PRODUCT MONOGRAPH

[Pr] Taro-Acitretin

(Acitretin Capsules)

10 mg and 25 mg

Taro Standard

Keratinization Disorder Treatment

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Capsules / 10 mg and 25 mg	Non-medicinal ingredients (in alphabetical order): Ammonium hydroxide, Gelatin, Iron oxide black, Iron oxide red, Iron oxide yellow, Maltodextrin, Microcrystalline cellulose, Potassium hydroxide, Propylene glycol, Shellac, Sodium lauryl sulfate, Sorbic acid, and Titanium dioxide.

INDICATIONS AND CLINICAL USE

Taro-Acitretin (Acitretin) is indicated for 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, Taro-Acitretin should be reserved for patients with the diseases listed above when these are unresponsive to or intolerant of standard treatment. Taro-Acitretin should only be prescribed by physicians knowledgeable and experienced in the use of systemic retinoids and who understand the risk of teratogenicity associated with Taro-Acitretin treatment (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **Boxed Serious Warnings and Precautions** and **Pregnancy, Lactation and Fertility**). It is recommended that renewal prescriptions of Taro-Acitretin be limited to a one-month supply in order to ensure patients return for regular follow-up appointments.

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

Pediatrics: The use of Taro-Acitretin in children is not recommended (see **WARNINGS AND PRECAUTIONS**).

Geriatrics (≥ 65 years of age): The effects of aging might be expected to increase some risks associated with acitretin treatment (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

Taro-Acitretin (acitretin) is contraindicated in pregnancy. Taro-Acitretin is highly teratogenic and must not be used by females who are pregnant or intend to become pregnant. Taro-Acitretin is also contraindicated in females of childbearing potential unless strict contraception is practiced 4 weeks before, during and for at least 3 years after treatment cessation. Taro-Acitretin must not be used by females who may not use reliable contraception while undergoing treatment and for at least 3 years following discontinuation of treatment. Retinoids are known to cause a very high percentage of severe birth defects as a result of *in utero* exposure. Potentially any exposed fetus can be affected. There are no accurate means of determining whether an exposed fetus has been affected. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy or within 3 years after the last dose, independent of previous treatment duration. Thereafter, the patient and physician should assess the risks and desirability of discontinuing effective contraception, based on the most current information available. *All of the conditions in WARNINGS AND PRECAUTIONS must be met before prescribing* Taro-Acitretin to any female of childbearing potential (see WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions and **Pregnancy, Lactation and Fertility**).

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 Taro-Acitretin or for 2 months after treatment cessation.

If pregnancy does occur during Taro-Acitretin treatment, Taro-Acitretin treatment must be stopped immediately and the physician and patient must discuss the desirability of continuing the pregnancy.

Taro-Acitretin should only be prescribed by physicians knowledgeable in the use of systemic retinoid treatment (see INDICATIONS AND CLINICAL USE).

Taro-Acitretin is also contraindicated in the following conditions:

- Patients with hypersensitivity to Taro-Acitretin (acitretin) or to any excipient in the formulation, or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Patients with hypersensitivity to other retinoids or to Vitamin A or its metabolites.

- Breast Feeding/Nursing Mothers: Clinical data indicates that acitretin is excreted in human milk. Therefore, nursing mothers should not receive Taro-Acitretin because of the potential for serious adverse reactions in nursing infants. Females should not breastfeed for at least 3 years following discontinuation of Taro-Acitretin.

- Consumption of alcohol (in drinks, food, or medicines):

    - In females of childbearing potential during treatment with Taro-Acitretin: Alcohol must not be ingested during treatment and for two months after cessation of treatment. Clinical evidence has shown that etretinate, the prodrug of acitretin, can be formed with concurrent ingestion of acitretin and alcohol. Measurable levels of etretinate have been detected in plasma samples of patients administered Taro-Acitretin. Etretinate is highly teratogenic and has a longer half-life (approximately 120 days) than acitretin. The length of time necessary to wait after termination of Taro-Acitretin 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 treatment, etretinate has been found in the blood of some patients up to 2.9 years after discontinuation of treatment.

    - Male patients are advised to avoid alcohol or limit consumption during treatment and for 2 months after cessation of treatment.

    - It is not known whether substances other than ethanol are associated with transesterification of acitretin to etretinate (see **DRUG INTERACTIONS**).

- Patients with severely impaired hepatic or renal function.

- Patients with chronic abnormally elevated blood lipid values.

- Patients taking tetracyclines. Since both acitretin and tetracycline can cause increased intracranial pressure, their combined use is contraindicated (see **DRUG INTERACTIONS**).

- Patients taking 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 **DRUG INTERACTIONS**).

- Hypervitaminosis A. Concomitant administration of acitretin and vitamin A or other retinoids is contraindicated due to increased risk of hypervitaminosis A (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Pregnancy Prevention:
Taro-Acitretin should only be prescribed by physicians knowledgeable in the use of systemic retinoids (see INDICATIONS AND CLINICAL USE).

Full patient information about the teratogenic risk and the strict pregnancy prevention measures should be given by the physician to all patients, male and female. In addition, when prescribing this drug to female patients of childbearing potential, physicians must use the Taro-Acitretin Pregnancy Prevention Program. The Prescribers' Program Guide explains all components of the program and how to best use them. The Pregnancy Prevention Program includes two educational guides: A General Medication Guide for all patients (male and female) and a Preventing Pregnancy and Precautions Guide that contains information for females of childbearing potential including mandatory effective contraception and specified pregnancy tests. The information must be reviewed by all patients (male and female) during the initial screening period prior to commencing Taro-Acitretin and guided by the prescribing physician. The Pregnancy Prevention Program's Prescribing Checklist must be completed by the physician when screening any female of childbearing potential. Additionally, the Pregnancy Prevention Program includes a Patient Knowledge Test – Understanding the Importance of Preventing Pregnancy document with questions and answers to enhance understanding of teratogenic risk. All patients (male and female) must read and understand and sign the Pregnancy Prevention Program's Informed Consent Form (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Pregnancy, Lactation, and Fertility).

The Taro-Acitretin Pregnancy Prevention Program materials are available from www.taro-acitretin.ca. Materials can also be requested by contacting Taro Canada Customer Service at (toll free) 1-800-268-1975.

Hepatic: Cases of jaundice with elevated serum bilirubin and transaminases, toxic hepatitis and acute reversible hepatic injury have occurred in patients taking acitretin in clinical trials. Cases of hepatitis and hepatic-related deaths have occurred in patients taking etretinate (acitretin is the active metabolite). Hepatic function should be checked before starting treatment with Taro-Acitretin and monitored during treatment (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Monitoring and Laboratory Tests).

Neurologic: There have been rare reports of pseudotumour cerebri (benign intracranial hypertension) (See WARNINGS AND PRECAUTIONS, Neurologic).

Psychiatric: Treatment with systemic retinoids can cause mood changes including irritability, aggression, depression, suicidal ideation/self-harm and suicide (see WARNINGS AND PRECAUTIONS, Psychiatric).

Pregnancy, Lactation and Fertility

Taro-Acitretin (acitretin) is highly teratogenic. The use of systemic retinoids in humans is associated with congenital abnormalities. There is an extremely high risk that major human fetal abnormalities (e.g., craniofacial defects, cardiac and vascular or CNS malformations, skeletal and thymic defects) will occur if pregnancy occurs during treatment with Taro-Acitretin or within 3 years of cessation of treatment. Any exposed fetus can be affected. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy, **independent of previous treatment duration.**

Major fetal abnormalities associated with retinoid administration during or before pregnancy have been reported, including meningomyelocoele, meningoencephalocoele, multiple synostosis, facial dysmorphia, 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 (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**).

