patient returned to normal after Soriatan' was discontinued.

If hepatotoxicity is suspected during treatment with `Soriatane', the drug should be discontinued and the etiology further investigated.

Ten of 652 patients treated in clinical trials of etretinate (`Tegison'), 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 four reports of hepatitis-related deaths worldwide; two of these patients had received etretinate for a month or less before presenting with hepatic symptoms.

## PRECAUTIONS

### General

Patients should be advised that a transient worsening of their psoriasis may occur during the initial Soriatan' (acitretin) treatment period.

### Benign Intracranial Hypertension (Pseudotumor Cerebri):

`Soriatane' and other retinoids have been associated with cases of pseudotumour cerebri (benign intracranial hypertension). Early symptoms and signs of benign intracranial hypertension include headache, nausea and vomiting and, visual disturbances. Patients with these symptoms should be examined for papilledema and if present, they should discontinue `Soriatane' immediately and be referred for neurological diagnosis and care.

As tetracyclines can also cause an increase in intracranial pressure, their combination with `Soriatane' should be avoided.

### Ophthalmic Effects

Drug-related ophthalmic effects (dry eyes, irritation of eyes, brow and lash loss, blepharitis and/or crusting of lids, photophobia, redness, recurrent styes, pannus and subepithelial corneal lesions) were noted during treatment with `Soriatane' in 29% of 252 patients who were followed with ophthalmic examinations. Patients should be advised that they may experience decreased tolerance to contact lenses during the initial treatment period.

Overall in clinical studies, decreased night vision was reported by two patients and blurring of vision by three patients.

The following additional ophthalmic effects have occurred in patients taking `Tegison' (etretinate), of which `Soriatane' is the active metabolite: decreased visual acuity, minimal posterior subcapsular cataract, iritis, blot retinal hemorrhage and scotoma.

Any patient receiving `Soriatane' therapy, experiencing visual difficulties should discontinue this drug and undergo ophthalmic evaluation.

### Lipids

Blood lipid determinations should be performed before `Soriatane' is administered and again at intervals of one or two weeks until the lipid response to the drug is established, which is usually within four to eight weeks. Approximately 65% of patients receiving `Soriatane' during clinical trials experienced an elevation in serum triglycerides. Approximately 30% developed a decrease in high density lipoproteins (HDL). Approximately 9% experienced elevated serum cholesterol levels. These effects of `Soriatane' were reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions.

Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with acute pancreatitis. Therefore, every attempt should be made to control significant elevations of triglycerides or HDL decreases by reduction of weight or restriction of dietary fat and alcohol intake while continuing `Soriatane' therapy.

If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of `Soriatane' should be considered. An associated risk of atherogenesis cannot be ruled out if these conditions persist. (ref. #4,5,6,9,10)

### Vitamin A

`Soriatane' is a derivative of vitamin A. To avoid the risk of additive toxic effects, patients should be advised against taking other systemic retinoids or vitamin supplements containing vitamin A.

### Methotrexate

Due to an increased hepatitis risk, the combined use of `Soriatane' and methotrexate should be avoided.

### Use in Pediatric Patients

Safety and efficacy of `Soriatane' in children have not been established. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostosis and premature epiphyseal closure have been reported with other systemic retinoids, including `Tegison' (etretinate) of which `Soriatane' is the active metabolite. Due to the uncertain effect of long-term `Soriatane' therapy on growth and skeletal development, `Soriatane' should only be used in pediatric patients with the most severe forms of keratinization disorders for which there are no effective alternative therapies. Pretreatment X-rays for bone age including X-rays of the knees are advised. Bone scans (scintigraphs) and/or X-rays should be considered at yearly intervals when monitoring children on long-term therapy. In addition pain or limitation of movement should be evaluated by appropriate radiological examination.

### Blood Donation

It is recommended that blood donation for transfusion purposes be deferred during therapy with `Soriatane' and for an undetermined period of time of at least two years duration after discontinuation of treatment. Theoretically, blood from such donors could present a small risk to the fetus if transfused to a pregnant mother during the first trimester of pregnancy (see CONTRAINDICATIONS).

### Drug Interactions

Concomitant administration of vitamin A and other systemic retinoids must be avoided due to the risk of possible additive toxic effects.

The concomitant administration of methotrexate and etretinate ('Tegison') has been associated with hepatitis, a similar increased hepatitis risk may be expected with the combined use of 'Soriatane' and methotrexate.

Preliminary studies indicated that 'Soriatane' does not influence the endogenous progesterone plasma concentrations induced by oral contraceptives. The effect of microdosed progesterone preparations may be diminished by interaction with acitretin. Therefore, microdosed progesterone preparations or "minipills" should not be used.

Concomitant administration of phenprocoumon and 'Soriatane' does not alter the hypothermic effect of phenprocoumon or the plasma disposition of 'Soriatane'.

The pharmacokinetics of 'Soriatane' and digoxin are not altered by concomitant multiple dose regimens of these two drugs.

Concomitant administration of cimetidine did not alter the oral bioavailability of 'Soriatane' or the isomerization to its 13-cis form. Single oral doses of 'Soriatane' did not affect the steady state plasma concentration or renal clearance of cimetidine.

Limited data which could not be duplicated, indicated that 'Soriatane' treatment either increased insulin sensitivity directly or interacted with glyburide to do so. Careful supervision of diabetic patients under treatment with 'Soriatane' is recommended.

#### ADVERSE REACTIONS

Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic and central nervous systems. Nearly all of the clinical adverse events reported to date with 'Soriatane' (acitretin) administration resemble those of the hypervitaminosis A syndrome. The tables below list, grouped by frequency, the adverse reactions reported during clinical trials in which patients were treated with 'Soriatane' for psoriasis.

ADVERSE EVENTS

<b>BODY SYSTEM</b>	<b>MOST FREQUENT &gt;10%</b>	<b>LESS FREQUENT<sup>a</sup> 1-10%</b>	<b>RARE<sup>a</sup> &lt;1.0%</b>
Skin and Appendages	Skin peeling/scaling Alopecia Pruritus Sticky skin Nail disorder Dry skin Erythematous rash Skin atrophy Hyperesthesia	Paronychia Paresthesia Psoriaform rash Rash Photosensitivity reaction Pyogenic granuloma Bullous eruption Skin ulceration Cold/clammy skin Increased sweating Purpura Abnormal hair texture Skin fissures Hypoesthesia Infection Seborrhea	Dermatitis Abnormal skin odour Skin nodule Skin hypertrophy Skin disorder Impaired healing Eczema Otitis externa Flushing Acne
Mucous Membranes	Cheilitis Rhinitis Dry mouth	Thirst Stomatitis Gingivitis Increased saliva Gingival bleeding Epistaxis	Ulcerative stomatitis Pharyngitis Anal disorder Nose bleeds Altered saliva
Eye Disorders	Xerophthalmia	Conjunctivitis/irritation Abnormal/blurred vision Blepharitis <sup>b</sup> Eye pain Photophobia	Abnormal lacrimation Decreased night vision Cataract Eye abnormality Pannus <sup>b</sup> Recurrent styes <sup>b</sup> Subepithelial corneal lesions <sup>b</sup>
Musculoskeletal	Arthralgia	Myalgia Spinal hyperostosis <sup>c</sup> Back pain Hypertonia Arthritis	Arthrosis Leg cramps Olecranon bursitis
CNS	Rigors	Headache Pain	Abnormal gait Pseudotumor cerebri

ADVERSE EVENTS (Cont'd)

<b>BODY SYSTEM</b>	<b>LESS FREQUENT<sup>a</sup> 1-10%</b>	<b>RARE<sup>a</sup> &lt;1.0%</b>
Gastrointestinal	Nausea Abdominal pain	Constipation Diarrhea Tenesmus Dyspepsia Glossitis Melena Tongue ulceration Pancreatitis
Special Senses/Other	Tinnitus Taste perversion Earache Ceruminosis	Deafness Taste loss
Psychiatric	Insomnia Nervousness	Depression Somnolence Dysphonia
Respiratory		Coughing Laryngitis Sinusitis Increased sputum
Urinary		Dysuria Abnormal urine Balanoposthitis
Reproductive		Leukorrhea
Cardiovascular		Increased bleeding time Chest pain Angioedema Vasculitis <sup>d</sup>
Body as a Whole	Fatigue Anorexia Increased appetite Impotence Edema	Malaise Fever Moniliasis <sup>e</sup> Muscle weakness Alcohol intolerance Hot flashes Hepatitis <sup>f</sup> Icterus <sup>f</sup>

<sup>a</sup> Some may bear no relationship to therapy.

