

DRUG NAME: TRETINOIN**SYNONYM(S):** All-trans retinoic acid, ATRA**COMMON TRADE NAME(S):** VESANOID® (notice of compliance,¹ December 1994)**CLASSIFICATION:** Differentiation inducing agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Tretinoin is a natural metabolite of retinol and belongs to a class of retinoids, which are structurally related to vitamin A and involved in regulation of various biological processes.² It induces terminal differentiation in several hemopoietic precursor cell lines and in cells from patients with acute promyelocytic leukemia (APL). The exact mechanism of action is not known, but tretinoin induces maturation of leukemic cells and appearance of normal hemopoietic cells.^{2,3} Tretinoin induces remissions in 64-100% of APL patients, with time to remission usually between 8 and 119 days of therapy.² Acquired resistance during therapy is common and the proposed mechanisms include reduced GI absorption, increased enzymatic metabolism and induction of cellular binding proteins which facilitate tretinoin transport to the metabolizing enzymes.^{4,5}

PHARMACOKINETICS:

Interpatient variability	considerable interpatient and inpatient variability in AUC; moderate variability in the time to peak plasma concentration after oral administration ⁵	
Oral Absorption	Well absorbed with 50% bioavailability. ⁴ Absorption is affected by biliary pH and fatty composition. ⁵ Effect of food on tretinoin absorption is unclear but increases bioavailability of retinoids as a class. Hence, tretinoin should be administered with food.	
	time to peak plasma concentration ⁶	1-2 h
Distribution	Rapidly and extensively distributed into tissues with high levels in liver, kidney, intestine; intermediate levels in serum, adrenal glands; low levels in testes, fat pads. ^{4,5}	
	cross blood brain barrier?	not detected in CSF ^{2,4}
	volume of distribution	no information found
	plasma protein binding	> 95%
Metabolism	Primarily by hepatic cytochrome P450. ⁴ Tretinoin may induce its own metabolism, with lower plasma level and AUC after 2-6 weeks of continuous treatment. ^{3,6}	
	active metabolite(s)	several ⁴
	inactive metabolite(s)	many ⁴
Excretion	fecal and renal excretion	
	urine ⁶	63% within 72 h
	feces ⁶	31% within 6 days
	terminal half life	0.7 h (range 0.5-2 h)
	clearance	no information found
Gender	no information found	
Elderly	no information found	
Children	time to peak plasma concentration 1-4 h	
Ethnicity	similar peak and time to peak plasma concentration in Japanese and European patients ⁷	

Adapted from reference³ unless specified otherwise.

USES:**Primary uses:***Leukemia, acute promyelocytic⁸⁻¹¹**Other uses:**Kaposi's sarcoma, AIDS-related^{12,13}
Myelodysplastic syndrome¹⁴

*Health Canada Therapeutic Products Programme approved indication

SPECIAL PRECAUTIONS:**Contraindicated** in patients with a history of hypersensitivity reaction to tretinoin or related compounds (eg, acitretin, isotretinoin, vitamin A)⁶ and in patients taking tetracyclines, low-dose progestogens and vitamin A.³**Carcinogenicity:** Short-term animal studies showed increased hepatic adenomas and carcinomas.⁶**Mutagenicity:** Not mutagenic in Ames test and mammalian *in vitro* mutation tests. Although it is clastogenic in some mammalian *in vitro* chromosome tests, tretinoin is not clastogenic in other mammalian *in vitro* and *in vivo* chromosome tests.⁶**Fertility:** Animal studies showed increased fetal resorption, testicular degeneration and increased numbers of immature spermatozoa.⁶**Pregnancy:** FDA Pregnancy Category D.⁶ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Tretinoin is highly teratogenic when taken during early pregnancy irrespective of treatment dose or duration and the following measures should be taken^{3,6}:

- Inform patient of the risks and hazards of pregnancy during and within one month after therapy is stopped.
- Perform pregnancy tests within one week before treatment is started. If possible, delay treatment until test results are available. If treatment cannot be delayed, use two forms of contraception. Additional monthly pregnancy testing is recommended during therapy.
- Use two reliable forms of contraception simultaneously during and for one month after therapy is stopped. Use contraception even after menopause unless the patient has had hysterectomy.

