# PACKAGE INSERT
# Targretin® (bexarotene) capsules, 75 mg

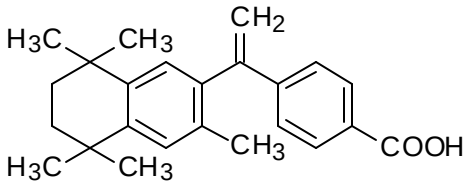
Rx only.

**Targretin® capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Targretin® capsules also caused birth defects when administered orally to pregnant rats. Targretin® capsules must not be administered to a pregnant woman. See CONTRAINDICATIONS.**

## DESCRIPTION

Targretin® (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid, and the structural formula is as follows:




Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Targretin® (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Bexarotene selectively binds and activates retinoid X receptor subtypes (RXRα, RXRβ, RXRγ). RXRs can form heterodimers with various receptor partners such as retinoic acid receptors (RARs), vitamin D receptor, thyroid receptor, and peroxisome proliferator activator receptors (PPARs). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular

differentiation and proliferation. Bexarotene inhibits the growth *in vitro* of some tumor cell lines of hematopoietic and squamous cell origin. It also induces tumor regression *in vivo* in some animal models. The exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

## Pharmacokinetics

### *General*

After oral administration of Targretin capsules, bexarotene is absorbed with a $T_{max}$ of about two hours. Terminal half-life of bexarotene is about seven hours. Studies in patients with advanced malignancies show approximate single dose linearity within the therapeutic range and low accumulation with multiple doses. Plasma bexarotene AUC and $C_{max}$ values resulting from a 300 mg dose were 35% and 48% higher, respectively, after a fat-containing meal than after a glucose solution (see **PRECAUTIONS: Drug-Food Interaction** and **DOSAGE AND ADMINISTRATION**). Bexarotene is highly bound (>99%) to plasma proteins. The plasma proteins to which bexarotene binds have not been elucidated, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding have not been studied (see **PRECAUTIONS: Protein Binding)**. The uptake of bexarotene by organs or tissues has not been evaluated.

### *Metabolism*

Four bexarotene metabolites have been identified in plasma: 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest that cytochrome P450 3A4 is the major cytochrome P450 responsible for formation of the oxidative metabolites and that the oxidative metabolites may be glucuronidated. The oxidative metabolites are active in *in vitro* assays of retinoid receptor activation, but the relative contribution of the parent and any metabolites to the efficacy and safety of Targretin® capsules is unknown.

### *Elimination*

The renal elimination of bexarotene and its metabolites was examined in patients with Type 2 diabetes mellitus. Neither bexarotene nor its metabolites were excreted in urine in appreciable amounts. Bexarotene is thought to be eliminated primarily through the hepatobiliary system.

### *Special Populations*

Elderly: Bexarotene $C_{max}$ and AUC were similar in advanced cancer patients <60 years old and in patients >60 years old, including a subset of patients >70 years old.

Pediatric: Studies to evaluate bexarotene pharmacokinetics in the pediatric population have not been conducted (see **PRECAUTIONS: Pediatric Use**).

Gender: The pharmacokinetics of bexarotene were similar in male and female patients with advanced cancer.

Ethnic Origin: The effect of ethnic origin on bexarotene pharmacokinetics is unknown.

Renal Insufficiency: No formal studies have been conducted with Targretin® capsules in patients with renal insufficiency. Urinary elimination of bexarotene and its known metabolites is a minor excretory pathway (<1% of administered dose), but because renal insufficiency can result in significant protein binding changes, pharmacokinetics may be altered in patients with renal insufficiency (see **PRECAUTIONS: Renal Insufficiency**).

Hepatic Insufficiency: No specific studies have been conducted with Targretin® capsules in patients with hepatic insufficiency. Because less than 1% of the dose is excreted in the urine unchanged and there is *in vitro* evidence of extensive hepatic contribution to bexarotene elimination, hepatic impairment would be expected to lead to greatly decreased clearance (see **WARNINGS: Hepatic Insufficiency**).

***Drug-Drug Interactions***

No specific studies to evaluate drug interactions with bexarotene have been conducted. Bexarotene oxidative metabolites appear to be formed by cytochrome P450 3A4.

Because bexarotene is metabolized by cytochrome P450 3A4, ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit juice, and other inhibitors of cytochrome P450 3A4 would be expected to lead to an increase in plasma bexarotene concentrations. Furthermore, rifampin, phenytoin, phenobarbital and other inducers of cytochrome P450 3A4 may cause a reduction in plasma bexarotene concentrations.