<sup>b</sup> Based on review of eye examination forms by consulting ophthalmologist (N=252).

<sup>c</sup> Incidence of 7% based on review of films by consulting radiologist (N=262).

<sup>d</sup> Vasculitis has not been documented with acitretin but has been seen with other retinoids.

<sup>e</sup> Increased incidence of vulvovaginitis due to *Candida albicans* has been noted during treatment with 'Soriatane'

<sup>f</sup> Events observed and reported rarely.

LABORATORY ABNORMALITIES

BODY SYSTEM	LABORATORY ABNORMALITY (%)	COMMENTS																								
Hepatic	<u>Increased</u> ALT (SGPT) (28%) AST (SGOT) (23%) LDH (21%) Alkaline Phosphatase (16%) GGTP (14%) Direct Bilirubin (11%)	- In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. - IF HEPATOTOXICITY IS SUSPECTED, THERAPY SHOULD BE DISCONTINUED (SEE CONTRAINDICATIONS AND WARNINGS).																								
	<u>Increased</u> Triglycerides (65%) Cholesterol (9%)  <u>Decreased</u> HDL (30%)	- These changes are more common in patients who are predisposed to hypertriglyceridemia (see PRECAUTIONS).  - The effects on triglycerides, cholesterol and HDL were reversible upon cessation of 'Soriatane' therapy.																								
	<u>Increased</u> Total Bilirubin (2%) Globulin (2%)  <u>Decreased</u> Serum Albumin (1%)																									
	Renal	<u>Increased</u> Uric Acid (17%) Creatinine (5%) BUN (2%)																								
Hematologic	<u>Increased</u> Reticulocytes (38%) WBC (11%) Eosinophils (8%) Monocytes (7%) Bands (4%) Basophils (3%)  <u>Decreased</u> WBC (7%)  <table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"><u>Increased</u></td> <td style="width: 50%;"><u>Decreased</u></td> </tr> <tr> <td>(16%)</td> <td>Neutrophils (</td> </tr> <tr> <td>5%)</td> <td></td> </tr> <tr> <td>(2%)</td> <td>Lymphocytes</td> </tr> <tr> <td>(11%)</td> <td></td> </tr> <tr> <td>(4%)</td> <td>Hemoglobin (</td> </tr> <tr> <td>9%)</td> <td></td> </tr> <tr> <td>(2%)</td> <td>Platelets (</td> </tr> <tr> <td>6%)</td> <td></td> </tr> <tr> <td>(3%)</td> <td>Hematocrit (</td> </tr> <tr> <td>5%)</td> <td></td> </tr> <tr> <td>(2%)</td> <td>RBC (3%)</td> </tr> </table>	<u>Increased</u>	<u>Decreased</u>	(16%)	Neutrophils (	5%)		(2%)	Lymphocytes	(11%)		(4%)	Hemoglobin (	9%)		(2%)	Platelets (	6%)		(3%)	Hematocrit (	5%)		(2%)	RBC (3%)	
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Urinary	RBC in urine (10%) WBC in urine (7%) Glycosuria (4%) Acetonuria (3%) Proteinuria (2%)															
Electrolytes	<table border="0"> <tr> <td><u>Increased</u></td> <td><u>Decreased</u></td> </tr> <tr> <td>(16%)</td> <td>Phosphorous (3%)</td> </tr> <tr> <td>(12%)</td> <td>Potassium (3%)</td> </tr> <tr> <td>(12%)</td> <td>Magnesium (12%)</td> </tr> <tr> <td>(2%)</td> <td>Sodium (1%)</td> </tr> <tr> <td>(4%)</td> <td>Calcium (2%)</td> </tr> <tr> <td>(2%)</td> <td>Chloride (3%)</td> </tr> </table>	<u>Increased</u>	<u>Decreased</u>	(16%)	Phosphorous (3%)	(12%)	Potassium (3%)	(12%)	Magnesium (12%)	(2%)	Sodium (1%)	(4%)	Calcium (2%)	(2%)	Chloride (3%)	
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Other reported laboratory abnormalities include: increased creatinine phosphokinase (37%), increased (21%) or decreased (7%) fasting blood sugar and increased (7%) or decreased (3%) iron.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

To date, there has been no experience with acute overdose of `Soriatane' (acitretin). In the event of acute overdosage, evacuation of the stomach should be considered during the first few hours after this overdose. Signs and symptoms of overdosage with `Soriatane' would probably be similar to acute vitamin A toxicity, i.e., severe headache, nausea or vomiting, drowsiness, irritability, and pruritus. Elevated intracranial pressure has been reported with both acute and chronic vitamin A overdoses as well as in patients treated with therapeutic doses of `Soriatane'. Patients with a `Soriatane' overdose should be monitored closely for signs of increased intracranial pressure. If overdosage occurs in patients already receiving therapeutic doses of `Soriatane', the drug must be discontinued immediately.

All female patients of childbearing potential who have taken an overdose of `Soriatane' must:

1. Have a pregnancy test at the time of the overdose.
2. Use an effective form of contraception for an undetermined period of time of at least two years duration after the overdose.

If the pregnancy test is positive, the patient should be fully counseled on the serious risk to the fetus from this exposure to `Soriatane' and the physician and patient should discuss the desirability of continuing the pregnancy (see CONTRAINDICATIONS AND WARNINGS).

## DOSAGE AND ADMINISTRATION

There is intersubject variation in the pharmacokinetics, clinical efficacy, and incidence of side effects with `Soriatane' (acitretin). Individualization of dosage is required to achieve maximum therapeutic response while minimizing side effects.

### Initial Therapy

`Soriatane' therapy should be initiated at 25 mg per day, given as a single dose with the main meal. If by four weeks the response is unsatisfactory, and in the absence of toxicity, the daily dose may be gradually increased to a maximum of 75 mg per day. The dose may be reduced if necessary to minimize side effects.

### Maintenance Therapy

#### Psoriasis

Maintenance doses of 25 to 50 mg per day may be given after initial response to treatment. The maintenance dose should be based on clinical efficacy and tolerability. It may be necessary in some cases to increase the dose to a maximum of 75 mg per day.

In general, therapy should be terminated when lesions have resolved sufficiently. Relapses may be treated as outlined for initial therapy.

#### Other Keratinization Disorders

Maintenance doses of 10 mg to a maximum of 50 mg per day may be given for disorders of keratinization.

