

DRUG NAME: Bexarotene**SYNONYM(S):****COMMON TRADE NAME(S):** TARGRETIN®**CLASSIFICATION:** miscellaneous, cytotoxic¹*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Bexarotene is part of a retinoid subclass selective for retinoid X receptors (RXRs). Activated RXRs function as transcription factors that regulate the expression of genes controlling cellular differentiation and proliferation.² As a retinoid, bexarotene is related to vitamin A and therapeutic agents tretinoin and acitretin. *In vitro*, bexarotene causes apoptosis of lymphoma cells by decreasing the protein levels of receptors RXR-alpha and RAR-alpha and anti-apoptotic protein (survivin), activating caspase-3, and cleaving poly (ADP-Ribose) polymerase (PARP).³

PHARMACOKINETICS:

Oral Absorption	time to peak plasma concentration = 2h; AUC and maximum concentration 48% higher after a fat-containing meal	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	>99%
Metabolism	four metabolites identified; cytochrome P450 3A4 is the major enzyme responsible for formation of oxidative metabolites; further metabolized by glucuronidation ⁴	
	active metabolite(s)	yes, but degree of relative activity unknown
	inactive metabolite(s)	yes
Excretion	primarily hepatobiliary	
	urine	<1%
	feces ⁴	primarily
	terminal half life	7h
	clearance	no information found
Sex	no significant difference	
Elderly	no significant difference in maximum concentration and AUC	

Adapted from standard reference² unless specified otherwise.**USES:****Primary uses:**

*Lymphoma, cutaneous T-cell

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:**Caution:**

- Vitamin A intake should be limited to $\leq 15,000$ IU/day to avoid the typical toxicities of dry skin, irritation, arthralgias, myalgias, abdominal pain, and hepatic changes.²
- In patients with a known hypersensitivity to retinoids, although clinical instances of cross-reactivity have not been reported²
- Due to photosensitization, minimize exposure to sunlight and artificial ultraviolet light.²
- Patients with 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 bexarotene.²

Laboratory Investigations^{2,5}:

- Baseline liver function tests should be obtained and monitored after 1, 2, and 4 weeks of treatment, and if stable, at least every eight weeks thereafter.
- Baseline thyroid function tests should be obtained and monitored during treatment.
- Baseline fasting blood lipid levels should be obtained. Fasting triglycerides should be normal or normalized with appropriate intervention prior to initiating therapy.
- Monitor for possible hypoglycemia in patients using insulin, agents enhancing insulin secretion, or insulin sensitizers.

Carcinogenicity: Long-term studies have not been conducted.²

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.² Not clastogenic in mammalian *in vivo* chromosome tests.²

Fertility: No formal fertility tests conducted.² Testicular degeneration occurred in one animal study.²

Pregnancy^{2,4}: FDA Pregnancy Category X. Studies with retinoids in animals or humans have shown fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant.

The following measures should be taken in **women**:

- Effective contraception must be used for one month prior to starting treatment, during therapy, and for at least one month following discontinuation of therapy. Two methods should be used simultaneously unless abstinence is the chosen method.²
- Avoid drugs that may interact with oral contraceptives.
- In women of child-bearing potential, a pregnancy test should be performed within the week prior to starting treatment and repeated monthly while on therapy.²
- Bexarotene therapy should be initiated on the second or third day of a normal menstrual period.²

Men with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must use condoms during sexual intercourse while on therapy and for at least one month after the last dose.²

Breastfeeding is not recommended due to the potential secretion into breast milk.^{2,5}

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.⁶

Most side effects are considered to be dose-dependent. Many of those listed with incidence <10% came from pooled data that included patients on doses >300 mg/m²/day i.e., above the usual recommended dose.