Concomitant administration of Targretin capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene, probably at least partially related to cytochrome P450 3A4 inhibition by gemfibrozil. Under similar conditions, bexarotene concentrations were not affected by concomitant atorvastatin administration. Concomitant administration of gemfibrozil with Targretin® capsules is not recommended (see **PRECAUTIONS: Drug-Drug Interactions**).

**Clinical Studies**

Targretin® capsules were evaluated in 152 patients with advanced and early stage cutaneous T-cell lymphoma (CTCL) in two multicenter, open-label, historically-controlled clinical studies conducted in the U.S., Canada, Europe, and Australia.

The advanced disease patients had disease refractory to at least one prior systemic therapy (median of two, range one to six prior systemic therapies) and had been treated with a median of five (range 1 to 11) prior systemic, irradiation, and/or topical therapies. Early disease patients were intolerant to, had disease that was refractory to, or had reached a response plateau of six months on, at least two prior therapies. The patients entered had been treated with a median of 3.5 (range 2 to 12) therapies (systemic, radiation, and/or topical).

The two clinical studies enrolled a total of 152 patients, 102 of whom had disease refractory to at least one prior systemic therapy, 90 with advanced disease and 12 with early disease. This is the patient population for whom Targretin® capsules are indicated.

Patients were initially treated with a starting dose of 650 mg/m$^2$/day with a subsequent reduction of starting dose to 500 mg/m$^2$/day. Neither of these starting doses was tolerated, and the starting dose was then reduced to 300 mg/m$^2$/day. If, however, a patient on 300 mg/m$^2$/day of Targretin® capsules showed no response after eight or more weeks of therapy, the dose could be increased to 400 mg/m$^2$/day.

Tumor response was assessed in both studies by observation of up to five baseline-defined index lesions using a Composite Assessment of Index Lesion Disease Severity (CA). This endpoint was based on a summation of the grades, for all index lesions, of erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. Also considered in response assessment was the presence or absence of cutaneous tumors and extracutaneous disease manifestations.

All tumor responses required confirmation over at least two assessments separated by at least four weeks. A partial response was defined as an improvement of at least 50% in the index lesions without worsening, or development of new cutaneous tumors or non-cutaneous manifestations. A complete clinical response required complete disappearance of all manifestations of disease, but did not require confirmation by biopsy.

At the initial dose of 300 mg/m$^2$/day, 1/62 (1.6%) of patients had a complete clinical tumor response and 19/62 (30%) of patients had a partial tumor response. The rate of relapse (25% increase in CA or worsening of other aspects of disease) in the 20 patients who had a tumor response was 6/20 (30%) over a median duration of observation of 21 weeks, and the median duration of tumor response had not been reached. Responses were seen as early as 4 weeks and new responses continued to be seen at later visits.

## INDICATIONS AND USAGE

Targretin® (bexarotene) capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

## CONTRAINDICATIONS

Targretin® capsules are contraindicated in patients with a known hypersensitivity to bexarotene or other components of the product.

### *Pregnancy: Category X*

Targretin® (bexarotene) capsules may cause fetal harm when administered to a pregnant woman. Targretin® capsules must not be given to a pregnant woman or a woman who intends to become pregnant. If a woman becomes pregnant while

taking Targretin® capsules, Targretin® capsules must be stopped immediately and the woman given appropriate counseling.

Bexarotene caused malformations when administered orally to pregnant rats during days 7-17 of gestation. Developmental abnormalities included incomplete ossification at 4 mg/kg/day and cleft palate, depressed eye bulge/microphthalmia, and small ears at 16 mg/kg/day. The plasma AUC of bexarotene in rats at 4 mg/kg/day is approximately one third the AUC in humans at the recommended daily dose. At doses greater than 10 mg/kg/day, bexarotene caused developmental mortality. The no effect dose for fetal effects in rats was 1 mg/kg/day (producing an AUC approximately one sixth of the AUC at the recommended human daily dose).