Taro-Acitretin is contraindicated in every female of childbearing potential unless all of the following conditions apply:

1. The patient has severe psoriasis or other severe disorder of keratinization which are resistant to standard therapies.
2. The patient is reliable in understanding and carrying out the physician's instructions.
3. The patient is able to comply with mandatory contraceptive measures reliably and without fail.
4. Before treatment with Taro-Acitretin, the patient has received from the physician and acknowledged understanding of, a detailed and careful oral and printed explanation of the precautions to be taken, the risk of very severe fetal malformation, and the possible consequences if pregnancy occurs during the course of treatment with acitretin or within 3 years of discontinuing. The Taro-Acitretin Pregnancy Prevention Program will be presented and all steps implemented. The explanation will include a line drawing, which is shown to the patient, of an infant with the characteristic deformities resulting from retinoid exposure during pregnancy.
5. It is absolutely essential that every female of childbearing potential who is to undergo treatment with Taro-Acitretin uses effective contraception (2 complementary methods, (i.e., one primary and one secondary method) without interruption for at least four weeks before, during, and for 3 years after the discontinuation of treatment with acitretin). The patient should be instructed to immediately contact a doctor or pharmacist in case of suspected pregnancy.
6. At the start of treatment, two negative serum or urine pregnancy tests (with a minimum sensitivity of 25 mIU/mL), from a licensed laboratory. The first test (with a negative result) is obtained at screening when Taro-Acitretin treatment is under consideration and the second (confirmatory) test (with a negative result) must be obtained up to 3 days before the first dose is given. During treatment, pregnancy tests should be arranged at 28-day intervals. A negative pregnancy test, not older than 3 days, is mandatory before a renewal prescription is provided at these visits. After stopping Taro-Acitretin treatment, pregnancy tests must be performed at 1-3 monthly intervals for a period of at least 3 years after the last dose is given. Pregnancy tests serve to reinforce to the patient the necessity of avoiding pregnancy and in the event of pregnancy, provide the physician and patient an immediate opportunity to discuss the serious risk to the fetus from this exposure to Taro-Acitretin and the desirability of continuing the pregnancy.
7. Treatment should not begin until the second or third day of the next menstrual period.
8. The same effective and uninterrupted contraceptive measures described above must be taken every time a course of Taro-Acitretin treatment is repeated, however long the intervening period may have been, and must be continued for 3 years after the last dose.

9. Should pregnancy occur, in spite of these precautions, there is a high risk of severe malformation of the fetus (e.g. craniofacial defects, cardiac and vascular or CNS malformations, skeletal and thymic defects) and the incidence of spontaneous abortion is increased. This risk applies especially during treatment with acitretin and 2 months after treatment. For 3 years after acitretin discontinuation, the risk is lower (particularly in females who have not consumed alcohol) but cannot be entirely excluded due to possible formation of etretinate.
10. The patient must avoid alcohol consumption during treatment and for 2 months after stopping treatment.
(see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**)

Contraception Method:

It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. Primary contraceptive method is a combination hormonal contraceptive product or an intrauterine device and it is recommended that a secondary method of contraceptive, i.e., a condom or diaphragm (cap) is also used. Low dose progesterone-only products (minipills) are not recommended due to indications of possible interference by Taro-Acitretin with their contraceptive effect (see **DRUG INTERACTIONS**).

Lactation:

Taro-Acitretin must not be given to nursing mothers. Clinical data indicate that acitretin is excreted in human milk. Therefore, nursing mothers should not receive Taro-Acitretin because of the potential for serious adverse reactions in nursing infants. Women should not breastfeed for an undetermined period of time of at least 3 years following discontinuation of Taro-Acitretin (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions).**

Male Patients:

For male patients treated with acitretin, available data, based on the level of maternal exposure from semen and seminal fluid indicate a minimal, if any, risk of teratogenic effects. Male patients should be reminded that they must not share their medication with anyone, particularly not females.

General

Transient Worsening:

Patients should be advised that a transient worsening of their psoriasis may occur during the initial Taro-Acitretin (acitretin) treatment period and usually does not require dose adjustment.

It should be emphasized that, at the present time, not all the consequences of life-long administration of acitretin are known.

Cardiovascular

Serum cholesterol and serum triglycerides (fasting values) should be performed before starting treatment with Taro-Acitretin and again at intervals of 4 weeks until the lipid response to the drug is established, which is usually within four to eight weeks, and thereafter every three months during treatment. Approximately 65% of patients receiving Acitretin 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 Acitretin were reversible upon cessation of treatment.

In patients with diabetes, alcoholism, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with acitretin, more frequent checks of serum values for lipids and/or glycaemia may be necessary.

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 fatal fulminant 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 Taro-Acitretin treatment. Consumption of alcohol is contraindicated during Taro-Acitretin treatment and for two months after cessation of treatment (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** and **ADVERSE REACTIONS).**

If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Taro-Acitretin should be considered. An associated risk of atherogenesis cannot be ruled out if these conditions persist. There have been post-marketing reports of acute myocardial infarction, thromboembolism and stroke in patients treated with Acitretin (see **ADVERSE REACTIONS**).

Post-marketing cases of capillary leak syndrome/retinoic acid syndrome have been reported with acitretin treatment.

Ear/Nose/Throat

Impaired hearing and tinnitus have been reported in some patients treated with Acitretin. Patients who experience tinnitus or hearing impairment should discontinue Taro-Acitretin treatment and be referred for specialized care for further evaluation.

Endocrine and Metabolism

Glucose Tolerance:

In diabetics or patients with risk factors/family history of diabetes, retinoids may affect glucose tolerance. Blood-sugar levels must therefore be checked more frequently than usual in the early stages of treatment. Elevated fasting blood glucose levels have been reported and new cases of diabetes have been diagnosed during Acitretin treatment (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**, **DRUG INTERACTIONS**, **Sulfonylurea (glyburide)**, and **ADVERSE REACTIONS**).

Gastrointestinal

Other retinoids have been temporally associated with inflammatory bowel disease (including regional ileitis, colitis and hemorrhage) in patients without a prior history of intestinal disorders. Therefore it is expected that some patients taking Taro-Acitretin could develop inflammatory bowel disease. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Taro-Acitretin immediately.

Hepatic/Biliary/Pancreatic

Hepatotoxicity:

Hepatic function should be checked before starting treatment with Taro-Acitretin, every 4 weeks for the first 2 months after commencement, and then at least 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, Taro-Acitretin 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 Acitretin. One of the 329 patients treated in clinical trials had clinical jaundice with elevated serum bilirubin and transaminases considered possibly related to Acitretin treatment. Liver function test results in this patient returned to normal after Acitretin was discontinued.

If hepatotoxicity is suspected during treatment with Taro-Acitretin, the drug should be discontinued and the etiology further investigated.

Ten of 652 patients treated in clinical trials of etretinate, (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 (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**, **Monitoring and Laboratory Tests** and **ADVERSE REACTIONS**).

Pancreatitis:

There have been some reports of fatal fulminant pancreatitis with Acitretin and other retinoids. This is sometimes associated with elevation of serum triglycerides in excess of 800 mg/dL or 9 mmol/L (see **ADVERSE REACTIONS**). Therefore, every attempt should be made to control significant triglyceride elevation (see **WARNINGS AND PRECAUTIONS, Cardiovascular**). Taro-Acitretin treatment should be discontinued if uncontrolled hypertriglyceridemia or if symptoms of pancreatitis occur.

Immune

Anaphylactic reactions have been very rarely reported. In individuals treated with systemic retinoids, these reactions were more serious after prior exposure to topical retinoids. Severe allergic reactions, including hypersensitivity to acitretin necessitate interruption of treatment and careful monitoring.

Musculoskeletal and Connective Tissue Disorders

In clinical trials with Acitretin, 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 Acitretin, 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. During the six-month period of observation, no bone changes were seen in patients who had normal pre-treatment X-rays. Other retinoids, including etretinate, 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 Taro-Acitretin treatment. Early recognition of musculoskeletal symptoms associated with Taro-Acitretin treatment may be important. There is some evidence that scintigraphic changes appear before radiographic findings. Scintigraphic changes may disappear after discontinuation of Taro-Acitretin treatment, however, radiographic changes may persist. Bone scintigraphy may be important in monitoring patients undergoing Taro-Acitretin treatment since scintigraphic changes seem to precede radiographic changes.

In adults, especially elderly, receiving long-term treatment with Taro-Acitretin, appropriate examinations should be periodically performed in view of possible ossification abnormalities. If such disorders arise, the continuation of treatment should be discussed with the patient on the basis of a careful risk/benefit analysis (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Possible related adverse events that are associated with Taro-Acitretin and other retinoid use are: Osteoporosis, osteopenia, bone fractures, delayed healing of bone fractures, myalgia, arthralgia and elevated serum creatine phosphokinase.

There have been occasional reports of bone changes in children, receiving long-term treatment with etretinate, including premature epiphyseal closure, skeletal hyperstosis, and extraosseus calcification (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Neurologic

Benign Intracranial Hypertension (Pseudotumour Cerebri):

Acitretin and other retinoids have been associated with rare cases of pseudotumour cerebri (benign intracranial hypertension). Early symptoms and signs of benign intracranial hypertension include headache, nausea and vomiting and visual disturbances and patients with such symptoms should be advised to discontinue acitretin immediately, be examined for papilledema, and be referred for neurological evaluation and care (see **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**).

As tetracyclines can also cause an increase in intracranial pressure, their combination with Taro-Acitretin should be avoided (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Ophthalmologic

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 Acitretin 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.

Decreased night vision and blurring of vision have been reported by some patients. Patients should be advised of these potential problems and warned to be cautious when driving or operating any vehicle at night (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

The following additional ophthalmic effects have occurred in patients taking etretinate (the prodrug of acitretin): Decreased visual acuity, minimal posterior subcapsular cataract, iritis, blot retinal hemorrhage and scotoma.

