DRUG NAME: Alitretinoin

SYNONYM(S): 9-*cis* retinoic acid[1]

COMMON TRADE NAME(S): TOCTINO®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Alitretinoin is a naturally occurring endogenous retinoid. It is a highly lipophilic derivative of vitamin A. Unlike other retinoids which are specific agonists of either retinoic acid receptor (RAR) or retinoid X receptor (RAX), alitretinoin uniquely binds to both receptor families. Activated retinoid receptors modulate gene transcription in cellular pathways involved in immune regulation, cell proliferation, and differentiation. The exact mechanism of action for alitretinoin is not known; however, alitretinoin is known to suppress the production of chemokines that are involved in the recruitment of leukocytes to sites of skin inflammation, reduce expansion of T-lymphocytes and antigen-presenting cells, and inhibit the effect on cell differentiation.[1-3]

PHARMACOKINETICS:

Oral Absorption	low and variable bioavailability; food significantly enhances systemic exposure and decreases variability in exposure	
Distribution	highly protein bound	
	cross blood brain barrier?	no information found
	volume of distribution	> 14 L
	plasma protein binding	99.1%
Metabolism	metabolized by CYP 2C9, CYP 2C8, and CYP 3A4	
	active metabolite(s)	(major) 4-oxo-alitretinoin; (minor) tretinoin, isotretinoin, 4-oxo-tretinoin, 4-oxo-isotretinoin
	inactive metabolite(s)	no information found
Excretion	mainly eliminated in urine as metabolites	
	urine	63% (<1% as unchanged parent drug)
	feces	30% (1% as unchanged parent drug)
	terminal half life	9 h (alitretinoin); 10 h (4-oxo-alitretinoin)
	clearance	no information found
Sex	no clinically significant difference	
Elderly	no clinically significant difference	

Adapted from standard reference[1,2] unless specified otherwise.

USES:

Primary uses:

Lymphoma, cutaneous T-cell[3,4]

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- pregnant or breastfeeding women[2]
- females of childbearing potential (FCBP), unless they can comply with the criteria of the TOCTINO® Pregnancy Prevention Program[2]
- history of hypersensitivity reaction to alitretinoin, other retinoids, allergy to peanut or soya, or hereditary fructose intolerace[2]
- hypervitaminosis A[2]

Caution:
- patients ***should not donate blood*** while taking alitretinoin and for one month after treatment has ended[2]
- ***changes in thyroid function tests*** have been reported, most often as a reversible reduction in thyroid stimulating hormone (TSH) levels and T4 (free thyroxine); alitretinoin is not recommended in patients with uncontrolled hypothyroidism[2]
- patients at high risk for ***cardiac events*** or those with an increased tendency to develop ***hypertriglyceridemia*** should be monitored for hypercholesterolemia and hypertriglyceridemia[2]
- ***decreased night vision*** has been reported; ability to drive or operate machinery at night may be compromised[2]
- ***concomitant medications*** that may reduce effectiveness of hormonal contraceptives should be avoided; effective contraception is imperative in females of child bearing potential (FCBP)[2]
- patients with a ***history of depression*** may be at increased risk for psychiatric adverse events[2]

Special populations:
- ***females of childbearing potential (FCBP)***, may be treated with alitretinoin provided they comply with the conditions of the TOCTINO® Pregnancy Prevention Program for at least one month before starting treatment, continually during treatment, and for at least one month after discontinuation of treatment[2]
- ***elderly patients*** are more likely to experience elevated triglyceride levels after 12 to 16 weeks of treatment[2]

Carcinogenicity: In animal studies, alitretinoin was found to be non-carcinogenic at doses expected during human clinical exposure.[2]

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

Fertility: In animal studies, reversible effects on the male reproduction organs, disturbed spermatogenesis, and associated degenerative lesions of the testes were observed at doses higher than those seen following human clinical exposure. Testicular toxicity is a known effect of retinoids and may be related to altered endogenous retinoid homeostasis.[2]

Pregnancy: Alitretinoin is a potent teratogen and is associated with an increased risk of spontaneous abortion. In animal studies, fetal malformations observed include facial dysmorphia, cleft palate, and abnormalities in the central nervous system, external ear, eye, cardiovascular system, thymus gland, and parathyroid gland. In male patients, small amounts of alitretinoin have been detected in semen but drug accumulation is not expected; these amounts are expected to have a negligible effect on the endogenous plasma levels of a female partner or fetus.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Alitretinoin is highly lipophilic, therefore the passage into human milk is considered highly likely.[2]