Women of child-bearing potential should be advised to avoid becoming pregnant when Targretin® capsules are used. The possibility that a woman of child-bearing potential is pregnant at the time therapy is instituted should be considered. A negative pregnancy test (e.g., serum beta-human chorionic gonadotropin, beta-HCG) with a sensitivity of at least 50 mIU/L should be obtained within one week prior to Targretin® capsules therapy, and the pregnancy test must be repeated at monthly intervals while the patient remains on Targretin® capsules. Effective contraception must be used for one month prior to the initiation of therapy, during therapy and for at least one month following discontinuation of therapy; it is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must use condoms during sexual intercourse while taking Targretin® capsules and for at least one month after the last dose of drug. Targretin® capsules therapy should be initiated on the second or third day of a normal menstrual period. No more than a one month supply of Targretin® capsules should be given to the patient so that the results of pregnancy testing can be assessed and counseling regarding avoidance of pregnancy and birth defects can be reinforced.

**WARNINGS**

*Lipid abnormalities:* Targretin capsules induce major lipid abnormalities in most patients. These must be monitored and treated during long term therapy. About 70% of patients with CTCL who received an initial dose of ≥300 mg/m$^2$/day of Targretin® capsules had fasting triglyceride levels greater than 2.5 times the upper limit of normal. About 55% had values over 800 mg/dL with a median of about 1200 mg/dL in those patients. Cholesterol elevations above 300 mg/dL occurred in approximately 60% and 75% of patients with CTCL who received an initial dose of 300 mg/m$^2$/day or greater than 300 mg/m$^2$/day, respectively. Decreases in high density lipoprotein (HDL) cholesterol to less than 25 mg/dL were seen in about 55% and 90% of patients receiving an initial dose of 300 mg/m$^2$/day or greater than 300 mg/m$^2$/day, respectively, of Targretin® capsules. The effects on triglycerides, HDL cholesterol, and total cholesterol were reversible with cessation of therapy, and could generally be mitigated by dose reduction or concomitant antilipemic therapy.

Fasting blood lipid determinations should be performed before Targretin® capsules therapy is initiated and weekly until the lipid response to Targretin® capsules is established, which usually occurs within two to four weeks, and at eight week intervals thereafter. Fasting triglycerides should be normal or normalized with appropriate intervention prior to initiating Targretin® capsules therapy. Attempts should be made to maintain triglyceride levels below 400 mg/dL to reduce the risk of clinical sequelae (see **WARNINGS:** *Pancreatitis*). If fasting triglycerides are elevated or become elevated during treatment, antilipemic therapy should be instituted, and if necessary, the dose of Targretin capsules reduced or suspended. In the 300 mg/m$^2$/day initial dose group, 60% of patients were given lipid lowering drugs. Atorvastatin was used in 48% (73/152) of patients with CTCL. Because of a potential drug-drug interaction (see **PRECAUTIONS: Drug-Drug Interactions**), gemfibrozil is not recommended for use with Targretin® capsules.

*Pancreatitis:* Acute pancreatitis has been reported in four patients with CTCL and in six patients with non-CTCL cancers treated with Targretin® capsules; the cases were associated with marked elevations of fasting serum triglycerides, the lowest being 770 mg/dL in one patient. One patient with advanced non-CTCL cancer died of pancreatitis. Patients with CTCL who have risk factors for pancreatitis (e.g., prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should generally not be treated with Targretin® capsules (see **WARNINGS:** *Lipids abnormalities* and **PRECAUTIONS: Laboratory Tests**).

*Liver function test abnormalities:* For patients with CTCL receiving an initial dose level of 300 mg/m$^2$/day of Targretin® capsules, elevations in liver function tests (LFTs) have been observed in 5% (SGOT/AST), 2% (SGPT/ALT), and 0% (bilirubin). In contrast, with an initial dose greater than 300 mg/m$^2$/day of Targretin® capsules, the incidence of LFT elevations was higher at 7% (SGOT/AST), 9% (SGPT/ALT), and 6% (bilirubin). Two patients developed cholestasis, including one patient who died of liver failure. In clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored after one, two and four weeks of treatment initiation, and if stable, at least every eight weeks thereafter during treatment. Consideration should be given to a suspension or discontinuation of Targretin® capsules if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

*Hepatic Insufficiency*: No specific studies have been conducted with Targretin® capsules in patients with hepatic insufficiency. Because less than 1% of the dose is excreted in the urine unchanged and there is *in vitro* evidence of extensive hepatic contribution to bexarotene elimination, hepatic impairment would be expected to lead to greatly decreased clearance. Targretin® capsules should be used only with great caution in this population.