Patients receiving Taro-Acitretin treatment should be carefully monitored for visual problems and any patient experiencing visual difficulties should discontinue this drug and undergo ophthalmic evaluation.

Psychiatric

Treatment with systemic retinoids can cause mood changes including irritability, aggression and depression. Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm/suicide have been reported in patients taking systemic retinoids as well as in patients taking Acitretin. All patients should be screened and monitored for signs of new or worsening depressive symptoms during treatment. Before starting treatment with Taro-Acitretin, physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression. If symptoms of a new depression develop or an existing depression worsens during treatment with Taro-Acitretin, the drug should be discontinued promptly and the patient referred for appropriate psychiatric assessment, treatment, and counselling, as necessary. However, discontinuation of Taro-Acitretin may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary (see **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**).

Skin

There have been very rare post-marketing reports of severe skin reactions (e.g., erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)) associated with other retinoids and these are therefore expected with Taro-Acitretin. These events may be serious and result in hospitalization, life threatening events, disfiguration, disability and/or death. Taro-Acitretin treatment should be discontinued if the patient develops any of the following reactions: rash, especially if associated with fever and/or malaise; conjunctivitis (red or inflamed eyes); blisters on legs, arms or face and/or sores in mouth, throat, nose or eyes; peeling skin or other serious skin reactions.

The effects of UV light are enhanced by retinoid treatment. Patients should avoid excessive exposure to sunlight and unsupervised use of sun lamps. Where necessary a sun-protection product with a high protection factor of at least SPF 30 should be used.

It is recommended that aggressive chemical dermabrasion, cutaneous laser treatment and wax epilation be avoided in patients on Taro-Acitretin treatment and for a sufficient period of time after the end of treatment because of the risk of hypertrophic scarring in atypical areas, epidermal stripping, dermatitis and more rarely hyper- or hypo-pigmentation in treated areas.

Concurrent administration of Taro-Acitretin with keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase. Patients should be advised to use a skin-moisturizing ointment or cream and a lip balm from the start of treatment as Taro-Acitretin is likely to cause dryness of the skin and lips.

Post-marketing cases of exfoliative dermatitis have been reported with acitretin treatment.

Special Populations

Pregnant Females: Taro-Acitretin is contraindicated for use by pregnant females. Taro-Acitretin is also contraindicated for use by female patients of childbearing potential unless strict conditions of use are followed **(**see **CONTRAINDICATIONS, WARNINGS AND**

PRECAUTIONS, Boxed Serious Warnings and Precautions and **Pregnancy, Lactation and Fertility**). The Taro-Acitretin Pregnancy Prevention Program must be followed by physicians and patients.

Nursing Females: Taro-Acitretin is contraindicated for use by nursing mothers. Clinical data indicate that acitretin is excreted in human milk (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions** and **Pregnancy, Lactation and Fertility**).

Pediatrics: Safety and efficacy of Acitretin has not been established in children. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostosis and premature epiphyseal closure have been reported with other systemic retinoids, including etretinate of which Acitretin is the active metabolite. Due to the uncertain effect of long-term Acitretin treatment on growth and skeletal development, Taro-Acitretin is not recommended for use in children (see **WARNINGS AND PRECAUTIONS, Musculoskeletal and Connective Tissue Disorders**).

Geriatrics (≥ 65 years of age): Clinical trials did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Geriatric patients, receiving treatment with acitretin should be examined appropriately and periodically in view of possible ossification abnormalities (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS, Musculoskeletal and Connective Tissue Disorders**).

Effects on ability to drive and use machinery: Decreased night vision has been reported with acitretin treatment (see **WARNINGS AND PRECAUTIONS, Ophthalmologic**). Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Blood Donation: Females of childbearing potential must not receive blood from patients being treated with Taro-Acitretin. Therefore donation of blood by a patient (Male or Female), being treated with Taro-Acitretin is prohibited during treatment and for 3 years after completion of treatment with Taro-Acitretin due to the risk of females of childbearing potential receiving blood from patients being treated with Taro-Acitretin.

Monitoring and Laboratory Tests

Pregnancy Tests: At the start of Taro-Acitretin treatment, two pregnancy tests must be obtained from a licensed laboratory (minimum sensitivity 25 mIU/mL). The first test (with a negative result) is obtained at screening when Taro-Acitretin treatment is under consideration and the second (confirmatory) test (with a negative result) must be obtained up to 3 days before the first dose is given. During treatment, pregnancy tests should be arranged at 28 day-intervals. A negative pregnancy test not older than 3 days is mandatory before a renewal prescription is provided at monthly follow-up visits with the physician. After stopping treatment, pregnancy tests should be performed at 1-3 monthly intervals for a period of 3 years after the last dose was given (see **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions** and **Pregnancy, Lactation and Fertility**).

Lipid Monitoring: Serum cholesterol and serum triglycerides (fasting values) should be performed before starting treatment with acitretin and again at intervals of 4 weeks until the lipid response to the drug is established, which is usually within four to eight weeks and thereafter every three months during treatment (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

In patients with diabetes, alcoholism, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with acitretin, more frequent monitoring of serum values for lipids, and/or glycaemia and other cardiovascular indicators, e.g., blood pressure, is necessary (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Glucose Monitoring: In diabetics or patients with risk factors/family history of diabetes, retinoids can alter glucose tolerance. Blood-sugar levels must therefore be checked more frequently than usual in the early stages of treatment (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

Signs of Depression: If symptoms of a new depression develop or an existing depression worsens during treatment with Taro-Acitretin, the drug should be discontinued promptly and the patient referred for appropriate psychiatric assessment, treatment and counselling (see **WARNINGS AND PRECAUTIONS, Psychiatric**).

Hepatic function: Hepatic function should be checked before starting treatment with Taro-Acitretin, every 4 weeks for the first 2 months after commencement, and then at least every 3 months during treatment. If abnormal results are obtained, weekly checks or drug withdrawal should be instituted. 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 Acitretin (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Bone: In adults, especially elderly, receiving treatment with Taro-Acitretin, appropriate examinations should be periodically performed in view of possible ossification abnormalities. If such disorders arise, the continuation of treatment should be discussed with the patient on the basis of a careful risk/benefit analysis.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Undesirable effects are seen in most patients receiving acitretin. An initial worsening of psoriasis symptoms is sometimes seen at the beginning of the treatment period.

The most frequent undesirable effects observed are symptoms of hypervitaminosis A.

Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the gastrointestinal system (e.g., dryness of the lips, which can be alleviated by application of a fatty

ointment), skin and subcutaneous tissue, and musculoskeletal, hepatobiliary and nervous systems.

Tables 1 and 2 below list, grouped by frequency, the adverse reactions reported during clinical trials in which patients were treated with Acitretin for psoriasis.

Table 3, under Post-Market Adverse Drug Reactions, lists undesirable effects for acitretin in clinical trials or as post-marketing events by System Organ Class and frequency.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1: Adverse Events Reported during Clinical Trials in which Patients were Treated with Acitretin for Psoriasis

MedDRA SYSTEM ORGAN CLASS	**VERY COMMON> 10% MedDRA PT**	**[a] COMMON 1-10% MedDRA PT**	**[a] UNCOMMON <1.0% MedDRA PT**
Ear and labyrinth disorders		Cerumen impaction Ear pain Tinnitus	Deafness
Eye Disorders	Xerophthalmia	Blepharitis[b] Conjunctivitis/ Eye irritation Eye pain Photophobia Visual impairment vision/ Vision blurred	Cataract Eye disorder[b] Corneal neovascularisation[b] Corneal lesion[b] Lacrimal disorder Night blindness
General disorders and administration site conditions	Chills	Fatigue Oedema Pain Thirst	Chest Pain Gait disturbance Impaired healing Malaise Pyrexia

MedDRA SYSTEM ORGAN CLASS	VERY COMMON> 10% MedDRA PT	[a]COMMON 1-10% MedDRA PT	[a]UNCOMMON <1.0% MedDRA PT
Gastrointestinal disorders	Cheilitis Dry mouth Lip dry	Abdominal pain Gingival bleeding Gingivitis Nausea Stomatitis Salivary hypersecretion	Anorectal disorder Constipation Diarrhea Dyspepsia Glossitis Melaena Tongue ulceration Mouth ulceration Pancreatitis Rectal tenesmus Saliva altered
Hepatobiliary disorders			Hepatitis[e] Jaundice[e]
Infections and infestations	Rhinitis	Infection Paronychia	Candidiasise Hordeolumb Laryngitis Otitis externa Pharyngitis Sinusitis
Investigations			Bleeding time prolonged Urine analysis abnormal
Metabolism and nutrition disorders		Decreased appetite Increased appetite	Alcohol intolerance
Musculoskeletal and connective tissue disorders	Arthralgia	Arthritis Back pain Bone Pain Exostosis[c] Myalgia	Bursitis Muscle spasms Muscular weakness Osteoarthritis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Pyogenic granuloma	
Nervous system disorders	Hyperaesthesia	Headache Dysgeusia Hypertonia Hypoaesthesia Paraesthesia	Ageusia Benign intracranial hypertension Somnolence
Psychiatric disorders		Insomnia Nervousness	Depression
Renal and urinary disorders			Dysuria