## PHARMACEUTICAL INFORMATION

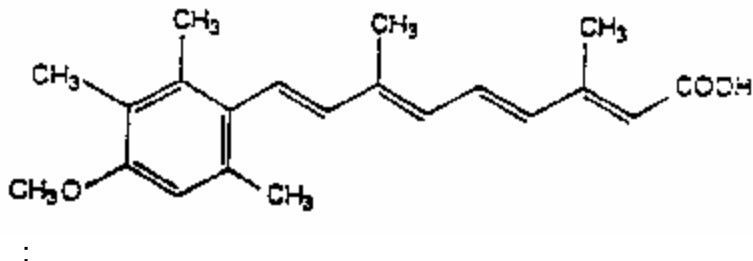
i) DRUG SUBSTANCE

Proper Name: Acitretin

Code: Ro 10-1670

Chemical Name: All-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid.

Structural



`Soriatane' (acitretin)

Molecular Formula: C<sub>21</sub>H<sub>26</sub>O<sub>3</sub>

Molecular Weight: 326.44

Description: Acitretin is a yellow to greenish-yellow crystalline powder which may have a faint odour. It is slightly soluble in pH 7.5 aqueous buffer (artificial intestinal juice) and very slightly soluble in water. pK<sub>a</sub> = 5. Melting range is 210 - 220 C.

ii) COMPOSITION

Each `Soriatane' capsule contains either 10 mg or 25 mg of acitretin, gelatin, maltodextrin, microcrystalline cellulose, and sodium ascorbate. Gelatin capsule shell ingredients include iron oxide (yellow, black and red) and titanium dioxide.

iii) STABILITY AND STORAGE RECOMMENDATIONS

Store at 15-30 C. Protect from light.

DOSAGE FORMS

Availability

`Soriatane' 10: Hard gelatin capsule (No. 4) containing 10 mg acitretin. Brown and white capsules.

`Soriatane' 25: Hard gelatin capsule (No. 1) containing 25 mg acitretin. Brown and yellow capsules.

`Soriatane' capsules 10 and 25 mg are available in units of 30 capsules contained in a "push-through blister" package.

INFORMATION FOR THE CONSUMER

`Soriatane'<sup>TM</sup> (acitretin) Capsules

INFORMATION FOR THE PATIENT

(MALE AND FEMALE)

`Soriatane' is a medicine used to treat certain severe types of skin disorders. For your own health, safety and well-being, it is **IMPORTANT** that you read the following information carefully.

**`Soriatane' CAN CAUSE DEFORMED BABIES IF IT IS TAKEN BY A FEMALE BEFORE OR DURING PREGNANCY. YOUR DOCTOR HAS A LINE DRAWING OF ONE OF THESE DEFORMED BABIES WHICH YOU SHOULD ASK TO SEE.**

**IMPORTANT INFORMATION FOR FEMALE PATIENTS  
OF CHILDBEARING POTENTIAL**

- DO NOT TAKE `Soriatane' IF YOU ARE OR MAY BECOME PREGNANT DURING TREATMENT OR FOR AN UNDETERMINED PERIOD OF TIME OF AT LEAST TWO YEARS DURATION AFTER TREATMENT HAS STOPPED. (DISCUSS THIS WITH YOUR DOCTOR.)
- YOU MUST AVOID BECOMING PREGNANT WHILE YOU ARE TAKING `Soriatane' AND FOR AN UNDETERMINED PERIOD OF TIME OF AT LEAST TWO YEARS DURATION AFTER YOU STOP TAKING `Soriatane'. (DISCUSS THIS WITH YOUR DOCTOR.)
- YOU MUST DISCUSS EFFECTIVE BIRTH CONTROL WITH YOUR DOCTOR BEFORE BEGINNING TREATMENT AND YOU MUST USE EFFECTIVE BIRTH CONTROL:
  - FOR AT LEAST ONE MONTH BEFORE YOU START `Soriatane';
  - WHILE YOU ARE TAKING `Soriatane'; AND
  - FOR AN UNDETERMINED PERIOD OF TIME OF AT LEAST TWO YEARS DURATION AFTER YOU STOP TAKING `Soriatane'. (DISCUSS THIS WITH YOUR DOCTOR.)

BEARING IN MIND THAT ANY METHOD OF BIRTH CONTROL CAN FAIL.

- IT IS RECOMMENDED THAT YOU EITHER ABSTAIN FROM SEXUAL INTERCOURSE OR USE TWO RELIABLE METHODS OF BIRTH CONTROL AT THE SAME TIME.
- DO NOT TAKE `Soriatane' UNTIL YOU ARE SURE THAT YOU ARE NOT PREGNANT.
- YOU MUST HAVE A SERUM OR URINE PREGNANCY TEST WITHIN TWO WEEKS BEFORE YOU START `Soriatane'.
- YOU MUST WAIT UNTIL THE SECOND OR THIRD DAY OF YOUR NEXT NORMAL MENSTRUAL PERIOD BEFORE YOU START `Soriatane'.

• CONTACT YOUR DOCTOR IMMEDIATELY IF YOU DO BECOME PREGNANT WHILE TAKING `Soriatane' OR AFTER TREATMENT HAS STOPPED. YOU SHOULD DISCUSS WITH YOUR DOCTOR THE SERIOUS RISK OF YOUR BABY HAVING SEVERE BIRTH DEFORMITIES BECAUSE YOU ARE TAKING OR HAVE TAKEN `Soriatane'. YOU SHOULD ALSO DISCUSS THE DESIRABILITY OF CONTINUING WITH YOUR PREGNANCY.

• DO NOT BREAST-FEED WHILE TAKING `Soriatane' OR FOR AN UNDETERMINED PERIOD OF TIME OF AT LEAST TWO YEARS DURATION AFTER TREATMENT HAS STOPPED. (DISCUSS THIS WITH YOUR DOCTOR.)

IMPORTANT INFORMATION FOR ALL PATIENTS  
(MALE AND FEMALE)

**PREGNANCY MUST BE AVOIDED BY ANY FEMALE TAKING `Soriatane' AS `Soriatane' CAN CAUSE DEFORMED BABIES. (SEE IMPORTANT INFORMATION FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL.)**

- Females: do not drink alcohol while taking "Soriatane" and for two months after you have stopped treatment.
- Males: avoid or limit consumption of alcohol while taking "Soriatane" and for two months after you have stopped treatment.
- Be sure to return to your doctor as scheduled. It is important for your doctor to see you regularly, preferably every month, when you are taking `Soriatane'. Blood tests and other tests allow your doctor to check your response to `Soriatane'. Discuss your progress and any concerns with your doctor.
- Do not give `Soriatane' to anyone else who may have similar symptoms. `Soriatane' has to be prescribed for each person by their own doctor because of possible side effects (see below). **IMPORTANT: `Soriatane' can cause deformed babies if taken by a female before or during pregnancy.**
- Do not donate blood while taking `Soriatane' or for an undetermined period of time of at least two years duration after treatment has stopped. This is because your blood should not be given to pregnant females.

\*PLEASE CONTINUE READING\*

OTHER INFORMATION FOR ALL PATIENTS  
(MALE AND FEMALE)

THINGS YOU SHOULD TELL YOUR DOCTOR BEFORE STARTING `Soriatane':

- Tell your doctor if you or any members of your family have diabetes, liver disease, heart disease, depression, alcoholism, or obesity.

**TREATMENT PROGRESS**

- A temporary worsening of your skin condition may occur during the first month of treatment with `Soriatane'. Occasionally, there will be more redness or itching at first, but this will normally fade as treatment continues. It may take two to three months before the full benefit of `Soriatane' is seen.
- Contact your doctor if you notice a worsening of your skin condition. This may happen within a few months after stopping `Soriatane'. Another course of treatment will usually produce the same response as the first course.