Table refers to oral dosing. For information regarding topical use, see paragraph following *Side Effects* table.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
allergy/immunology	allergic reaction
blood/bone marrow/ febrile neutropenia	<i>anemia</i> (6%)
	eosinophilia (<10%)
	<i>leukopenia</i> (17%, severe 4%); typical onset 4-8 weeks
	lymphocytosis (<10%)
	neutropenia (severe 16%)
	thrombocythemia (<10%)
	thrombocytopenia (<10%)
cardiovascular (arrhythmia)	syncope (<10%)
	tachycardia (10%)
cardiovascular (general)	angina pectoris (<10%)
	hypertension (<10%)
	right heart failure (<10%)
coagulation	coagulation time increased (<10%)
constitutional symptoms	chills (10%)
	fatigue/lethargy
	fever (5%)
	weight decreased (<10%)
	weight increased (<10%)
dermatology/skin	acne (<10%)
	alopecia (4%)
	<i>dry skin</i> (11%)
	exfoliative dermatitis (10%, severe 1%)
	pruritis
	rash, macular papular, pustular, unspecified, vesicular bullous (17%, severe 4%)
	serous drainage (<10%)
	skin nodule (<10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	skin ulcer (<10%)
endocrine	hypothyroidism (29%, severe 2%); see paragraph following Side Effects table
gastrointestinal	<i>emetogenic potential: rare⁷</i>
	anorexia (2%, Grade I and II only)
	cheilitis (<10%)
	colitis (<10%)
	constipation (<10%)
	diarrhea (7%, severe 2%)
	dry mouth (<10%)
	dyspepsia (<10%)
	flatulence (<10%)
	gastroenteritis (<10%)
	gingivitis (<10%)
	melena (<10%)
	nausea (16%)
	vomiting (4%, Grade I and II only)
hemorrhage	hemorrhage, not otherwise specified (<10%)
hepatobiliary/pancreas	pancreatitis (severe 1%)
infection	cellulitis (<10%)
	infection (1%, severe 1%)
	monilia (<10%)
	otitis externa (<10%)
	pneumonia (Grade I and II only)
	sepsis (<10%)
	urinary tract infection (<10%)
lymphatics	peripheral edema (13%, severe 4%)
metabolic/laboratory	ALT elevation (2%, Grade I and II only)
	amylase elevation (<10%)
	AST elevation (5%, Grade I and II only)
	bilirubinemia (severe 1%)
	creatinine elevation (<10%)
	hyperglycemia (<10%)
	hypoproteinemia (<10%)
	lipid abnormalities: hypercholesterolemia (32%, severe 25%), hyperlipemia (79%, severe 26%), hypertriglyceridemia (severe 28%); see paragraph following Side Effects table
	LDH elevation (7%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
musculoskeletal	arthralgia (<10%)
	arthrosis (<10%)
	asthenia (20%, severe 1%)
	ataxia (<10%)
	muscle spasm
	myalgia (<10%)
neurology	agitation (<10%)
	cerebrovascular accident (<10%)
	confusion (<10%)
	depression (<10%)
	dizziness (<10%)
	hyperesthesia (<10%)
	hypoesthesia (<10%)
	insomnia (5%)
	myasthenia (<10%)
neuropathy (<10%)	
ocular/visual	blepharitis (<10%)
	cataracts (19%); new or worsening of previous
	conjunctivitis (<10%)
	corneal lesion (<10%)
	dry eyes (<10%)
	keratitis (<10%)
	visual field defect (<10%)
pain	abdominal pain (11%)
	back pain (2%)
	bone pain (<10%)
	breast pain (<10%)
	chest pain (<10%)
	ear pain (<10%)
	headache (30%, severe 4%)
pulmonary	bronchitis (<10%)
	cough (<10%)
	dyspnea (<10%)
	hemoptysis (<10%)
	hypoxia (<10%)
	pharyngitis (<10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	pleural effusion (<10%)
	pulmonary edema (<10%)
	rhinitis (<10%)
renal/genitourinary	albuminuria (<10%)
	dysuria (<10%)
	hematuria (<10%)
	kidney function abnormality (<10%)
	urinary incontinence (<10%)
	urinary urgency (<10%)
syndromes	flu syndrome (4%)

Adapted from standard reference² unless specified otherwise.