MedDRA SYSTEM ORGAN CLASS	VERY COMMON> 10% MedDRA PT	[a] COMMON 1-10% MedDRA PT	[a] UNCOMMON <1.0% MedDRA PT
Reproductive system and breast disorders		Erectile dysfunction	Balanoposthitis Genital discharge
Respiratory, thoracic and mediastinal disorders		Epistaxis	Cough Dysphonia Sputum increased
Skin and subcutaneous tissue disorders	Alopecia Dry skin Erythema Nail disorder Pruritus Rash erythematous Skin atrophy Skin exfoliation Sticky skin	Cold sweat Dermatitis bullous Dermatitis psoriasiform Hair texture abnormal Hyperhidrosis Photosensitivity reaction Purpura Seborrhoea Skin fissures Skin ulcer Rash	Acne Angioedema Dermatitis Eczema Skin disorder Skin hypertrophy Skin mass Skin odour abnormal
Vascular disorders			Flushing Hot flush Vasculitis[d]

a Some may bear no relationship to treatment.
b Based on review of eye examination forms by consulting ophthalmologist (N=252).
c Incidence of 7% based on review of films by consulting radiologist (N=262).
d Vasculitis has not been documented with acitretin but has been seen with other retinoids.
e Events observed and reported rarely.

Table 2: Abnormal Hematologic Clinical Chemistry Findings (shown as % change) Reported during Clinical trials in which Patients were Treated with Acitretin for Psoriasis

SYSTEM ORGAN CLASS/LABORATORY ABNORMALITY MedDRA PT	% CHANGE INCREASED	% CHANGE DECREASED	COMMENTS
INVESTIGATIONS:			
Alanine aminotransferase	28		If hepatotoxicity is suspected, treatment should be discontinued (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).
Aspartate aminotransferase	23		
Blood lactate dehydrogenase	21		
Blood alkaline phosphatase	16		
Gamma-glutamyltransferase	14		
Bilirubin conjugated	11		
Blood triglycerides	65		The effects on triglycerides, cholesterol and HDL were reversible upon cessation of Acitretin treatment. (see **WARNINGS AND PRECAUTIONS**).
Blood cholesterol	9		
High density lipoprotein		30	
Blood bilirubin	2		
Globulins	2		
Blood albumin		1	
Blood uric acid	17		
Blood creatinine	5		
Blood urea	2		
Reticulocyte count	38		
White blood cell count	11	7	
Eosinophil count	8		
Monocyte count	7		
Band neutrophil count	4		
Basophil count	3		
Neutrophil count	16	5	
Lymphocyte count	2	11	

SYSTEM ORGAN CLASS/LABORATORY ABNORMALITY MedDRA PT	% CHANGE INCREASED	% CHANGE DECREASED	COMMENTS
Haemoglobin	4	9	
Platelet count	2	6	
Haematocrit	3	5	
Red blood cell count	2	3	
Blood phosphorus	16	13	
Blood potassium	12	3	
Blood magnesium	12	12	
Blood sodium	2	1	
Blood calcium	4	2	
Blood chloride	2	3	
Blood creatine phosphokinase	37		Other reported laboratory abnormalities.
Blood glucose	21	7	
Blood iron	7	3	
Red blood cells urine	10		Urinary abnormalities
White blood cells urine positive	7		
RENAL and URINARY DISORDERS:			See additional urinary abnormalities under INVESTIGATIONS above.
Glycosuria	4		
Ketonuria	3		
Proteinuria	2		

Post-Market Adverse Drug Reactions

Undesirable effects reported for acitretin in post-market, either spontaneously or in clinical trials, are listed below, in Table 3, by System Organ Class and frequency. Frequencies are defined as:

Very common ([redacted]/10)
Common ([redacted]/100 to <1/10)
Uncommon ([redacted]/1,000 to <1/100)
Rare ([redacted]/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Table 3: Undesirable Effects Reported for Acitretin in Post-Market Spontaneous Events or Clinical Trials*

System Organ Class /Frequency	**Undesirable Effect**
Infections and infestations Frequency not known	Vulvo-vaginitis due to *Candida albicans*
Immune system disorders Frequency not known	Type I Hypersensitivity (angioedema, urticaria)
Nervous system disorders Common Uncommon Rare Very rare	Headache Dizziness Neuropathy peripheral Benign intracranial hypertension
[1]**Cardiovascular Disorders** Frequency not known Frequency not known Frequency not known	Acute myocardial infarction Thromboembolism Stroke
Eye disorders Very common Uncommon Very rare	Drying of and inflammation of mucous membranes (e.g. conjunctivitis, xerophthalmia), which may lead to intolerance of contact lenses Vision blurred Night blindness, ulcerative keratitis
Ear and labyrinth disorders Frequency not known	Hearing impaired, tinnitus
Vascular disorders Frequency not known	Flushing, capillary leak syndrome/retinoic acid syndrome
Respiratory, thoracic and mediastinal disorders Very common	Drying of and inflammation of mucous membranes (e.g. epistaxis and rhinitis)
Gastrointestinal disorders Very common	Dry mouth, thirst

System Organ Class /Frequency	**Undesirable Effect**
Common	Stomatitis, gastro-intestinal disorders (e.g. abdominal pain, diarrhoea, nausea, vomiting)
Uncommon	Gingivitis
Frequency not known	Dysgeusia, rectal hemorrhage
Hepatobiliary disorders Uncommon	Hepatitis
Very rare	Jaundice
Psychiatric Frequency not known	Aggressive feelings and/or
Frequency not known	Suicidal thoughts
Skin and subcutaneous tissue disorders Very common	Cheilitis, pruritus, alopecia, skin exfoliation (all over the body, particularly on the palms and soles)
Common	Skin fragility, sticky skin, dermatitis, hair texture abnormal, brittle nails, paronychia, erythema
Uncommon	Rhagades, dermatitis bullous, photosensitivity reaction
Frequency not known	Pyogenic granuloma, skin atrophy, madarosis, exfoliative dermatitis
Musculoskeletal and connective tissue disorders Common	Arthralgia, myalgia
Very rare	Bone pain, exostosis (maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic lesions and in extraskeletal calcification, as has been observed in long-term systemic treatment with retinoids)
General disorders and administration site conditions Common	Peripheral oedema
Investigations Very common	Liver function test abnormal (transient, usually reversible elevation of transaminases and alkaline phosphatases) Lipids abnormal (during treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients and during long-term treatment. An associated risk of atherogenesis cannot be ruled out if these conditions persist)

* Post-market events are reported voluntarily from a population of uncertain size, therefore it is not always possible to reliably estimate their frequency or establish a causal relationship.

[1] Acitretin has been associated with abnormal lipid values including hyperglyceridemia and decreased HDL and this potentially may increase the risk of the cardiovascular risk status of patients taking Acitretin.

Although no causal relationship has been established, there are reports of patients taking Acitretin who have had acute myocardial infarction and thromboembolic events.

DRUG INTERACTIONS

Serious Drug Interactions

Vitamin A/retinoids: Concomitant administration of Taro-Acitretin (acitretin) and vitamin A and other systemic retinoids must be avoided due to the risk of possible additive toxic effects and increased risk of hypervitaminosis A (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Methotrexate: The combined administration of Taro-Acitretin and methotrexate is contraindicated because of an increased risk of hepatitis reported to result from the combination of methotrexate and etretinate (see **CONTRAINDICATIONS**).

Tetracycline: Combined use of Taro-Acitretin and tetracyclines is contraindicated since both can cause increased intracranial pressure (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, **Neurologic**).

Alcohol: Clinical evidence has shown that etretinate (prodrug of acitretin) can be formed with concurrent ingestion of acitretin and alcohol (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**, **Established or Potential Drug-Drug Interactions**).

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

Drug/Substance	Ref	Effect	Clinical comment
Vitamin A/retinoids	T/C	Additive effect/Vitamin A toxicity	Risk of possible additive toxic effects/ hypervitaminosis A (see **CONTRAINDICATIONS**)
Methotrexate	C	Additive	Risk of hepatitis (see **CONTRAINDICATIONS**)
Tetracycline	T/C	Additive	Taro-Acitretin and tetracycline both can cause increased intracranial pressure (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Neurologic**).
Ethanol (alcohol in drinks, food, medicine)	T/C	[1]Transesterification	Conversion of Taro-Acitretin (acitretin) to etretinate (see **CONTRAINDICATIONS**).