**SIDE EFFECTS**

- In the first few weeks, perhaps before you see any healing, **you may begin to have some side effects. Some of the most common are:** chapped lips; peeling of fingertips, palms, and soles; loss of hair (see below); itching, sticky skin; or runny or dry nose. **Check with your doctor to see if any change in your medication is needed, especially if these effects become bothersome.**

- Most patients experience some degree of hair loss, but the condition varies among patients. The extent of hair loss that you may experience and whether or not all your hair will return to normal after treatment cannot be predicted.
- If you wear contact lenses, you may find them uncomfortable during and after treatment because `Soriatane` may cause dry eyes.
- **Tell your doctor if any of your side effects do not clear up in a few weeks after you stop taking `Soriatane`.**

#### **SPECIAL PRECAUTIONS YOU SHOULD TAKE:**

- **Do not use vitamin preparations or health food supplements that contain vitamin A.** `Soriatane` is related to vitamin A. The vitamin A in these products may add to the unwanted effects of `Soriatane`. Check with your doctor or pharmacist if you are unsure about the vitamin A content of any product you are taking.
- **Protect yourself from excessive exposure to the sun.** `Soriatane` may increase the sensitivity of your skin to the sun.
- A few patients on `Soriatane` have experienced decreased night vision. Since the onset can be sudden, you should be particularly careful when driving or operating any vehicle at night. If you experience any visual difficulties, stop taking `Soriatane` and consult your doctor.

#### **SPECIAL SYMPTOMS YOU SHOULD TELL YOUR DOCTOR ABOUT:**

- **Tell your doctor if you have aches or pains in bones or joints, or difficulty in moving.** Bone changes have been detected by X-ray examination in patients taking `Soriatane`. The extent of any harm from these changes is not presently known.
- **TELL YOUR DOCTOR AS SOON AS POSSIBLE, IF YOU EXPERIENCE ANY OF THE FOLLOWING SYMPTOMS** BECAUSE THESE SIDE EFFECTS MAY POSSIBLY RESULT IN PERMANENT EFFECTS. THESE SYMPTOMS MAY BE EARLY SIGNS OF RARE, BUT MORE SERIOUS SIDE EFFECTS WHICH YOUR DOCTOR MAY WANT TO CHECK AS SOON AS POSSIBLE:
  - HEADACHES, NAUSEA, VOMITING, BLURRED VISION, OTHER VISUAL PROBLEMS, CHANGES IN MOOD.
  - PERSISTENT FEELING OF DRY EYES, DECREASE IN NIGHT VISION.
  - ACHES OR PAINS IN BONES OR JOINTS, OR DIFFICULTY IN MOVING.
  - YELLOWING OF THE SKIN OR EYES AND/OR DARK URINE, FLU-LIKE SYMPTOMS.
- **Tell your doctor about any unusual or severe symptoms that appear during treatment.**

#### **GENERAL GUIDELINES WHEN TAKING YOUR MEDICATION...**

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

- **Keep `Soriatane' out of the reach of children.**
- **Read your prescription label carefully** and be sure to take the exact amount of medicine prescribed by your doctor. Your doctor may change your prescribed dose from time to time, therefore, it is important that you check the label after each refill. If you have any questions call your doctor.
- **Take `Soriatane' with food or just after a meal.** If you forget to take a dose of `Soriatane', it may be taken later the same day, but, do not take more `Soriatane' in one day than your doctor has prescribed.
- **Protect `Soriatane' capsules from sunlight and heat.** `Soriatane' does not need to be refrigerated.

**THIS SUMMARY DOES NOT CONTAIN ALL KNOWN INFORMATION ABOUT `Soriatane'. TALK TO YOUR DOCTOR IF YOU HAVE ANY QUESTIONS.**

## ANIMAL PHARMACOLOGY

### Pharmacokinetics

In general, the absorption and disposition of acitretin in animals support the pharmacokinetics of acitretin in humans. In the dog and monkey, oral absorption of acitretin was rapid with peak plasma concentrations reached in 1-4 hours, although absorption was not dose proportional. The elimination half-life in the dog following oral administration was approximately two hours. In the rat, plasma concentrations of acitretin in males were higher than in females. Gender differences in the disposition of acitretin were also found in the dog in that the total clearance and volume of distribution in females were less than in males although the elimination half-life remained unchanged. Excretion of acitretin differed as well, with the rat excreting 80% and 2-20% in the bile and urine, respectively and the dog excreting 96% and 4% in the feces and urine, respectively.

## HUMAN PHARMACOLOGY

### Pharmacokinetics

#### Single Dose

Following administration of a single oral dose of 50 mg of acitretin to 18 healthy male subjects (ages 18-40, weighing 63.6-96.0 kg), maximum plasma acitretin concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in two to five hours (mean 2.7 hours) (Table 1).

CHARACTERISTICS	N	AGE	SEX M/F	DOSE FORM	ORAL DOSE (mg)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	TOTAL AUC (ng·hr/mL)	t (hr)	(C <sub>min</sub> )S <sub>S</sub> (ng/mL)
Single Dose Healthy	18	18-40	18/0	Capsule	50	416(31)	2.7(37)	2,249(28)*	—	—
Dose Proportionality Healthy	18	18-40	18/0	Capsule Capsule Capsule Capsule	25 50 75 100	299(30) 562(42) 851(39) 1,151(39)	3.0(35) 4.0(86) 3.0(41) 3.0(52)	1,301(27) 2,792(39) 3,727(37) 5,424(31)	—	—
Bioavailability Healthy	24	20-40	21/3	Capsule Capsule Suspension	10 25 25	111(32) 321(28) 255(39)	3.3(43) 3.0(38) 3.8(43)	572(31) 1,672(31) 1,592(33)	—	—
Multiple Dose Severe psoriasis	11	21-70	11/0	Capsule (Single Dose) Capsule (Day 58)	50 50/day	— 306(51)	— 3.5(20)	2,056(22) 2,472(45)	— 50(28)	— 24(38)

\*AUC<sub>0-15</sub>

Table 1: Acitretin pharmacokinetic parameters ± (%CV)

#### Dose Proportionality

Eighteen healthy male subjects (ages 18-40 years, weighing 60-87 kg) received single oral 25, 50, 75, and 100 mg doses of acitretin with food. The oral absorption of acitretin increased proportionally with dose as seen in Figure 1 and Table 1. A dose-proportional appearance of metabolite was also observed (Figure 2).

In the absence of food, acitretin absorption increased in a proportional manner in the range of 25-50 mg, however, at single oral doses of 75 mg and 100 mg the oral absorption increased in a linear but less than proportional manner. A nonproportional appearance of metabolite was also seen at higher doses.

Figure 1: Mean acitretin plasma concentrations following administration of 25 mg (Treatment A), 50 mg (Treatment B), 75 mg (Treatment C) and 100 mg (Treatment D) of acitretin, with food, in 18 healthy male subjects.