*Thyroid axis alterations:* Targretin® capsules induce biochemical evidence of or clinical hypothyroidism in about half of all patients treated, causing a reversible reduction in thyroid hormone (total thyroxine [total T4]) and thyroid-stimulating hormone (TSH) levels. The incidence of decreases in TSH and total T4 about 60% and 45%, respectively, in patients with CTCL receiving an initial dose of 300 mg/m$^2$/day. Hypothyroidism was reported as an adverse event in 29% of patients. Treatment with thyroid hormone supplements should be considered in patients with laboratory evidence of hypothyroidism. In the 300 mg/m$^2$/day initial dose group, 37% of patients were treated with thyroid hormone replacement. Baseline thyroid function tests should be obtained and patients monitored during treatment.

*Leukopenia*: A total of 18% of patients with CTCL receiving an initial dose of 300 mg/m$^2$/day of Targretin® capsules had reversible leukopenia in the range of 1000 to <3000 WBC/mm$^3$. Patients receiving an initial dose greater than 300 mg/m$^2$/day of Targretin® capsules had an incidence of leukopenia of 43%. No patient with CTCL treated with Targretin® capsules developed leukopenia of less than 1000 WBC/mm$^3$. The time to onset of leukopenia was generally four to eight weeks. The leukopenia observed in most patients was explained by neutropenia. In the 300 mg/m$^2$/day initial dose group, the incidence of NCI Grade 3 and Grade 4 neutropenia, respectively, was 12% and 4%. The leukopenia and neutropenia experienced during Targretin® capsules therapy resolved after dose reduction or discontinuation of treatment, on average within 30 days in 93% of the patients with CTCL and 82% of patients with non-CTCL cancers. Leukopenia and neutropenia were rarely associated with severe sequelae or serious adverse events. Determination of WBC with differential should be obtained at baseline and periodically during treatment.

*Cataracts:* Posterior subcapsular cataracts were observed in preclinical toxicity studies in rats and dogs administered bexarotene daily for 6 months. In 15 of 79 patients who had serial slit lamp examinations, new cataracts or worsening of previous cataracts were found. Because of the high prevalence and rate of cataract formation in older patient populations, the relationship of Targretin® capsules and cataracts cannot be determined in the absence of an appropriate control group. Patients treated with Targretin® capsules who experience visual difficulties should have an appropriate ophthalmologic evaluation.

## PRECAUTIONS

***Pregnancy:*** **Category X**. See **CONTRAINDICATIONS**.

***General:*** Targretin® capsules should be used with caution in patients with a known hypersensitivity to retinoids. Clinical instances of cross reactivity have not been noted.

*Vitamin A Supplementation:* In clinical studies, patients were advised to limit vitamin A intake to ≤15,000 IU/day. Because of the relationship of bexarotene to

vitamin A, patients should be advised to limit vitamin A supplements to avoid potential additive toxic effects.

*Patients with Diabetes Mellitus*: Caution should be used when administering Targretin® capsules in patients using insulin, agents enhancing insulin secretion (e.g., sulfonylureas), or insulin-sensitizers (e.g., troglitazone). Based on the mechanism of action, Targretin® capsules could enhance the action of these agents, resulting in hypoglycemia. Hypoglycemia has not been associated with the use of Targretin® capsules as monotherapy.

*Photosensitivity*: Retinoids as a class have been associated with photosensitivity. *In vitro* assays indicate that bexarotene is a potential photosensitizing agent. Mild phototoxicity manifested as sunburn and skin sensitivity to sunlight was observed in patients who were exposed to direct sunlight while receiving Targretin® capsules. Patients should be advised to minimize exposure to sunlight and artificial ultraviolet light while receiving Targretin® capsules.

***Laboratory Tests***

Blood lipid determinations should be performed before Targretin® capsules are given. Fasting triglycerides should be normal or normalized with appropriate intervention prior to therapy. Hyperlipidemia usually occurs within the initial two to four weeks. Therefore, weekly lipid determinations are recommended during this interval. Subsequently, in patients not hyperlipidemic, determinations can be performed less frequently (see **WARNINGS:** *Lipid abnormalities*).

A white blood cell count with differential should be obtained at baseline and periodically during treatment. Baseline liver function tests should be obtained and should be carefully monitored after one, two and four weeks of treatment initiation, and if stable, periodically thereafter during treatment. Baseline thyroid function tests should be obtained and then monitored during treatment as indicated (see **WARNINGS:** *Leukopenia, Liver function test abnormalities, and Thyroid axis alterations*).