Low dose progesterone-only contraceptive (minipills)	C	Possible interference with contraceptive effect	Not a reliable form of contraceptive when taking Taro-Acitretin.
Phenytoin	T	Reduced protein binding	Clinical significance is unknown. Caution to be exercised when using these drugs together.
Sulfonylurea (glyburide)	C	Increased insulin sensitivity	Careful supervision and monitoring of diabetic patients recommended

Legend: C = Case Study; T = Theoretical

[1] It is not known whether substances other than ethanol are associated with transesterification.

Drug Interactions Overview

In addition to the drug interactions indicated as serious above (see **DRUG INTERACTIONS, Boxed Serious Drug Interactions**), the following considerations for drug interactions may apply:

Oral Contraceptives: Low dose progesterone-only products (minipills) may be an inadequate method of contraception during Taro-Acitretin treatment and are not recommended due to indications of possible interference with their contraceptive effect (see **WARNINGS AND PRECAUTIONS, Pregnancy, Lactation and Fertility**).

Phenytoin: If Taro-Acitretin is given concurrently with phenytoin, it must be remembered that Taro-Acitretin partially reduces phenytoin's protein binding. The clinical significance of this is unknown. Therefore, caution should be exercised when using these drugs together.

Sulfonylurea (glyburide): Limited data indicates that Acitretin treatment either increased insulin sensitivity directly or interacted with glyburide to do so. Careful supervision of diabetic patients under treatment with Taro-Acitretin is recommended (see also **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

Warfarin: Investigations into the effect of Acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction.

Phenprocoumon: Concomitant administration of phenprocoumon and Taro-Acitretin does not alter the hypothrombinemic effect of phenprocoumon or the plasma disposition of Taro-Acitretin.

Digoxin: The pharmacokinetics of Taro-Acitretin and digoxin are not altered by concomitant multiple dose regimens of these two drugs.

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

Drug-Herb Interactions

St. John's Wort: Taro-Acitretin use is associated with depression in some patients (see **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions, Psychiatric** and **ADVERSE REACTIONS**). Female patients of childbearing potential 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.

Drug-Lifestyle Interactions:

Photosensitivity: Patients taking Taro-Acitretin should avoid excessive exposure to sunlight and unsupervised use of sun lamps. Where necessary a sun-protection product with a high protection factor of at least SPF 30 should be used (see **WARNINGS AND PRECAUTIONS, Skin**).

Driving or operating machinery: Patients should be advised of the potential problem of decreased night vision and warned to be cautious when driving or operating any vehicle at night (see **WARNINGS AND PRECAUTIONS, Ophthalmologic**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Taro-Acitretin should only be prescribed by qualified physicians experienced in the use of systemic retinoids who understand the risk of teratogenicity associated with Taro-Acitretin (acitretin) treatment (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Boxed Serious Warnings and Precautions**).

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

Recommended Dose, Dosage Adjustment, and Administration

The capsules should preferably be taken once daily with a meal or following a meal. The following serves a guideline:

Initial Treatment:
Taro-Acitretin treatment 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 Treatment:

Psoriasis

Maintenance doses of 25 mg 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, treatment should be terminated when lesions have resolved sufficiently. Relapses may be treated as outlined for initial treatment.

Other Keratinization Disorders

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

Missed Dose

A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, the patient should skip the missed dose and continue with the regular dosing schedule. Doses should not be doubled up on the following day.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

To date, there has been no experience with acute overdose of Acitretin. In the event of acute overdosage, acitretin must be withdrawn at once. Evacuation of the stomach should be considered during the first few hours after overdose. Signs and symptoms of overdosage with Acitretin are identical to acute vitamin A toxicity, i.e., severe headache, nausea or vomiting, drowsiness, irritability, and pruritus. Specific treatment is unnecessary because of the low acute toxicity of the preparation. Elevated intracranial pressure has been reported with both acute and chronic vitamin A overdoses as well as in patients treated with therapeutic doses of Acitretin. Patients with a Taro-Acitretin overdose should be monitored closely for signs of increased intracranial pressure. If overdosage occurs in patients already receiving therapeutic doses of Taro-Acitretin, the drug must be discontinued immediately.

All female patients of childbearing potential who have taken an overdose of Taro-Acitretin must:

- Have a pregnancy test at the time of the overdose.
- Use an effective form of contraception for at least 3 years duration after the overdose.

If the pregnancy test is positive, the patient should be fully counselled on the serious risk to the fetus from exposure to Taro-Acitretin and the physician and patient should discuss the desirability of continuing the pregnancy (see **CONTRAINDICATIONS, WARNINGS AND**

PRECAUTIONS, Boxed Serious Warnings and Precautions, Pregnancy, Lactation and Fertility).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Taro-Acitretin (acitretin) is a retinoid, an aromatic analogue of vitamin A. The mechanism of action of acitretin 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.

Pharmacodynamics

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.

Pharmacokinetics

Oral absorption of acitretin was optimal when given with food. Following administration of a single oral dose of 50 mg acitretin 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 acitretin (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 acitretin 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).

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 (main metabolite). 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, of which acitretin is the active metabolite, have been detected in plasma samples of patients administered acitretin. 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

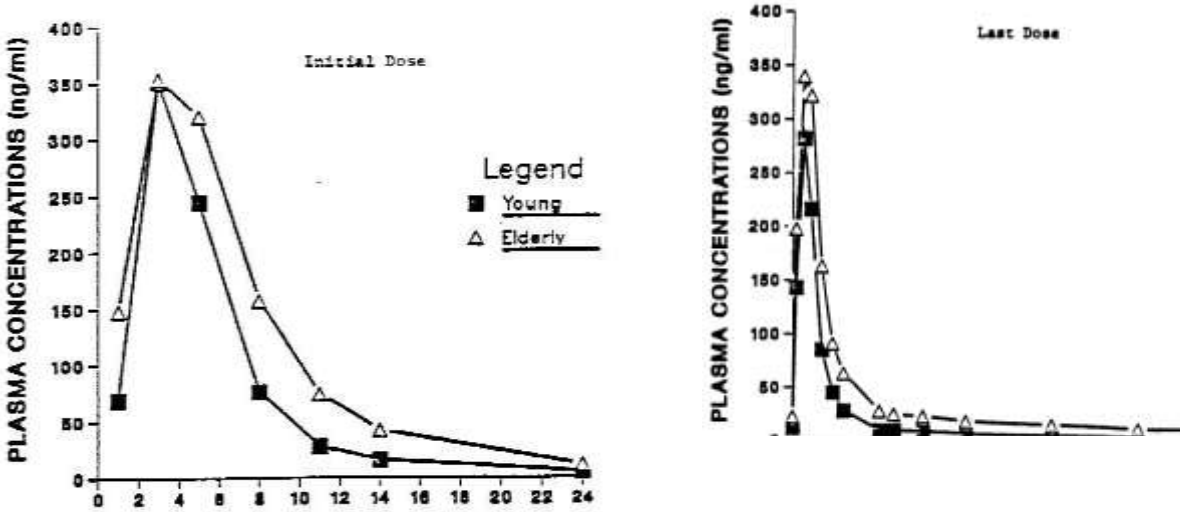
healthy volunteers, all 10 subjects formed etretinate following the ingestion of a single 100 mg oral dose of acitretin in the presence of alcohol (1.4 g/kg ethanol over approximately 3 hours). Peak concentrations of etretinate measured in these subjects ranged from 22 ng/mL to 105 ng/mL (mean: 55 ng/mL). 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 treatment, 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 Acitretin (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.

Special Populations and Conditions

Geriatrics

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_{0-24} (Figure 1). 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 1: 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.

STORAGE AND STABILITY

Store at 15-25°C. Protect from heat and light. The product is sensitive to moisture. Therefore store in original package.

SPECIAL HANDLING INSTRUCTIONS

Keep out of reach of children. The medicine should not be used after the expiry date (EXP) shown on the package. Taro-Acitretin (acitretin) is highly teratogenic. Due to the risk of fetal malformations, this medicine (capsules) must not be passed on to other people. Unused or expired products should be returned to a pharmacy for disposal.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Taro-Acitretin 10: Hard gelatin capsule containing 10 mg acitretin. Brown and white capsules with "024" in black lettering.

Taro-Acitretin 25: Hard gelatin capsule containing 25 mg acitretin. Brown and yellow capsules with "025" in black lettering.