Hypothyroidism^{8,9}: Although the incidence is significant, patients may not be overtly hypothyroid and signs and symptoms can be subtle. Monitoring of free thyroxine levels over time may be useful. Supplementation should continue until three months after bexarotene therapy has been completed.

Lipid abnormalities^{2,5} including elevations in fasting triglycerides (TG) and cholesterol and decreases in HDL-cholesterol occur in most patients. Fasting blood lipid levels should be done before therapy is initiated, weekly until lipid response is established (usually within 2-4 weeks), and then every eight weeks.² TG level should be maintained below 4.5 mmol/L using antilipemic therapy and if necessary, bexarotene dose should be reduced or interrupted.² The effects on triglycerides, HDL cholesterol, and total cholesterol are reversible with cessation of therapy. The following dosage guidelines have been used⁸:

Fasting triglycerides (mmol/L)	Dose
<3.5	100%
3.5 – 4.4	200 mg/m ² /day
≥4.5	suspend treatment until TG controlled

Topical use: Plasma concentrations generally were low or undetectable following single or multiple daily topical applications.¹⁰ Most commonly observed side effects include: rash, pruritis, skin disorders (e.g., inflammation, excoriation, sticky or tacky skin sensation), pain, and contact dermatitis.¹⁰ To minimize the risk of systemic exposure patients should be instructed to wash their hands after application of bexarotene and to avoid nail biting or finger licking.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
atorvastatin ²	no significant effect on bexarotene pharmacokinetics		concomitant administration appears to be possible
gemfibrozil ^{2,4}	substantial increase in plasma concentration of bexarotene	at least partially related to CYP 3A4 inhibition	concomitant administration not recommended
grapefruit juice ^{2,4}	may increase plasma concentration of bexarotene	may inhibit CYP 3A4 metabolism of bexarotene in the intestinal wall	avoid grapefruit and grapefruit juice

AGENT	EFFECT	MECHANISM	MANAGEMENT
tamoxifen ^{2,4,11}	35% decrease in tamoxifen plasma concentrations	unknown; likely due to induction of CYP 3A4 by bexarotene	clinical significance unclear; consider alternate agent(s)
vitamin A ²	may increase bexarotene toxicity	additive	avoid concurrent therapy; limit vitamin A intake to <15,000 IU/day

See **Pregnancy** under **Special Precautions** section regarding drugs that can interact with contraception.

Inhibitors of CYP 3A4 may cause an increase in plasma bexarotene concentrations.²

Inducers of CYP 3A4 may cause a reduction in plasma bexarotene concentrations.²

Bexarotene may induce CYP 3A4 resulting in increased substrate metabolism and reduction in substrate plasma concentrations (including oral or other systemic hormonal contraceptives).²

Topical: Avoid concomitant use of diethyltoluamide (DEET) with topical bexarotene as increased DEET toxicity was observed in animals.¹⁰

SUPPLY AND STORAGE:

Oral²: Eisai Inc. supplies bexarotene as 75 mg capsules. Store at room temperature or refrigerate. Protect from light.

Topical¹²: Eisai Inc. supplies bexarotene as a 1% gel. Store at room temperature. Protect from light.

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in **bold, italics**

Oral²: ***300 mg/m²*** (range 100-400 mg/m²) ***PO once daily.***
Round dose to the nearest 75 mg.
Administer with food.

Topical^{5,12}: Apply to affected area(s) four times daily (range once every other day to four times daily).
Start with one application every other day, and increase at weekly intervals i.e., to once daily, twice daily, three times daily, then finally four times daily, according to tolerance.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

<i>Dosage in renal failure:</i>	no formal studies have been conducted ² ; although urinary elimination is minor (<1%), renal insufficiency may result in protein binding changes leading to altered pharmacokinetics ²
<i>Dosage in hepatic failure:</i>	not studied; hepatic impairment would be expected to lead to greatly decreased clearance ² ; use with caution ² ; consider discontinuation if AST, ALT, or bilirubin values reach greater than three times the upper limit of normal ²
<i>Dosage in dialysis:</i>	no information found

Children:

Oral & Topical: safety and effectiveness not established²

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