***Drug-Food Interaction***

In all clinical trials, patients were instructed to take Targretin® capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and $C_{max}$ values were substantially higher following a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data are based upon administration with food, it is recommended that Targretin® capsules be administered with food (see **CLINICAL PHARMACOLOGY: Food Effects** and **DOSAGE AND ADMINISTRATION**).

***Drug-Drug Interactions***

No formal studies to evaluate drug interactions with bexarotene have been conducted. Bexarotene oxidative metabolites appear to be formed by cytochrome P450 3A4.

On the basis of the metabolism of bexarotene by cytochrome P450 3A4, ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit juice, and other inhibitors of cytochrome P450 3A4 would be expected to lead to an increase in plasma bexarotene concentrations. Furthermore, rifampin, phenytoin, phenobarbital, and other inducers of cytochrome P450 3A4 may cause a reduction in plasma bexarotene concentrations.

Concomitant administration of Targretin® capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene, probably at least partially related to cytochrome P450 3A4 inhibition by gemfibrozil. Under similar conditions, bexarotene concentrations were not affected by concomitant atorvastatin administration. Concomitant administration of gemfibrozil with Targretin® capsules is not recommended.

***Renal Insufficiency***

No formal studies have been conducted with Targretin® capsules in patients with renal insufficiency. Urinary elimination of bexarotene and its known metabolites is a minor excretory pathway for bexarotene (<1% of administered dose), but because renal insufficiency can result in significant protein binding changes, and bexarotene is >99% protein bound, pharmacokinetics may be altered in patients with renal insufficiency.

***Protein Binding***

Bexarotene is highly bound (>99%) to plasma proteins. The plasma proteins to which bexarotene binds have not been elucidated, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding have not been studied.

***Drug/Laboratory Test Interactions***

CA125 assay values in patients with ovarian cancer may be increased by Targretin® capsule therapy.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Long-term studies in animals to assess the carcinogenic potential of bexarotene have not been conducted. Bexarotene is not mutagenic to bacteria (Ames assay) or mammalian cells (mouse lymphoma assay). Bexarotene was not clastogenic *in vivo* (micronucleus test in mice). No formal fertility studies were conducted with bexarotene. Bexarotene caused testicular degeneration when oral doses of 1.5 mg/kg/day were given to dogs for 91 days (producing an AUC of approximately one fifth the AUC at the recommended human daily dose).

***Use in Nursing Mothers***

It is not known whether bexarotene is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bexarotene, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

***Pediatric Use***
Safety and effectiveness in pediatric patients have not been established.

***Geriatric Use***
Of the total patients with CTCL in clinical studies of Targretin® capsules, 64% were 60 years or older, while 33% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to Targretin® capsules cannot be ruled out. Responses to Targretin® capsules were observed across all age group decades, without preference for any individual age group decade.

**ADVERSE REACTIONS**
The safety of Targretin® capsules has been evaluated in clinical studies of 152 patients with CTCL who received Targretin® capsules for up to 97 weeks and in 352 patients in other studies. The mean duration of therapy for the 152 patients with CTCL was 166 days. The most common adverse events reported with an incidence of at least 10% in patients with CTCL treated at an initial dose of 300 mg/m$^2$/day of Targretin® capsules are shown in Table 1. The events at least possibly related to treatment are lipid abnormalities (elevated triglycerides, elevated total and LDL cholesterol and decreased HDL cholesterol), hypothyroidism, headache, asthenia, rash, leukopenia, anemia, nausea, infection, peripheral edema, abdominal pain, and dry skin. Most adverse events occurred at a higher incidence in patients treated at starting doses of greater than 300 mg/m$^2$/day (see Table 1).

Adverse events leading to dose reduction or study drug discontinuation in at least two patients were hyperlipemia, neutropenia/leukopenia, diarrhea, fatigue/lethargy, hypothyroidism, headache, liver function test abnormalities, rash, pancreatitis, nausea, anemia, allergic reaction, muscle spasm, pneumonia, and confusion.

The moderately severe (NCI Grade 3) and severe (NCI Grade 4) adverse events reported in two or more patients with CTCL treated at an initial dose of 300 mg/m$^2$/day of Targretin® capsules (see Table 2) were hypertriglyceridemia, pruritus, headache, peripheral edema, leukopenia, rash, and hypercholesteremia. Most of these moderately severe or severe adverse events occurred at a higher rate in patients treated at starting doses of greater than 300 mg/m$^2$/day than in patients treated at a starting dose of 300 mg/m$^2$/day.