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

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clinically important[5,6]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	eosinophilia (1-5%)
	monocytopenia (16-22%)
	neutropenia (1-5%)
	reticulocytopenia (1-5%)
ear and labyrinth	tinnitus
endocrine	diabetes mellitus; class effect of retinoids
eye see paragraph following **Side Effects** table	abnormal eye sensation, eye irritation (<2%)
	blurred vision (<1%)
	cataract (<1%)
	conjunctivitis (1-2%)
	decreased night vision
	dry eye (2-3%)
gastrointestinal	*emetogenic potential:* minimal (rare)[7]
	cheilitis/cheilosis (1-6%)
	diarrhea (1%)
	dry lip (4-6%)
	dry mouth (3%)
	dyspepsia (<2%)
	inflammatory bowel disease; see paragraph following **Side Effects** table
	nausea (2-3%)
	pancreatitis
	vomiting (<2%)
	upper abdominal pain (1%)
general disorders and administration site conditions	fatigue (2%)
	peripheral edema
immune system	anaphylactic reaction, hypersensitivity
infections and infestations	folliculitis (<1%)
	herpes simplex (1%)
	influenza (1-2%)
	nasopharyngitis (5-6%)
	pharyngitis (1%)
	rhinitis (<1%)
	upper respiratory tract infection (1-2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
investigations	blood creatine phosphokinase increase (2-3%)
	blood triglyceride increase (5-35%); see paragraph following **Side Effects** table
	cholesterol increase (5-10%)
	HDL decrease (5-10%)
	LDL increase (>10%)
	T4 decrease (3-10%)
	serum iron decrease (1-5%)
	total iron binding capacity decrease (1-5%)
	transaminase increase; dose reduction may be required
	TSH decrease (6-8%)
	weight increase (1%)
musculoskeletal and connective tissue	ankylosing spondylitis (<1%)
	arthralgia (1-2%)
	back pain (1-2%)
	exostosis (<1%)
	myalgia (1%)
	pain in extremity (<2%)
nervous system	***benign intracranial hypertension*** (<1%); see paragraph following **Side Effects** table
	dizziness (1-2%)
	headache (11-22%)
psychiatric see paragraph following **Side Effects** table	depression (2-3%)
	insomnia (1%)
	sleep disorder (<1%)
respiratory, thoracic and mediastinal	epistaxis (<1%)
	pharyngolaryngeal pain (1%)
skin and subcutaneous tissue	alopecia (2%)
	asteatotic eczema (<1%)
	cheilosis (4-6%)
	dermatitis (1-2%)
	dry skin (3%)
	eczema (4%)
	erythema (2-7%)
	hair texture changes; mostly hair curling
	nail disorder

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pruritus (1%)
	rash (1%)
	photosensitivity reaction; see paragraph following **Side Effects** table
	skin exfoliation (<1%)
vascular	flushing (2-6%)
	hot flush (<2%)
	hypertension (1-2%)
	vasculitis (<1%)

Adapted from standard reference[1,2] unless specified otherwise.

Benign intracranial hypertension has been reported with alitretinoin, and in some cases, has involved concurrent use of tetracyclines. Monitor patients for symptoms of benign intracranial hypertension, which can include headache, nausea and vomiting, visual disturbances, and papilloedema and immediately discontinue alitretinoin if symptoms develop.[2]

Hypertriglyceridemia has been reported in up to 35% of patients. Triglyceride levels greater than 9 mmol/L (800 mg/dL) can be associated with pancreatitis, which may be fatal. Consider more frequent monitoring of serum cholesterol and triglycerides in patients with cardiovascular risk factors or who have an increased risk of developing hypertriglyceridemia (e.g., diabetes mellitus, obesity, increased alcohol intake, familial history of hypertriglyceridemia or lipid metabolism disorders). Alitretinoin should be permanently discontinued if hypertriglyceridemia cannot be controlled or if symptoms of pancreatitis occur.[2]

Inflammatory bowel disease (IBD), including regional ileitis, has been rarely reported, but has occurred in patients without history of intestinal disorders. Treatment discontinuation is recommended if patients experience abdominal pain, rectal bleeding, or severe diarrhea.[2]

Ophthalmologic adverse effects may include dry eyes, corneal opacities, keratitis, conjunctivitis, and decreased night vision. Dry eyes can be relieved with the application of a lubricating eye ointment or tear replacement therapy. Intolerance to contact lenses may occur. Decreased night vision may affect ability to drive or operate machinery. Dry eye and decreased night vision usually resolve after discontinuation of treatment. Ophthalmology consult may be required. Dose interruption or discontinuation may be required to manage symptoms.[2]

Psychiatric adverse events may include depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms. In rare instances, suicidal ideation, suicide attempts, and suicide have been reported. Patients with a history of depression may be at increased risk of psychiatric adverse events. Treatment interruption is recommended for development of depression, mood disturbance, psychosis, or aggression. Psychiatric referral may be required.[2]