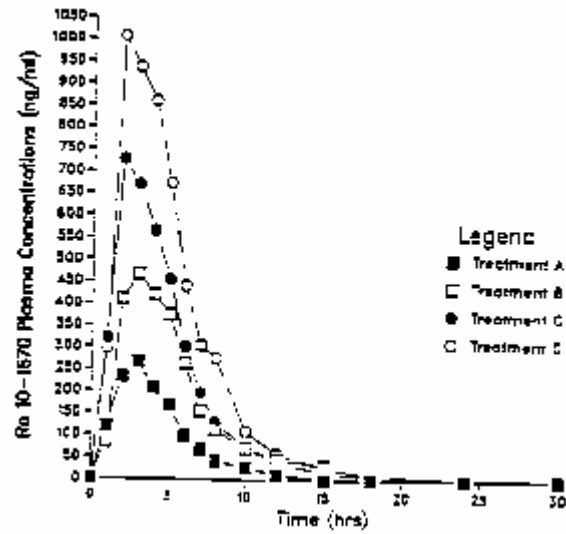
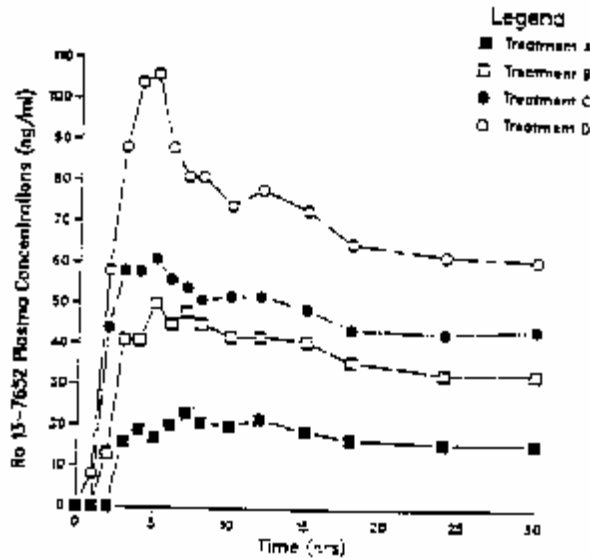


Figure 2: Mean 13-cis metabolite concentrations following administration of 25 mg (Treatment A), 50 mg (Treatment B), 75 mg (Treatment C), and 100 mg (Treatment D) of acitretin with food in 18 healthy male subjects.



## Bioavailability

The rate and extent of absorption of acitretin were approximately doubled, compared to administration under fasting conditions, when acitretin was given with food as a single 50 mg dose.

A single 50 mg capsule of acitretin was administered with food to 12 healthy male subjects (ages 21-25, weighing 57-79 kg). The mean absolute bioavailability of the capsule was approximately 59% (range 36-95%).

Twenty-four healthy subjects (21 males, 3 females, ages 20-40, weighing 71.8-86.8 kg) received single oral doses of acitretin as a 10 mg and 25 mg capsule, and a 25 mg oral suspension, with food. Pharmacokinetic parameters are shown in Table 1. Acitretin, when given as 10 mg and 25 mg capsule formulations, was bioavailable (90% and 105% respectively) relative to the 25 mg oral suspension. The relative formation of the active 13-cis metabolite was not altered by dose or dosage formulation.

## Multiple Dose

The pharmacokinetics of acitretin was established in a study involving 11 male patients (ages 21-70 years, weighing 55-81 kg) with severe psoriasis. Of the 11 patients, 6 received daily single oral 50 mg doses of acitretin for 58 days and 5 received single oral doses ranging from 20 to 50 mg for two months to one year. Pharmacokinetic parameters are presented in Table 1 and Figure 3. The mean terminal elimination half-life for acitretin, which cannot be observed after single dosing, because concentrations fall below the assay sensitivity limit during the distribution phase, was 50 hours (Range 33-60 hours). The mean accumulation ratio for acitretin as determined by comparing the AUC values after the last and first doses was 1.4, and was predictable from linear pharmacokinetics. There was no unexpected accumulation. Average trough concentrations (~24 ng/mL) remained constant throughout the study.

The mean terminal elimination half-life for the metabolite, which could also be accurately estimated only after multiple doses of acitretin, was 75 hours (Range 53-99 hours). The mean accumulation ratio was 0.9 and average trough concentrations (~116 ng/mL) remained constant throughout the study.

Figure 3:

Mean acitretin and

13-cis metabolite plasma concentrations (n=6) after the initial and last

dose of a 58-day regimen of acitretin (50 mg/day). ( $C_{\min}$ )<sub>ss</sub> during

therapy are also included.

In patients administered multiple oral doses of `Soriatane' for up to nine months, the range of elimination half-life ( $t_{1/2}$ ) values observed was 33-92 hours for acitretin (harmonic mean = 48 hours) and 28-123 hours for cis-acitretin (harmonic mean = 64 hours).

Psoriatic patients (ages 25-84, weighing 55-98 kg) received daily 10 mg, 25 mg or 50 mg doses of acitretin for eight weeks. Steady-state concentrations of acitretin and metabolite were reached within two weeks. Mean steady-state trough concentrations for both drugs increased with dose in a proportional manner. Acitretin trough plasma concentrations ranged between 6 and 7 ng/mL (n=21), 11 and 14 ng/mL (n=18) and 19 and 25 ng/mL (n=18) over the eight-week period at daily oral doses of 10 mg, 25 mg and 50 mg, respectively. In this same study, acitretin plasma concentrations were not detectable (<4-6 ng/mL) in all 67 patients three weeks after cessation of therapy. Plasma concentrations of the 13-cis metabolite were not detectable (<4-6 ng/mL) in 61 of these 67 patients and ranged from 6-22 ng/mL for the remaining six patients. The highest concentration was observed in a patient with impaired hepatic function. When this patient was excluded, the range of values was 6-12 ng/mL.

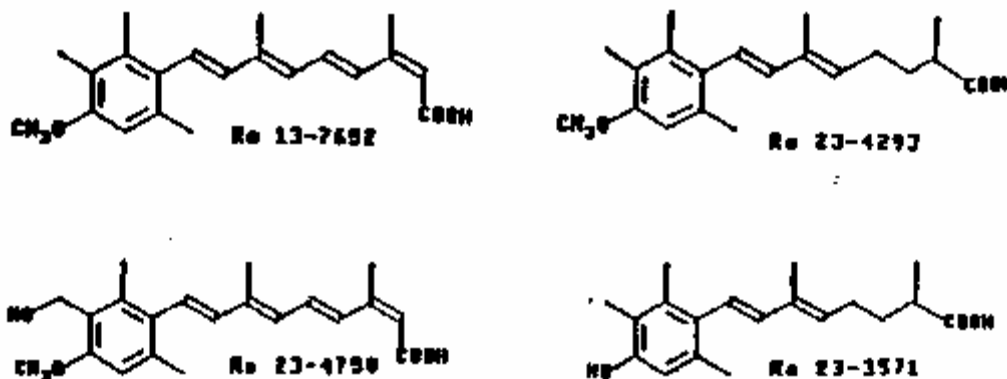
Plasma levels of acitretin and 13-cis acitretin were below the limit of quantification (2-6 ng/mL) within 37 days post-therapy, without exception, in plasma samples obtained from 117 patients following cessation of `Soriatane' treatment.

#### Absorption, Metabolism and Excretion

Following oral absorption, acitretin undergoes metabolism and interconversion by simple isomerization to its 13-cis form (main metabolite). The steady-state plasma trough concentrations of this biologically active metabolite are 5-6 fold higher than acitretin and decline essentially in parallel with those of the parent drug. Three metabolites other than

the 13-cis isomer have been identified in plasma (Figure 4). The metabolites of acitretin may be essentially the same metabolites found for etretinate since the metabolic route of etretinate occurs exclusively via formation of acitretin. Acitretin is more than 98% bound to plasma proteins, primarily albumin.

Figure 4: Structures of acitretin metabolites.