As shown in Table 3, in patients with CTCL receiving an initial dose of 300 mg/m$^2$/day, the incidence of NCI Grade 3 or 4 elevations in triglycerides and total cholesterol was 28% and 25%, respectively. In contrast, in patients with CTCL receiving greater than 300 mg/m$^2$/day, the incidence of NCI Grade 3 or 4 elevated triglycerides and total cholesterol was 45% and 45%, respectively. Other Grade 3 and 4 laboratory abnormalities are shown in Table 3.

In addition to the 152 patients enrolled in the two CTCL studies, 352 patients received Targretin® capsules as monotherapy for various advanced malignancies at doses from 5 mg/m$^2$/day to 1000 mg/m$^2$/day. The common adverse events (incidence greater than 10%) were similar to those seen in CTCL.

In the 504 patients (CTCL and non-CTCL) who received Targretin® capsules as monotherapy, drug-related serious adverse events that were fatal in one patient each, were acute pancreatitis, subdural hematoma, and liver failure.

In the patients with CTCL receiving an initial dose of 300 mg/$m^2$/day of Targretin® capsules, adverse events reported at an incidence of less than 10%, and not included in Tables 1-3 or discussed in other parts of labeling and possibly related to treatment were as follows:

**Body as a Whole:** chills**,** cellulitis, chest pain, sepsis, and monilia.

**Cardiovascular:** hemorrhage, hypertension, angina pectoris, right heart failure, syncope, and tachycardia.

**Digestive:** constipation, dry mouth, flatulence, colitis, dyspepsia, cheilitis, gastroenteritis, gingivitis, liver failure, and melena.

**Hematic and Lymphatic:** eosinophilia, thrombocythemia, coagulation time increased, lymphocytosis, and thrombocytopenia.

**Metabolic and Nutritional:** LDH increased, creatinine increased, hypoproteinemia, hyperglycemia, weight decreased, weight increased, and amylase increased.

**Musculoskeletal:** arthralgia, myalgia, bone pain, myasthenia, and arthrosis.

**Nervous:** depression, agitation, ataxia, cerebrovascular accident, confusion, dizziness, hyperesthesia, hypesthesia, and neuropathy.

**Respiratory:** pharyngitis, rhinitis, dyspnea, pleural effusion, bronchitis, cough increased, lung edema, hemoptysis, and hypoxia.

**Skin and Appendages:** skin ulcer, acne, alopecia, skin nodule, macular papular rash, pustular rash, serous drainage, and vesicular bullous rash.

**Special Senses:** dry eyes, conjunctivitis, ear pain, blepharitis, corneal lesion, keratitis, otitis externa, and visual field defect.

**Urogenital:** albuminuria, hematuria, urinary incontinence, urinary tract infection, urinary urgency, dysuria, kidney function abnormal, and breast pain.

Table 1. Adverse Events with Incidence ≥10% in CTCL Trials

| | Initial Assigned Dose Group ($mg/m^2$/day) | |
|---|---|---|
| | 300 | >300 |
| **Body System**<br>Adverse Event[1,2] | N=84<br>N (%) | N=53<br>N (%) |
| METABOLIC AND NUTRITIONAL DISORDERS | | |
| Hyperlipemia | 66 (78.6) | 42 (79.2) |
| Hypercholesteremia | 27 (32.1) | 33 (62.3) |
| Lactic dehydrogenase increased | 6 (7.1) | 7 (13.2) |
| BODY AS A WHOLE | | |
| Headache | 25 (29.8) | 22 (41.5) |
| Asthenia | 17 (20.2) | 24 (45.3) |
| Infection | 11 (13.1) | 12 (22.6) |
| Abdominal pain | 9 (10.7) | 2 (3.8) |
| Chills | 8 (9.5) | 7 (13.2) |
| Fever | 4 (4.8) | 9 (17.0) |
| Flu syndrome | 3 (3.6) | 7 (13.2) |
| Back pain | 2 (2.4) | 6 (11.3) |
| Infection bacterial | 1 (1.2) | 7 (13.2) |
| ENDOCRINE | | |
| Hypothyroidism | 24 (28.6) | 28 (52.8) |
| SKIN AND APPENDAGES | | |
| Rash | 14 (16.7) | 12 (22.6) |
| Dry skin | 9 (10.7) | 5 (9.4) |
| Exfoliative dermatitis | 8 (9.5) | 15 (28.3) |
| Alopecia | 3 (3.6) | 6 (11.3) |
| HEMIC AND LYMPHATIC SYSTEM | | |
| Leukopenia | 14 (16.7) | 25 (47.2) |
| Anemia | 5 (6.0) | 13 (24.5) |
| Hypochromic anemia | 3 (3.6) | 7 (13.2) |
| DIGESTIVE SYSTEM | | |
| Nausea | 13 (15.5) | 4 (7.5) |
| Diarrhea | 6 (7.1) | 22 (41.5) |
| Vomiting | 3 (3.6) | 7 (13.2) |
| Anorexia | 2 (2.4) | 12 (22.6) |
| CARDIOVASCULAR SYSTEM | | |
| Peripheral edema | 11 (13.1) | 6 (11.3) |
| NERVOUS SYSTEM | | |
| Insomnia | 4 (4.8) | 6 (11.3) |