Non-medicinal ingredients (in alphabetical order): Ammonium hydroxide, Gelatin, Iron oxide black, Iron oxide red, Iron oxide yellow, Maltodextrin, Microcrystalline cellulose, Potassium hydroxide, Propylene glycol, Shellac, Sodium lauryl sulfate, Sorbic acid, and Titanium dioxide.

Taro-Acitretin capsules 10 and 25 mg are available in units of 30 (3 x 10's) capsules per carton in a Alu-Alu blister package.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

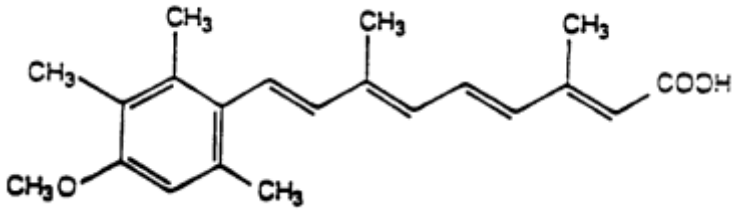
Proper name: Acitretin

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

Molecular formula: $C_{21}H_{26}O_3$

Molecular mass: 326.44

Structural formula:



Physicochemical properties: 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_a = 5. Melting range is 210 - 220°C.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDY

Fasting study:
A blinded, randomized, two treatment, three period, three sequence, single dose, replicated crossover bioequivalence study of Acitretin 25 mg Capsules of Taro Pharmaceuticals Inc. and [Pr]Soriatane® (Acitretin) 25 mg Capsules of Actavis Group PTC ehf (marketed by Tribute Pharmaceuticals Canada Inc.) was conducted in 60 healthy adult male subjects under fasting conditions. The results from the 54 subjects who completed all periods of the study are presented below.

Number of subjects completed all the three periods of studies: 54
Number of subjects whose data were used in calculating pharmacokinetic parameters: 54 (All-trans-acitretin and 13-cis-acitretin)
Number of subjects whose data were used in calculating statistical parameters: 54 for All-trans-acitretin and 53 for 13-cis-acitretin.

Acitretin 25 mg Capsule Acitretin (N = 54) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/ml)	658.3 739.5 (46.7)	627.4 721.8 (52.2)	105.2	96.9 to 114.1
AUC_I (ng.h/ml)	720.1 790.3 (42.7)	678.5 766.6 (48.9)	106.3	98.6 to 114.5
C_{max} (ng/ml)	100.4 117.7 (50.3)	94.8 111.8 (55.2)	106.4	96.2 to 117.6
T_{max}§ (h)	2.6 (42.6)	2.9 (41.2)		
$T_{½}$§ (h)	8.2 (79.4)	7.6 (60.7)		

* Acitretin 25 mg Capsules of Taro Pharmaceuticals Inc.
† PrSoriatane® (Acitretin) 25 mg Capsules of Actavis Group PTC ehf (marketed by Tribute Pharmaceuticals Canada Inc.); purchased in Canada.
§ Expressed as arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Pharmacokinetics

Animals

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.

Humans

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 5).

Table 5: Summary of Acitretin Pharmacokinetic Parameters (mean ± %CV)

CHARACTERISTICS	N	AGE	SEX M/F	DOSAGE FORM	ORAL DOSAGE (mg)	Cmax (ng/mL)	tmax (hr)	TOTAL AUC (ng. hr/mL)	$T_{1/2}$ (hr)	$(Cmin)_{SS}$ (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 Study	11	21-70	11/0	Capsule (Single Dose) Capsule (on Day 58 of Multiple Dose)	50 50/day	– 306(51)	– 3.5(20)	2,056(22) 2,472(45)	– 50(28)	– 24(38)

*AUC_{0-15}

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 2 and Table 5. A dose-proportional appearance of metabolite was also observed (Figure 3).

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 non proportional appearance of metabolite was also seen at higher doses.

Figure 2: 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.

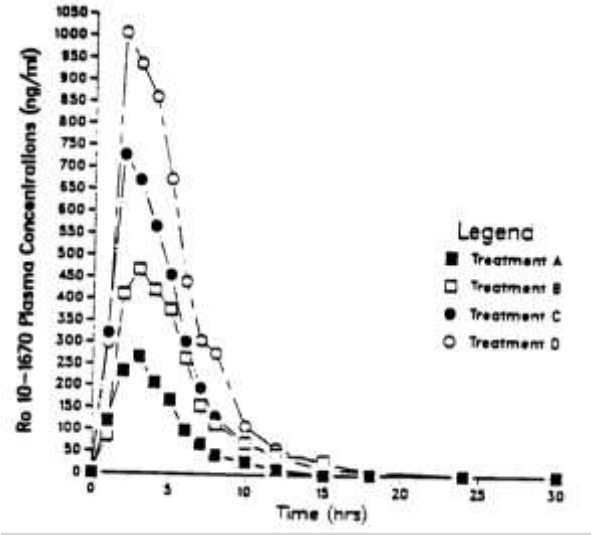
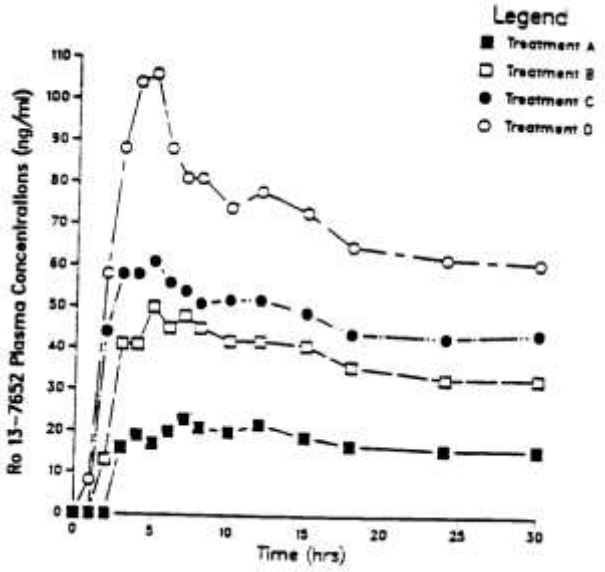


Figure 3: Mean 13-cis Metabolite Concentrations Following Administration of 25 mg (Treatment A), 50 mg (Treatment B), 75 mg (Treatment C), and 100 mg (Treatment D) of Acitretin with Food in 18 Healthy Male Subjects.



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 5. 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.

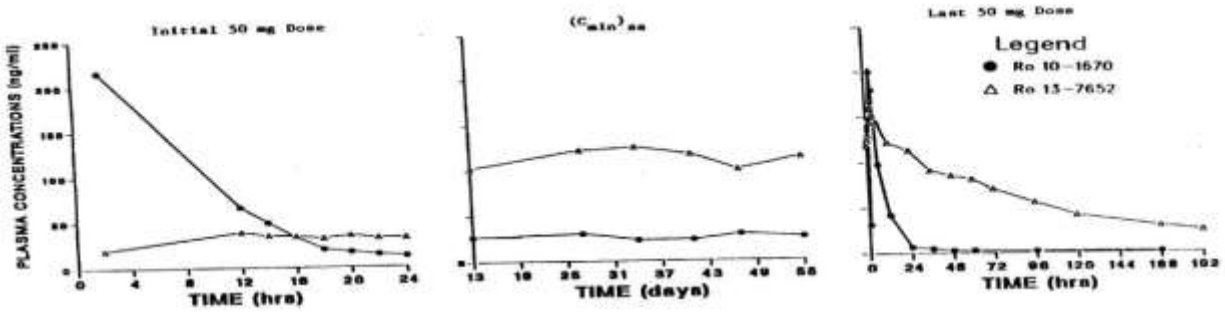
Multiple Dose

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 5 and Figure 4. 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 4: 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). ($Cmin_{ss}$ during Treatment are also Included)



In patients administered multiple oral doses of Acitretin 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 treatment. 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-treatment, without exception, in plasma samples obtained from 117 patients following cessation of Acitretin 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 identified in plasma may be 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.