(13-cis metabolite)

Following the administration of a radiolabelled single 25 mg oral dose of acitretin to healthy volunteers, plasma <sup>14</sup>C-radioactivity declined with a terminal elimination half-life of approximately 60 hours\*, and could not be totally associated with either acitretin or the 13-cis metabolite. Approximately 84% of the oral dose was recovered as <sup>14</sup>C-radioactivity within 18 days; 37% was recovered in the urine and 47% in the feces. Acitretin or active 13-cis metabolite was not detected in any of the urine samples.

\* For most of the subjects, the terminal phase contained an insufficient number of data points to accurately determine the half-life.

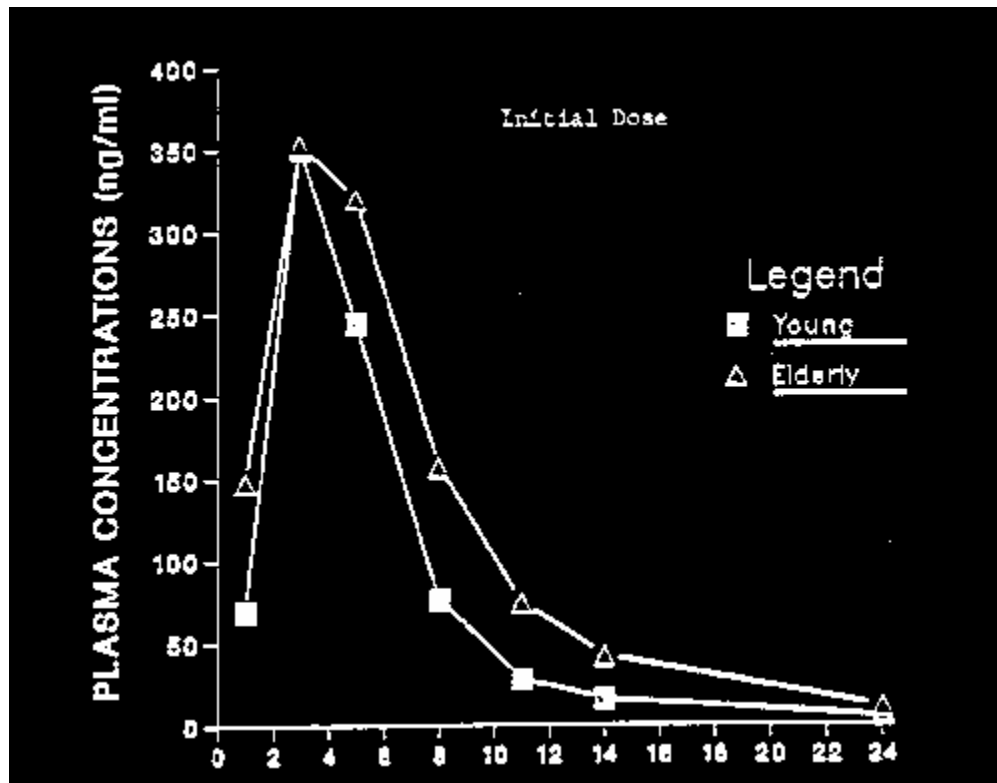
### Effects of External Factors

#### Age

The effect of age on the pharmacokinetics of acitretin was investigated in eight elderly male subjects (64-72 years, weighing 67.2-89.0 kg) and six young healthy male subjects (24-32 years, weighing 60.0-89.0 kg) who received single and multiple oral doses of acitretin. Plasma concentrations of acitretin in the elderly subjects were 49% higher after the first and last drug dose as assessed by AUC<sub>0-24</sub> (Figure 5). The trough plasma concentrations at steady-state for acitretin were also two-fold higher for the elderly group during multiple 25 mg oral doses. The range of terminal elimination half-lives observed for acitretin were 37-96 hours (harmonic mean = 54 hours) in elderly and 39-70 hours (harmonic mean = 53 hours) in young subjects.

Figure 5: Mean acitretin plasma concentration-time profiles after the first and last oral dose of acitretin in young and elderly subjects.





## End-Stage Renal Failure

A preliminary study was conducted in three male subjects (ages 29-63 years, weighing 56-73 kg) with end-stage renal failure and on hemodialysis, who received a single 50 mg oral dose of acitretin with food. The pharmacokinetics of acitretin appeared to be unaffected in the three subjects. Additionally, arterial and venous plasma concentrations of acitretin were virtually identical and neither drug nor metabolite was found in the dialysate samples.

## TOXICOLOGY

### Acute Toxicity

#### LD<sub>50</sub>(Acitretin)

SPECIES	STRAIN	ROUTE	LD <sub>50</sub> (mg/kg)	OBSERVATION PERIOD	SIGNS AND SYMPTOMS
Mouse	Fü SPF	Oral i.p.	>8,000 >250 <500	30 days 30 days	Decreased respiratory rate, alopecia, weight loss.
Rat	Fü SPF	Oral i.p.	>8,000 500	30 days 30 days	Decreased respiratory rate, alopecia, weight loss.
Rabbit	New Zealand White	Oral	>1,000	14 days	Alopecia, unkempt appearance, reddening about eyes, nose, mouth and/or genital area.
Dog	Beagle	Oral	>1,000	14 days	Diarrhea.

### Long-Term Toxicity

#### 1. Two-Week Intravenous - Rats

Acitretin was administered as a mixed micelle formulation intravenously for two weeks to male rats (10/group) at doses of 0 (saline control), 0.5 or 2.0 mg/kg/day. There was no mortality. A dose-related increase in adrenal weight was observed which was statistically significant for the high-dose group (13% greater than control).

#### 2. Two-Week Intravenous - Dogs

A two-week intravenous study was conducted in male dogs (3/group) with a mixed micelle formulation at doses of 0 (saline control), 1, or 5 mg/kg/day. No mortality

was noted and no findings were observed that distinguished treated from control dogs.

### 3. Four-Week Oral - Primates

Acitretin was orally administered as a spray dried powder formulation (15% free acid) to two primates (1/sex) at escalating doses of: 20 mg/kg/day (Week 1), 40 mg/kg/day (Week 2), 80 mg/kg/day (Week 3) and 160 mg/kg/day (Week 4).

There was no control group in this study. No mortality was observed. At the end of the study, the erythrocyte counts were decreased to about 15-26% of the predosing values at doses greater than 40 mg/kg/day. Reticulocyte counts were increased after one week of dosing with 20 mg/kg/day and were increased 5-10 fold over predose values when measured at the end of the second week of study, after one week of dosing with 40 mg/kg/day.

### 4. Six-Month Oral - Rats

Dose selection for a six-month study in rats was based upon the results from two preliminary dose range studies. In the first study, acitretin was administered orally as a wet milled beadlet preparation (11.2% free acid) to male rats (10/group) by dietary admixture at doses of 0 (control diet), 5, 10, 20, 40 and 80 mg/kg/day for two to four weeks. The higher doses of 20, 40 and 80 mg/kg/day were very poorly tolerated. Rats in these groups showed dose-related deterioration of general condition, emaciation, decreased diameter of the long bones, single or multiple fractures, and elevated serum alkaline phosphatase activity and serum triglyceride levels. In the second study, a spray dried powder (15% free acid) was administered to male rats (10/group) at doses of 0 (control diet) 1, 3, 5, 10, and 15 mg/kg/day for four weeks. Marked treatment related effects at 10 and 15 mg/kg/day included: rough/dull hair, occasional hyperkeratosis of the tail, loosened incisors, moderate to marked decrease in long bone diameter, focally thickened long bones, and single and/or multiple fractures of long bones.