[1] Preferred English term coded according to Ligand-modified COSTART 5 Dictionary.
[2] Patients are counted at most once in each AE category.

Table 2. Incidence of Moderately Severe and Severe Adverse Events Reported in at Least Two Patients (CTCL Trials)

| | Initial Assigned Dose Group (mg/m$^2$/day) | | | |
|---|---|---|---|---|
| | 300 (N=84) | | >300 (N=53) | |
| | Mod Sev | Severe | Mod Sev | Severe |
| **Body System** Adverse Event[1,2] | N (%) | N (%) | N (%) | N (%) |
| BODY AS A WHOLE | | | | |
| Asthenia | 1 (1.2) | 0 (0.0) | 11 (20.8) | 0 (0.0) |
| Headache | 3 (3.6) | 0 (0.0) | 5 (9.4) | 1 (1.9) |
| Infection bacterial | 1 (1.2) | 0 (0.0) | 0 (0.0) | 2 (3.8) |
| CARDIOVASCULAR SYSTEM | | | | |
| Peripheral edema | 2 (2.4) | 1 (1.2) | 0 (0.0) | 0 (0.0) |
| DIGESTIVE SYSTEM | | | | |
| Anorexia | 0 (0.0) | 0 (0.0) | 3 (5.7) | 0 (0.0) |
| Diarrhea | 1 (1.2) | 1 (1.2) | 2 (3.8) | 1 (1.9) |
| Pancreatitis | 1 (1.2) | 0 (0.0) | 3 (5.7) | 0 (0.0) |
| Vomiting | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| ENDOCRINE | | | | |
| Hypothyroidism | 1 (1.2) | 1 (1.2) | 2 (3.8) | 0 (0.0) |
| HEM. & LYMPH. SYS. | | | | |
| Leukopenia | 3 (3.6) | 0 (0.0) | 6 (11.3) | 1 (1.9) |
| META. AND NUTR. DIS. | | | | |
| Bilirubinemia | 0 (0.0) | 1 (1.2) | 2 (3.8) | 0 (0.0) |
| Hypercholesteremia | 2 (2.4) | 0 (0.0) | 5 (9.4) | 0 (0.0) |
| Hyperlipemia | 16 (19.0) | 6 (7.1) | 17 (32.1) | 5 (9.4) |
| SGOT/AST increased | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| SGPT/ALT increased | 0 (0.0) | 0 (0.0) | 2 (3.8) | 0 (0.0) |
| RESPIRATORY SYSTEM | | | | |
| Pneumonia | 0 (0.0) | 0 (0.0) | 2 (3.8) | 2 (3.8) |
| SKIN AND APPENDAGES | | | | |
| Exfoliative dermatitis | 0 (0.0) | 1 (1.2) | 3 (5.7) | 1 (1.9) |
| Rash | 1 (1.2) | 2 (2.4) | 1 (1.9) | 0 (0.0) |

[1] Preferred English term coded according to Ligand-modified COSTART 5 Dictionary.
[2] Patients are counted at most once in each AE category. Patients are classified by the highest severity within each row.