TOXICOLOGY

Single-dose Toxicity

LD_{50} (Acitretin)

SPECIES	STRAIN	ROUTE	LD_{50} (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, unkept appearance, reddening around eyes, nose, mouth and/or genital area
Dog	Beagle	Oral	>1,000	14 days	Diarrhea

Repeat-dose Toxicity

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
Rat	M/10	i.v. (mixed micelle formulation)	0 (control) 0.5 or 2.0	2 weeks	No mortality; Statistically significant dose-related increase in adrenal weight at 2.0 mg/kg/day dose (13% higher than control)
Dog	M/3	i.v, (mixed micelle formulation)	0 (control) 1.0 or 5.0	2 weeks	No mortality; No findings distinguished treated from control dogs
Primates	1M/1F	Oral (spray dried powder formulation)	Escalating: 20 (Wk 1) 40 (Wk 2) 80 (Wk 3)	4 weeks	No mortality observed. At the end of the study, the erythrocyte counts were decreased to about 15-26% of the predosing values at doses

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
			160 (Wk 4)		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.
Rats	M/10	Oral (wet milled beadlet preparation)	0 (control) 5 10 20 40 80	Preliminary Study (dose ranging): 2-4 wks	The higher doses 20, 40, 80, mg/kg/day were very poorly tolerated. Rats showed dose-related deterioration of general condition, emaciation, decreased diameter of long bones, single and multiple fractures, elevated serum alkaline phosphatase activity and serum triglyceride levels
Rats	M/10	Oral (spray dried powder)	0 (control) 1 3 5 10 15	Preliminary Study (dose ranging): 4 weeks	Marked treatment effects at doses of 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 or single and/or multiple fractures of long bones.
Rats	24/sex/ group	Oral (spray dried powder)	0 (control) 0.5 *(this group was increased to 6.0 for Wks 14-18) 1.0 3.0	6 months (26-week dosing period)	*As no major side effects were noted at any of the doses for the first 13 wks, <u>the 0.5 dose group was increased to 6.0 for Wks 14-18:</u> <u>Female rats</u>: presented with failure to gain weight, slight sensitivity to handling, tendency toward decreased motor activity, slight to moderate elevations in serum alkaline phosphatase (149 U/L: 96 U/L control) and elevations (25-70%) in levels of serum cholesterol, triglycerides, and high density lipoprotein. No major bone changes were observed in these female rats. <u>Male rats:</u> 17/24 showed effect characteristic of hypervitaminosis A, i.e., weight loss, increased sensitivity to handling, decreased motor activity, fractures, erythema,

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
					crusting of the skin, rough fur. During Wk 18: Serum phosphatase (35 %). Moderate elevations in serum triglyceride concentrations (120 mg/100 mL; 70 mg/100 mL (control). No changes in serum cholesterol of serum low or high density lipoprotein concentrations. Moderate alterations of the ossification of the epiphyseal line in long bones were noted in these rats at necropsy at the end of the study. These groups (M/F) were placed on an unmedicated diet for one week at Wk 19 and restated on 0.5 mg/kg/day dose. The clinical changes reversed during Wks 20-26. At the end of the 26-week dosing period, 16 rats/sex/group were necropsied; the other 8 rats/sex/group were maintained without treatment for 4 wks to determine reversibility. Dosages of 0.5 and 1.0 mg/kg/day were tolerated without effects. <u>Female rats in the 3.0 dose group</u> 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. <u>Male rats in the 3.0 dose group</u> presented with slightly greater decreases in body weight gain (11%), increase in serum alkaline phosphatase (10-15%), and a slight tendency to premature ossification of the epiphyseal line. 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.
Dog	6/sex/ Group	Oral (spray dried powder in	0 (control) 5 15	1 year	A preliminary dose range finding study was conducted in 2 dogs (1/sex) in ascending dose fashion

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
		gelatin capsules)	50*		[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)]. In the one-year study, male dogs treated at the high dose (50 mg/kg/day) developed severe otitis externa by 5-6 wks. Treatment was interrupted during Weeks 7-8 and for female dogs during Wks 21-22. Due to persistent recurrence of the condition, the high dose was decreased to 30 mg/kg/day from Wk 17 for males and Wk 27 for females. At 26 weeks and at 1 year, 2/sex group were killed, necrsopsied and 2 male dogs (1 - 0/ 1- high dose) were maintained for 3 months without treatment to determine reversibility of effects. At doses of 5 and 15 mg/kg/day, mild to moderate reddening of the skin was noted and presented histopathologically as hypertrophy/hyperplasia. The cutaneous effects seen at the 50 mg/kg/day dose were severe and required a decrease to a dose of 30 mg/kg/day. Other clinical findings: A slight decrease in the number of spermatozoa in the testes of one dog at 26 weeks of treatment at the 15 mg/kg/day dose; this improved by 1 yr and reversed during the recovery period. Elevated leucocyte counts were observed in two dogs of each sex (1.38 – 2.20 x 10^{10} L (treated); 9.5. x 10^{9} L (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

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
					approximately 50% at the 6-month sacrifice but the decreases were less pronounced at one year. 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 6 months but the severity diminished by the end of the study. All clinical findings reversed during the recovery period.
Rat	Wistar/ 20/sex/ dose	Oral (Feed admixture)	0 (control) 2 4 10	18 months	2, 4 mg/kg/day group: Overall clinical tolerance was good. Minor symptoms were not considered treatment-related, except crust formation on the eyelids, more frequently in males in the 4 mg/kg/day group. 10 mg/kg/day groups: Definite systemic toxicity and treatment was interrupted in Weeks 27 and 28, and in Weeks 54 and 55 due to severe side effects. After 3-4 months treatment at the highest dose, 70 % (26/37) developed signs indicative of long bone fractures. At the end of the study, most of these rats had multiple bone fractures. At study-end, most of the rats in the 10 mg/kg/day 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. No bone fractures occurred in any other dosage group. In addition to the clinical signs related to bone

SPECIES	STRAIN SEX/#/ group	ROUTE	DOSE/ mg/kg/day	DURATION /animals/ group	OBSERVATIONS/RESULTS
					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

SPECIES	STRAIN	ROUTE	DOSE mg/kg/day	DURATION	OBSERVATIONS/RESULTS
Rats	Wistar (50/sex/ group)	Oral	0 (control -1) 0.5 1 2 0 (control -2)	104 - week	A total of 159 rats (83 males/76 females) died or were killed during the course of the study. The number of premature killings was slightly increased in high-dose group males due to drug-related clinical symptoms. Most animals died or were killed during the last quarter of the study. Spontaneous deaths or euthanasia 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:

- 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.

- 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.

- Unscheduled DNA synthesis in rat hepatocytes at concentrations up to 100 mcg/mL and human fibroblasts at concentrations up to 200 mcg/mL.

- Induction of Chromosomal Aberrations in Human Lymphocytes at concentrations up to 200 mcg/mL with metabolic activation by hepatic S-9.

- Mouse Micronucleus Assay at a single oral dose of 3 mg/kg

Reproduction and Teratology

Fertility and General Reproductive Performance in 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, pupilary 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).

Embryotoxicity and Teratology

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).

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.

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.

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, and 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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PART III: CONSUMER INFORMATION

[Pr]Taro-Acitretin
(Acitretin Capsules)
10 mg and 25 mg
Taro Standard

This leaflet is part III of a three-part "Product Monograph" published when Taro-Acitretin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Taro-Acitretin. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Taro-Acitretin (Acitretin) is used in the treatment of:

- Severe psoriasis
- Other disorders of keratinization in adult patients who have not responded to standard treatments.

What it does:
Taro-Acitretin (Acitretin) is a retinoid. It works by leading to a more normal pattern of growth for skin cells.

When it should not be used:

Taro-Acitretin can cause severely deformed babies. In order to take this drug, a female patient must use an effective birth control method 4 weeks before the start of treatment, during treatment and until at least 3 years after the last dose of Taro-Acitretin.

Do not consume alcohol during the treatment and until at least 2 months after the last dose of Taro-Acitretin.

Do not breastfeed during treatment and until at least 3 years after the last dose of Taro-Acitretin.

Do not use Taro-Acitretin if you:

- Are allergic to acitretin, or other retinoids, or Vitamin A, or its metabolites, or any of the other ingredients in Taro-Acitretin
- Are pregnant or plan to get pregnant
- Are breastfeeding
- Have severe liver or kidney disease
- Have consistent high blood lipid levels
- Take tetracyclines
- Take methotrexate
- Have high vitamin A levels (hypervitaminosis A)

Information for the patient (male and female):

Taro-Acitretin can cause severely deformed babies if it is taken by a female before or during pregnancy and for at least 3 years after stopping.

What the medicinal ingredient is:
Acitretin

What the non-medicinal ingredients are (in alphabetical order):
Ammonium hydroxide, Gelatin, Iron oxide black, Iron oxide red, Iron oxide yellow, Maltodextrin, Microcrystalline cellulose, Potassium hydroxide, Propylene glycol, Shellac, Sodium lauryl sulfate, Sorbic acid, and Titanium dioxide.

What dosage forms it comes in:
Each Taro-Acitretin capsule contains either 10 mg or 25 mg of acitretin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

You must avoid becoming pregnant while you are taking Taro-Acitretin and until at least 3 years after you stop taking Taro-Acitretin (discuss this with your doctor).