Breastfeeding is not recommended due to the potential secretion into breast milk.^{3,6}**SIDE EFFECTS:**

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in bold, italics I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
auditory/hearing	ototoxicity (19-25%) ^{12,13}		E		
blood/bone marrow febrile neutropenia	basophilia (severe, rare) ^{15,16}		E		
	hyperleukocytosis (75%)	I	E		
cardiovascular (general)	pericarditis (6%) ⁹		E	D	
	edema (> 25%)		E		
coagulation	thrombosis/embolism (8%) ⁹		E	D	
constitutional symptoms	fatigue (> 25%)		E		
	fever (> 25%)	I	E		

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in <i>bold, italics</i> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
	shivering (> 25%)	I	E		
	weight gain (32%) ⁹		E		
dermatology/skin	cheilitis (24-65%) ²		E		
	mucosal and skin dryness (24-65%) ²		E		
	photosensitivity (rare)	I	E		
	pruritus/rash (24-65%) ²		E		
gastrointestinal	<i>emetogenic potential: rare</i> ¹⁷				
	gastritis (rare) ²		E		
	nausea/vomiting (51%) ⁹	I	E		
hemorrhage	dermal bleeding (> 25%)		E		
hepatic	elevated bilirubin (16%) ⁹		E		
	elevated hepatic enzymes (> 25%)		E		
lymphatics	cervical/tonsillar lymphadenopathy (10%) ⁹		E		
metabolic/laboratory	hypercalcemia (rare) ^{2,18}		E		
	hypercholesterolemia (> 25%)		E		
	hyperhistaminemia (rare)		E		
	hyperlipidemia (rare) ²		E		
	hypertriglyceridemia (> 25%)		E		
ocular/visual	visual disturbance, photophobia, conjunctivitis (rare)		E		
pain	abdominal pain (> 25%)		E		
	arthralgia (20-30%) ²		E		
	back pain (> 25%)		E		
	bone pain (20-30%) ²		E		
	chest pain (> 25%)		E		
	headache (29-90%) ²	I	E		
pulmonary	coughing (> 25%)		E		
	dyspnea (> 25%)		E		
	nasal congestion (24-65%) ²		E		
renal/genitourinary	increased serum creatinine (20-56%) ²		E		
sexual/reproductive function	penile or scrotal ulceration (rare) ^{2,19}		E		
syndromes	pseudotumor cerebri (rare) ^{20,21}	I	E		
	retinoic acid syndrome (25%) ^{2,5}	I	E		
	Sweet's syndrome (rare) ^{22,23}		E	D	

Adapted from reference 3 unless specified otherwise.

Headache occurring several hours after tretinoin ingestion is the most common side effect.²⁴ It differs from that associated with pseudotumor cerebri in that it is often transient, mild in intensity and well controlled with mild analgesics.²⁰ Patients usually develop a tolerance with continued tretinoin therapy.²⁴

Basophilia/Hyperhistaminemia: Basophilia-associated hyperhistaminemia has been rarely reported. The severity of symptoms depends on the level of plasma histamine.¹⁵ Severe symptoms include tachycardia, shock due to vasodilatation, and gastric and duodenal ulceration.¹⁶ Prophylactic H₂- or H₁-antagonist has been used to prevent symptoms mediated via H₂- and H₁-receptors.¹⁵

Pseudotumor cerebri: Also known as benign or idiopathic intracranial hypertension. It is characterized by signs and symptoms of intracranial hypertension without evidence of infective or space occupying lesions.²⁰ Symptoms include severe headache which may be aggravated by analgesic or narcotic overuse,²⁰ nausea and vomiting, papilledema, retinal hemorrhages, visual changes (eg, intermittent visual loss), ophthalmoplegia.⁵ The onset of symptoms is about 3-17 days of tretinoin therapy.^{21,25} Pseudotumor cerebri is more common in children than in adults and may be due to their increased sensitivity to the CNS effects of tretinoin.² The cause and appropriate management of pseudotumor cerebri have not been established. Narcotic analgesics (eg, codeine, morphine) or temporary discontinuation of tretinoin in non-responding cases may help reduce severe headache, nausea and vomiting. Diuretics (acetazolamide, furosemide) or lumbar puncture may reduce CSF pressure to maintain a final pressure not greater than 15 mm of water.^{20,25}