Based on the preliminary studies, doses of 0 (control diet) 0.5, 1.0 and 3.0 mg/kg/day were chosen for the six-month study in rats (24/sex/group). Acitretin was administered orally as a spray dried powder (15% free acid). The dosage for the low dose group was increased to 6.0 mg/kg/day for weeks 14-18 of the study because no major side effects were noted at any of the original doses during the first 13 weeks of the study. They were then placed on an unmedicated diet for one week (week 19) and were restarted at their original dose (0.5 mg/kg/day) for weeks 20-26. At the end of the 26-week dosing period, 16 rats/sex/group were sacrificed and necropsied; the remaining eight were maintained for four weeks without treatment to study the reversibility of effects.

No mortality was noted. The dosages 0.5 and 1.0 mg/kg/day were tolerated without effects. In the 3.0 mg/kg/day dose group, female rats presented with minimal 4.5% decreases in body weight-gain, and slight to moderate 25-70% increases in plasma cholesterol, triglycerides, and low and high density lipoproteins. Male rats in this dose group presented with a slightly greater decrease in body weight gain (11%), an increase in serum alkaline phosphatase activity (10-15%) and a slight tendency to premature ossification of the epiphyseal line.

When the dose for the low dose group was increased from 0.5 to 6.0 mg/kg/day during weeks 14-18 of the study, female rats presented with a failure to gain weight, slight sensitivity to handling, a tendency toward decreased motor activity, and slight to moderate elevations in serum alkaline phosphatase (149 U/L : 96 U/L (control))

and in the levels of serum cholesterol, triglycerides and low and high density lipoproteins (25-70%). No major bone changes were noted. Seventeen of 24 male rats showed the effects characteristic of hypervitaminosis A in rodents: weight loss, increased sensitivity to handling, decreased motor activity, fractures, erythema, crusting of the skin and rough fur. Moderate elevations in serum triglyceride concentrations occurred in week 18 (120 mg/100 mL : 70 mg/100 mL (control)). Serum phosphatase activity increased approximately 35%. There were no changes in serum cholesterol or serum low or high density lipoprotein concentrations. Moderate alterations of the ossification of the epiphyseal line in long bones were noted in the male rats at necroscopy at the end of the 26-week study.

Clinical changes reversed when the 6.0 mg/kg/day dose was decreased back to 0.5 mg/kg/day (weeks 20-26) and during the recovery period in the other groups.

## 5. One-Year Oral - Dogs

A preliminary dose range finding study with a wet milled beadlet preparation (11.2% free acid) was conducted in two dogs (1/sex) in ascending dose fashion (10 mg/kg/day (Week 1); 20 mg/kg/day (Week 2); 30 mg/kg/day (Week 3); 40 mg/kg/day (Week 4); 60 mg/kg/day (Week 5); 100 mg/kg/day (Week 6).

Based on the preliminary study, a one-year oral toxicity study was conducted in dogs (6/sex/group) with a spray dried powder preparation (25% free acid) at doses of 0 (empty gelatin capsule) 5, 15 and 50 mg/kg/day. Treatment at the high doses was interrupted 5-6 weeks into the study because of the development of severe otitis externa in the male dogs. Male dogs were untreated during weeks 7-8 and female dogs during weeks 21-22. Due to the persistent recurrence of otitis externa, the high dose was decreased to 30 mg/kg/day from week 17 for male dogs and from week 27 for female dogs, onward. An interim sacrifice (2/sex/ group) occurred after 26 weeks of treatment and at the conclusion of the scheduled one year dosing period. Two male dogs from the control and high dose groups, were maintained without treatment at the end of the study for three months and then were necropsied to determine the reversibility of treatment related effects.

At 5 and 15 mg/kg/day doses, mild to moderate reddening of the skin was noted which presented histopathologically as hypertrophy/hyperplasia. A slight decrease in the number of spermatozoa was noted in the testes of one dog after 26 weeks of treatment at 15 mg/kg/day, which improved by the end of the study and reversed during the recovery period. Cutaneous effects at the high dose of 50 mg/kg/day were severe and required a decrease in dose to 30 mg/kg/day.

Elevated leukocyte counts were observed in two dogs of each sex (13,800-22,000 cmm : 9,500 cmm (control)). Increased numbers of immature unsegmented granulocytes (secondary to severe otitis externa) were seen at week 13. A female dog developed cervical ankylosis. Prostate and testes weights were decreased by approximately 50% at the interim six-month sacrifice but the decreases were less pronounced at the end of the study. Almost all treated dogs showed some dose-related hypertrophic and/or hyperplastic alterations of the epidermis and the sebaceous and ceruminous glands. Additionally, in the high-dose dogs, moderate to marked chronic, relapsing, suppurative inflammation was seen in the external ear canal. Mild to moderate spermatogenic arrest and the appearance of multinucleated giant cells were noted in the testes of one mid- and both high-dose males at six-months but the severity diminished by the end of the study.

All clinical findings reversed during the recovery period.

## 6. Eighteen-Month Oral - Rats

Acitretin (25% free acid) was administered orally as a feed admixture to Wistar rats (20/sex/dose) at doses of 0 (control diet), 2, 4, or 10 mg/kg/day for 18 months.

The overall clinical tolerance of acitretin was good in the 2 and 4 mg/kg/day groups. Minor symptoms occurring in these groups were not considered treatment-related, with the exception of crust formation on the eyelids which was more often present in males of the 4 mg/kg/day group. Definite systemic toxicity was observed at a dose of 10 mg/kg/day. Treatment was interrupted in weeks 27 and 28 and in weeks 54 and 55 due to severe side effects. After 3 to 4 months of acitretin administration, 26 of 37 rats (70%) developed clinical signs indicative of long bone fractures. By the end of the study, most of the rats in this group had multiple bone fractures. Severe osteoporosis and multiple fractures of the extremities, shoulder blades and/or spinal column were diagnosed in 5 male and 5 female rats in which x-ray examinations were conducted. No bone fractures occurred in any other dosage group. In addition to the clinical signs related to bone fractures, crust formation on the eyelids and nose were seen in the high-dose group.

No major hematologic changes were observed. A minimal reduction of erythrocytes (RBC) developed after 4 weeks in male rats administered 4 or 10 mg/kg/day. Maximal reductions in RBC occurred in weeks 13, 26 and 39 (10% - 4 mg/kg/day; 12% - 10 mg/kg/day). An RBC decrease was observed in high-dose group females after week 13, with a maximal reduction of 13% in week 53. In the mid-dose group, the RBC reduction was significant only in week 39. Corresponding minimal reductions in hemoglobin and hematocrit and minimal to slight increases in MCV and MCH were observed in high-dose group males and females and mid-dose group males. An increased number of reticulocytes was also noted in males and females of the high-dose group. Occasionally, these values slightly exceeded normal physiologic limits.

A slight but dose dependent increase in kidney weight was noted in males of the 4 and 10 mg/kg/day groups but with no histomorphologic correlate. A trend to a slight increase in extramedullary hematopoiesis in the spleen of treated rats was considered to result from the slightly increased RBC count. This mostly minimal to slight change was more often seen in animals of the high-dose group.

## Carcinogenicity

### 1. 104-Week Oral - Rats

A 104-week oral carcinogenicity study was performed in Wistar rats (50/sex/group) at acitretin doses of 0 (control -1), 0.5, 1, 2 or 0 (control-2) mg/kg/day.

A total of 159 rats (83 males/76 females) died or were sacrificed during the course of the study. The number of premature sacrifices was slightly increased in high-dose group males due to drug-related clinical symptoms. Most animals died or were sacrificed during the last quarter of the study. Spontaneous deaths or sacrifices were frequently related to tumours of the pituitary gland.