Retinoid therapy may enhance the effects of ***UV light*** on the skin. To prevent ***photosensitivity reactions***, excessive exposure to sunlight and the use of sun lamps should be avoided. When necessary, advise patients to apply sun-protection products with at least SPF 15. Dry skin or dry lips can be relieved with skin moisturizing ointment/creams and lip balm.[2]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[2]	~50% increase in C_{max} and AUC of alitretinoin and ~13% increase in C_{max} and AUC of 4-oxo-alitretinoin	strong inhibition of CYP 3A4 by ketoconazole	consider dose reduction of alitretinoin to 10 mg PO once daily
methotrexate[1,2]	increased risk of liver toxicity	alitretinoin may enhance the hepatotoxic effect of methotrexate	avoid concurrent use; if concurrent use cannot be avoided, monitor for liver toxicity
tetracyclines[2]	may increase intracranial pressure (resulting in benign intracranial hypertension)	additive toxicity with concurrent use of retinoids and tetracyclines	avoid concurrent use
vitamin A[2]	increased risk of developing hypervitaminosis A	additive toxicity with concurrent use of retinoids and vitamin A	avoid concurrent use
microdosed progesterone preparations (e.g., progestin-only contraceptive, "minipill")[1,2]	decreased contraceptive effectiveness of progesterone preparations	retinoic acid derivatives may decrease the serum concentration of the concurrent progestin	avoid concurrent use

Alitretinoin is a substrate of **CYP 2C9**, **CYP 2C8**, and **CYP 3A4**. Strong ***inhibitors*** of these enzymes may increase the plasma concentrations of alitretinoin. Avoid concurrent use with *strong* CYP 2C9, CYP 2C8, and CYP 3A4 *inhibitors*. If coadministration cannot be avoided, consider a dose reduction of alitretinoin to 10 mg PO daily.[2]

Alitretinoin is a weak **inhibitor** of **CYP 2C8** *in vitro* and may increase the plasma concentrations of CYP 2C8 substrates. Monitor for adverse events related to CYP 2C8 substrate if coadministration cannot be avoided.[2]

SUPPLY AND STORAGE:

Oral: GlaxoSmithKline Inc. supplies alitretinoin as 10 mg and 30 mg soft capsules. Store at room temperature. Keep in original outer carton to protect from light. Capsules contain soybean oil and partially hydrogenated soybean oil.[2]

Additional information:

- alitretinoin is available in cartons of 3 blister strips with 10 capsules each for a 30 day supply[2]
- capsules contain sorbitol; patients with hereditary fructose intolerance may experience symptoms of intolerance[2]
- capsules are specially designed to ensure specific absorption characteristics; therefore, opening, crushing, dividing or grinding capsules may alter the pharmacokinetics of alitretinoin[8]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

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Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:[2,9]	***30 mg*** (range 10-30 mg) ***PO once daily*** Administer with food (preferably with a main meal) Swallow whole; do not crush or chew
Concurrent radiation:	no information found
Dosage in renal failure:	mild/moderate impairment: no information found severe impairment: not recommended[2]
Dosage in hepatic failure:	not recommended[2]
Dosage in dialysis:	no information found

Children: not recommended for use in patients under 18 years of age[2]

REFERENCES:

1. AHFS Drug Information® - Lexicomp Online (database on the Internet). Alitretinoin. Wolters Kluwer Clinical Drug Information Inc., 2021. Available at: http://online.lexi.com. Accessed 31 August, 2021
2. GlaxoSmithKline Inc. TOCTINO® product monograph. Mississauga, Ontario; 23 June 2019
3. Alhusayen R, Vu TT, Almuhanna N, et al. Evaluation of alitretinoin for treatment of mycosis fungoides and sezary syndrome. Dermatoloy 2021(237):479-485
4. Kasper C, Herzinger T, Ruzicka T, et al. Treatment of cutaneous T-cell lymphoma with oral alitretinoin. JEADV 2015;29:783-788
5. Cheng, Winnie. Pharmacist, BC Cancer. Personal Communication. October 7,2021
6. Ho, Vincent. Dermatologic Oncologist, BC Cancer. Personal Communication. October 7,2021
7. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
8. Lucia Molina. GlaxoSmithKline Inc. Medical Information. September 27,2021
9. BC Cancer Lymphoma Tumour Group. (LYALIT) BC Cancer Protocol Summary for Treatment of Cutaneous T-Cell Lymphoma (Mycosis Fungoides/Sezary Syndrome) with Alitretinoin. Vancouver, British Columbia: BC Cancer; November 1, 2021

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