Table 3. Treatment-Emergent Abnormal Laboratory Values in CTCL Trials

| | Initial Assigned Dose (mg/m$^2$/day) | | | |
|---|---|---|---|---|
| | 300 | | >300 | |
| | N=83[1] | | N=53[1] | |
| Analyte | Grade 3[2] (%) | Grade 4[2] (%) | Grade 3 (%) | Grade 4 (%) |
| Triglycerides[3] | 21.3 | 6.7 | 31.8 | 13.6 |
| Total Cholesterol[3] | 18.7 | 6.7 | 15.9 | 29.5 |
| Alkaline Phosphatase | 1.2 | 0.0 | 0.0 | 1.9 |
| Hyperglycemia | 1.2 | 0.0 | 5.7 | 0.0 |
| Hypocalcemia | 1.2 | 0.0 | 0.0 | 0.0 |
| Hyponatremia | 1.2 | 0.0 | 9.4 | 0.0 |
| SGPT/ALT | 1.2 | 0.0 | 1.9 | 1.9 |
| Hyperkalemia | 0.0 | 0.0 | 1.9 | 0.0 |
| Hypernatremia | 0.0 | 1.2 | 0.0 | 0.0 |
| SGOT/AST | 0.0 | 0.0 | 1.9 | 1.9 |
| Total Bilirubin | 0.0 | 0.0 | 0.0 | 1.9 |
| ANC | 12.0 | 3.6 | 18.9 | 7.5 |
| ALC | 7.2 | 0.0 | 15.1 | 0.0 |
| WBC | 3.6 | 0.0 | 11.3 | 0.0 |
| Hemoglobin | 0.0 | 0.0 | 1.9 | 0.0 |

[1] Number of patients with at least one analyte value post-baseline.
[2] Adapted from NCI Common Toxicity Criteria, Grade 3 and 4, Version 2.0. Patients are considered to have had a Grade 3 or 4 value if either of the following occurred: a) Value becomes Grade 3 or 4 during the study; b) Value is abnormal at baseline and worsens to Grade 3 or 4 on study, including all values beyond study drug discontinuation, as defined in data handling conventions.
[3] The denominator used to calculate the incidence rates for fasting Total Cholesterol and Triglycerides were N=75 for the 300 mg/m$^2$/day initial dose group and N=44 for the >300 mg/m$^2$/day initial dose group.

## OVERDOSAGE

Doses up to 1000 mg/m$^2$/day of Targretin® capsules have been administered in short-term studies in patients with advanced cancer without acute toxic effects. Single doses of 1500 mg/kg and 720 mg/kg were tolerated without significant toxicity in rats and dogs, respectively. These doses are approximately 30 and 50 times, respectively, the recommended human dose on a mg/m$^2$ basis.

No clinical experience with an overdose of Targretin® capsules has been reported. Any overdose with Targretin® capsules should be treated with supportive care for the signs and symptoms exhibited by the patient.

## DOSAGE AND ADMINISTRATION

The recommended initial dose of Targretin® capsules is 300 mg/m$^2$/day. (See Table 4.) Targretin® capsules should be taken as a single oral daily dose with a meal. See **CONTRAINDICATIONS: Pregnancy Category X** section for

precautions to prevent pregnancy and birth defects in women of child-bearing potential.

Table 4. Targretin® Capsule Initial Dose Calculation According to Body Surface Area

| Initial Dose Level (300 mg/m$^2$/day) | | Number of 75 mg Targretin Capsules |
|---|---|---|
| Body Surface Area (m$^2$) | Total Daily Dose (mg/day) | |
| 0.88 - 1.12 | 300 | 4 |
| 1.13 - 1.37 | 375 | 5 |
| 1.38 - 1.62 | 450 | 6 |
| 1.63 - 1.87 | 525 | 7 |
| 1.88 - 2.12 | 600 | 8 |
| 2.13 - 2.37 | 675 | 9 |
| 2.38 - 2.62 | 750 | 10 |

Dose Modification Guidelines: The 300 mg/m$^2$/day dose level of Targretin® capsules may be adjusted to 200 mg/m$^2$/day then to 100 mg/m$^2$/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m$^2$/day is well tolerated, the dose may be escalated to 400 mg/m$^2$/day with careful monitoring.

Duration of Therapy: In clinical trials in CTCL, Targretin® capsules were administered for up to 97 weeks.

Targretin® capsules should be continued as long as the patient is deriving benefit.

**HOW SUPPLIED**

Targretin® capsules are supplied as 75-mg off-white, oblong soft gelatin capsules, imprinted with "Targretin," in high density polyethylene bottles with child-resistant closures.

Bottles of 100 capsules..... NDC 64365-502-01

Store at 2°-25°C (36°-77°F). Avoid exposing to high temperatures and humidity after the bottle is opened. Protect from light.

Manufactured for: Ligand Pharmaceuticals Incorporated
San Diego, CA 92121

by: R.P. Scherer
St. Petersburg, FL 33716

Ligand Part # (Rev. 1299)
R.P. Scherer Part # (Rev. 1299)