Oral administration of 0.5 mg/kg/day acitretin was tolerated without drug-related side effects. In the mid-dose group, the incidence of slight to moderate incrustations in the periocular or nasal areas was slightly increased in males and females. These findings were usually noted towards the end of the study. In the high-dose group, incrustations in the periocular or nasal area and fractures of the long bones were observed from 6 months onwards. By the end of the study, most of the rats

from the high-dose group had developed these symptoms. In males, stagnation of body weight gain was noted between study weeks 72 and 77.

Drug-related non-neoplastic lesions were seen in the bones of high-dose group animals. Slight to moderate osteoporosis was observed in the femurs of 6 male and 2 female rats, and in the sternum of 5 male and 2 female rats. Calluses were noted in the femurs of 20 males and 20 females, in the sterni of 6 males and 6 females, in the spinal vertebrae of 1 male, and in grossly changed forelimb bones of 13 males and 11 females. Increased erythropoiesis was noted in the spleen of 26 males and 37 females of the high-dose group, in comparison to seven males and 19 females of control group -1, and 12 males and 25 females of control group -2. This increase was considered to be secondary to repeated bone injuries and associated hemorrhages rather than a primary effect of acitretin.

Neoplastic lesions, which were observed primarily in the endocrine and reproductive organs and the skin, were considered to reflect the spectrum of spontaneous findings commonly diagnosed in aged rats of this strain.

### Mutagenicity

No evidence of mutagenicity for acitretin was observed in the following assays:

1. Ames Mutagenicity Assay using S. typhimurium strains: TA 98, TA 100, TA 1535, and TA 1537 at concentrations up to 30 mcg/plate with and without metabolic activation by hepatic S-9; or using S. typhimurium strains: TA 98, TA 100, TA 1535, TA 1537, TA 1538, and E. coli strain WP2 uvr at concentrations up to 5,000 mcg/plate with and without metabolic activation by hepatic S-9.
2. Hamster V-79/HGPRT Assay in the cell line, V-79 derived from Chinese hamster lung cells at maximum concentrations of 1 mcg/mL without metabolic activation and 200 mcg/mL with metabolic activation by hepatic S-9.
3. Unscheduled DNA synthesis in rat hepatocytes at concentrations up to 100 mcg/mL and human fibroblasts at concentrations up to 200 mcg/mL.
4. Induction of Chromosomal Aberrations in Human Lymphocytes at concentrations up to 200 mcg/mL with metabolic activation by hepatic S-9.
5. Mouse Micronucleus Assay at a single oral dose of 3 mg/kg.

### Reproduction and Teratology

#### 1. Fertility and General Reproductive Performance - Rats

Fertility and reproductive performance was conducted in 36 rats/sex treated with acitretin (in a rape seed oil formulation) at oral doses of 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day. The dosing of male rats was initiated 70 days prior to mating and continued throughout the mating period. The dosing of the female rats was initiated 14 days prior to mating and was continued throughout the mating, gestation, and lactation periods (including day 22 of lactation). Two successive generations were also studied.

No drug-related parental mortality and no signs of parental toxicity were noted in this study. Survivability of the offspring in the 3.0 mg/kg/day high-dose group was reduced (24.6% mortality compared to 8.8% for the control group) and some of the physical and developmental tests such as hair growth, ear opening, auditory startle,

pupillary contraction, and memory retention were adversely affected. There were no treatment related effects observed during the F1 progeny mating studies nor on the survivability and weight development of the F2 progeny.

No effects were observed with the two lowest doses (0.3 and 1.0 mg/kg/day).

## 2. Embryotoxicity and Teratology

### a) Mice

An embryotoxicity/teratogenicity study was conducted in 36 female mice given acitretin orally (as a rape seed oil formulation) at doses of 0 (vehicle control), 1, 3, and 10 mg/kg/day from day 7 through day 16 of gestation (mating = Day 1). The study included postnatal evaluation.

There were no signs of adverse maternal effects in any of the dose groups. Vaginal bleeding was noted in all dose groups and some of these animals died. In three mice with vaginal bleeding that survived, complete resorption of all fetuses was noted. The resorption rate for the high-dose group was increased (25.8% compared to 10.2% for the control group).

Dose-dependent teratogenic effects were observed in the mid- and high- dose (3 and 10 mg/kg/day) groups. Skeletal malformations (cervical, neural arches and long bones) and soft tissue malformations (exencephaly, cleft palate, unilateral kidney agenesis and enlarged renal pelvis) were observed.

No embryotoxicity, teratogenicity or adverse effects on postnatal development of offspring were noted in the low-dose group (1.0 mg/kg/day).

### b) Rats

An embryotoxicity/teratogenicity study with acitretin was conducted in 36 female rats at oral doses of 0 (vehicle control), 7.5, 15 and 30 mg/kg/day. Acitretin was administered as a rape seed oil formulation from day 7 to 16 of gestation (mating = day 1). The study included postnatal evaluation of the pups.

No compound-related maternal toxicity or mortality was noted, nor were there drug-related adverse effects on the resorption rate, average litter size, or mean body weight of live fetuses.

Severe isolated malformations (malformed axial skeleton, exencephaly and ectopy of intestines) were noted in two fetuses in the low-dose group (7.5 mg/kg/day). As these deviations were isolated and not dose-related, they may be of a spontaneous nature. The 15 and 30 mg/kg/day, doses were considered to be teratogenic. At 15 mg/kg/day, abnormally shaped humeri were observed; the same malformation as well as malformed radii, ulnae and cleft palate were noted at 30 mg/kg/day.

No effects were noted during postnatal evaluation of offspring from the low- and mid-dose groups. At 30 mg/kg/day pup survival was reduced but the surviving pups were not considered to be adversely affected.

The highest dose of acitretin which provided no evidence for teratogenicity in the rat was 7.5 mg/kg/day.

c) Rabbits

An embryotoxicity/teratogenicity study in rabbits (20 females/group) was conducted with acitretin (in a rape seed oil formulation) at oral doses of 0 (vehicle control), 0.2, 0.6 and 2.0 mg/kg/day. Acitretin was administered from Day 7 to Day 19 of gestation (mating = Day 1).

Maternal weight gain was not adversely affected in any of the dose groups. The dose of 0.6 mg/kg/day resulted in a low incidence of cleft palate and brain anomalies. The 2.0 mg/kg/day dose was teratogenic (open eyes, ectrodactyl, spina bifida, ectopie of abdominal viscera, and bilateral apical deficiencies of the distal phalanges of forelimbs and hind limbs) and resulted in a statistically significant resorption rate (56%). The 24-hour postnatal survival rate of kits (80%) was significantly reduced at the high dose.

No embryotoxic, teratogenic or effects on the course or outcome of the pregnancy were noted at 0.2 mg/kg/day.

3) Peri-/Postnatal Development in Rats

A peri-/postnatal study was conducted in rats (24 females/group) with acitretin (in a rape seed oil formulation) at oral doses of 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day. Acitretin was administered from Day 16 of pregnancy to Day 22 of lactation (mating = Day 1). The study included postnatal evaluation of pups for physical and functional development.

No effects were seen on maternal mortality, maternal weight gain, median duration of gestation or resorption rate. No effects were seen on macroscopic and visceral examination of the pups. No alterations were observed in learning or memory ability or in functional development of the offspring. At 3.0 mg/kg/day, pup survival was approximately 84% compared to 94% for the control group. Incisor eruption delay was the only physical effect noted in the high-dose offspring.

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