You must discuss **effective birth control** with your doctor before beginning treatment and you must use effective birth control without interruption as follows:

- for at least one month before you start Taro-Acitretin;
- while you are taking Taro-Acitretin; and
- for at least 3 years after you stop taking Taro-Acitretin (discuss this with your doctor); and
- bearing in mind that any method of birth control can fail,
- it is recommended that you either abstain from sexual intercourse or use two effective methods of birth control at the same time (discuss this with your doctor).
- Low dose progesterone-only (Micronor 28) may not be an effective method to prevent pregnancy during treatment with Taro-Acitretin and is not recommended for use.

Do not take Taro-Acitretin until you are sure that you are not pregnant:

- You must have 2 negative pregnancy tests before you start Taro-Acitretin. The first test (with a negative result) is obtained at screening when Taro-Acitretin treatment is under consideration. A second (confirmatory) test (with a negative result) must be obtained not older than 3 days before the first dose.
- You must wait until the second or third day of your next menstrual period before you start Taro-Acitretin.
- During treatment, you must have a pregnancy test at 28-day intervals. A negative pregnancy test, from

a licensed laboratory, not older than 3 days is mandatory before you can receive another prescription for Taro-Acitretin.
- After stopping treatment, you must have pregnancy tests every 1-3 months for **at least 3 years** after your last dose.

Every time you start a new course of treatment with Taro-Acitretin, however long the intervening period may have been, you must use effective and uninterrupted birth control, during treatment and for **at least 3 years** after you stop taking Taro-Acitretin.

Contact your doctor immediately if you do become pregnant while taking Taro-Acitretin or after treatment has stopped. You should discuss the serious risk of having a baby with severe birth deformities because you are taking or have taken Taro-Acitretin, as well as available options, with your doctor.

Do not breastfeed while taking Taro-Acitretin and until at least 3 years after the treatment has stopped.

Male and female patients should avoid consuming alcohol while taking Taro-Acitretin and until least 2 months after the treatment has stopped.

Male and female patients should not donate blood while taking Taro-Acitretin and until at least 3 years after the treatment has stopped.

You should have been counselled using the manufacturer's Taro-Acitretin Pregnancy Prevention Program which includes:
- Comprehensive information about the risks of this drug
- A line drawing of a deformed baby
- A checklist of the criteria you had to meet before receiving this drug
- Detailed information on birth control options
- A chart outlining the Taro-Acitretin Pregnancy Prevention Program
- An informed consent form for you to review and sign (for males and females)

If you were not counselled using the Taro-Acitretin Pregnancy Prevention Program, please visit www.taro-acitretin.ca for important information or contact Taro Canada Customer Service at (toll-free) 1-800-268-1975.

Before taking Taro-Acitretin, talk to your doctor if you have any of the following conditions:

- high cholesterol or triglycerides
- high blood sugar
- liver or kidney problems
- mood changes
- skin problems
- high pressure in the brain (intracranial hypertension)
- eye problems or wear contact lenses. Taro-Acitretin may cause dry eyes, light sensitivity, or other eye problems.

While taking Taro-Acitretin you should avoid prolonged exposure to sunlight or sun lamps. Use protective clothing or hat or sunscreen with SPF 30 or more.

Taro-Acitretin is not recommended for use in children.

INTERACTIONS WITH THIS MEDICATION

Before taking Taro-Acitretin tell your doctor or pharmacist about all other medications you take including medications that you bought without prescription, vitamins, and natural products. Particularly if you are taking the following:
- Vitamin A
- Methotrexate
- Tetracyclines, phenytoin
- Glyburide, or a sulfonylurea
- St John's Wort
- Alcohol because it can convert Taro-Acitretin to etretinate, a chemical that also causes birth defects and stays in the body longer.
- Low dose of progesterone-only contraceptive (Micronor 28)

PROPER USE OF THIS MEDICATION

You should take Taro-Acitretin as told by your doctor.

Usual dose:
For Severe psoriasis: starting dose of 25 mg once daily; maintenance daily dose from 25 mg to 50 mg; maximum daily dose of 75 mg.

For Other disorders of keratinization: 10 mg once daily; maximum daily dose of 50 mg

Take Taro-Acitretin once daily with food or after a meal.

Overdose:

If you think you have taken too much Taro-Acitretin, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose, take it as soon as you remember on the same day. Skip that dose if you do not remember until the next day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The first few weeks before you begin to see any healing, you may begin to have some side effects.

Side effects of Taro-Acitretin include the following:

Very common:
Dry eyes, particularly if you wear contact lenses;
Dry mouth, chapped lips, runny or dry nose;
Dry skin, peeling of fingertips and/or palms and soles, itchiness, rash, sticky skin, brittle nails;
Chills, joint pain, increased sensitivity to touch.

Most patients experience some degree of hair loss or abnormal hair texture 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.

Common:
Nosebleeds;
Ear problems such as pain, wax build-up, or buzzing in the ear;
Eye problems such as blurred vision, light sensitivity, pain, impaired vision;
Inflammation along the edge of the eyelid (blepharitis), inflammation or infection of the membrane lining the eyelids (conjunctivitis);
Tiredness, pain, thirst;
Swelling of leg, foot, ankle (oedema);
Bleeding or inflammation of the gums, or inflammation of the mucous lining of the mouth;
Nausea or abdominal pain;
Infections, including skin around the finger nail;
Decreased or increased appetite;
Back pain, bone pain or muscle pain;
Headache, trouble sleeping;
Skin problems such as cold sweat, excessive sweating, sensitivity to sunlight, inflamed, ulcerated, and oily or cracked skin.

Uncommon:
Decrease in night vision, or other eye problems, impaired hearing.

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

SERIOUS SIDE EFFECTS:
Seek emergency treatment, if you experience any of the following symptoms:

- Shortness of breath, dizziness, nausea, chest pain, weakness or trouble speaking as these can be signs of a heart attack, or stroke.
- Swelling of a leg, foot, ankle or arm as these can be signs of a blood clot.
- Worsening depression, suicidal thoughts or thoughts of self-harm.

OTHER SERIOUS SIDE EFFECTS:

- Headaches, abdominal pain, diarrhea, rectal bleeding, nausea, vomiting, blurred vision, other visual problems.
- Decrease in night vision.
- Persistent feeling of dry eyes
- Yellowing of the skin or eyes and/or dark urine, flu-like symptoms.

Aches or pains in bones or joints, or difficulty in moving. Bone changes have been detected by X-ray examination in patients taking Taro-Acitretin. The extent of any harm from these changes is not presently known.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain			√
	Diarrhea			√
	Headache			√
	Nausea			√
	Vomiting			√
	Fragile skin	√		
	Hair loss	√		
	Inflamed lips	√		
	Itching	√		
	Peeling of fingertips	√		
	Peeling skin all over the body	√		
	Redness or rash		√	
	Sticky skin	√		
Uncommon	Blurred vision			√
	Dizziness			√
	Persistent feeling of dry eyes		√	
	Yellowing of the skin or eyes			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	and/or flu-like symptoms and/or dark urine			√
	Shortness of breathe			√
	Weakness		√	
	Nausea		√	
	Dizziness			√
	Chest pain			√
	Trouble speaking			√
	Swelling of a leg, ankle, foot or arm			√
Rare/ very rare	**Decreased night vision**		√	
	Impaired hearing		√	
	Aches or Pain in Joints or Difficulty Moving		√	
	Rectal bleeding			√
	Changes in Mood/ depression			√
	Thoughts of suicide			√
	Aggressive behavior			√
Unknown frequency	**Allergic reactions:** Rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing			√
	Capillary leak syndrome: Sudden swelling in one part or all over your body, weight gain, fever, lightheadedness, feeling faint or muscle aches			√
	Exfoliative dermatitis: Red, swollen, itchy, painful or peeling skin. It can begin in a small area and then spread over large areas of your body.			√
	Madarosis: Eyelash and sometimes eyebrow loss		√	

This is not a complete list of side effects. For any unexpected effects while taking Taro-Acitretin contact your doctor or pharmacist.

THIS SUMMARY DOES NOT CONTAIN ALL KNOWN INFORMATION ABOUT TARO-ACITRETIN. TALK TO YOUR DOCTOR IF YOU HAVE ANY QUESTIONS.

HOW TO STORE IT

Store at 15-25°C. Protect Taro-Acitretin capsules from heat, light and moisture. Store in original package. Taro-Acitretin does not need to be refrigerated. Taro-Acitretin should not be used after the expiry date (EXP) shown on the package.

Keep Taro-Acitretin and all medications out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.taro.ca

or by contacting the sponsor,
Taro Pharmaceuticals Inc., at: **1-800-268-1975**

Important safety information about Taro-Acitretin and Taro-Acitretin Pregnancy Prevention Program is also available from :

- Online: www.taro-acitretin.ca

This leaflet was prepared by :
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