Retinoic acid syndrome is characterized by some or all of the following symptoms: fever, dyspnea, hypotension, bone pain, respiratory distress, pulmonary infiltrates, hyperleukocytosis, pleural or pericardial effusion, weight gain, lower extremity edema, congestive heart failure, renal failure and multi-organ failure.^{3,5,26} The earliest manifestations of the syndrome are dyspnea, rales, fever and/or unexplained weight gain.⁵ Although the syndrome may occur without concomitant hyperleukocytosis, the risk may be increased if rapidly evolving hyperleukocytosis occurs during tretinoin therapy.^{6,26} The onset of symptoms is about 7-12 days of tretinoin therapy.²⁶ Potential causes of the syndrome include release of vasoactive cytokines, increased adhesion molecules on myeloid cell surfaces, and acquisition of migratory properties by leukemic cells.^{24,26} Due to the severity and poor prognosis of the syndrome once the full-blown signs have been developed, prophylaxis or early treatment are mandatory^{3,26}:

- For patients with WBC > 5 x 10⁹/L at diagnosis of APL or any time during tretinoin therapy, use combination of tretinoin and anthracycline-based chemotherapy.
- For patients with WBC < 5 x 10⁹/L on day 0 of tretinoin therapy and if WBC becomes ≥ 6 x 10⁹/L on day 1-6, ≥ 10 x 10⁹/L on day 7-10, or ≥ 15 x 10⁹/L on day 11-28 of tretinoin therapy, add full-dose anthracycline-based chemotherapy to tretinoin therapy.
- For patients with early signs of the syndrome any time during tretinoin therapy, start dexamethasone IV 10 mg every 12 hours for at least 3 days until symptom resolution.

Sweet's syndrome is a hyperinflammatory reaction of neutrophil infiltration of the skin and internal organs. Symptoms include fever, painful erythematous cutaneous plaques involving the extremities and the trunk, and prominent musculoskeletal involvement (eg, myositis, fasciitis).^{22,27} The onset of symptoms is about 7-34 days of tretinoin therapy. The cause of the syndrome is unknown and symptoms generally resolve within 48 hours of corticosteroid therapy.^{22,23}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole ^{3,4,28}	increased tretinoin AUC	inhibits tretinoin metabolism	avoid concurrent therapy outside clinical trials
progestogen (low dose) ³	decreased contraceptive efficacy of progestogens	unknown	avoid concurrent therapy
tetracyclines ³	may increase intracranial pressure	additive	avoid concurrent therapy
vitamin A ³	may increase tretinoin toxicity	additive	avoid concurrent therapy

Tretinoin is metabolized by cytochrome P450 (CYP) and CYP inducers (eg, glucocorticoids, phenobarbital, rifampin) or inhibitors (eg, cimetidine, cyclosporine, erythromycin, diltiazem, verapamil) may potentially affect its pharmacokinetics. However, there are no data to suggest that concurrent administration of these medications increases or decreases tretinoin efficacy or toxicity.³

SUPPLY AND STORAGE:

Capsules: 10 mg. Store at room temperature. Protect from light. Keep bottle tightly closed.³

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

	BCCA usual dose noted in <i>bold, italics</i>
<i>Oral:</i>	<i>45 mg/m²/day PO in 2 divided doses</i> Round dose to the nearest 10 mg. Administer with food. ³
<i>Duration of therapy:</i>	Treatment should be continued for 30 days after complete remission or for a maximum of 90 days, whichever occurs first. ⁶
<i>Dosage in renal failure:</i>	25 mg/m ² /day is recommended as a precautionary measure, as studies have not been done in patients with renal dysfunction ³
<i>Dosage in hepatic failure:</i>	25 mg/m ² /day is recommended as a precautionary measure, as studies have not been done in patients with hepatic dysfunction ³
<i>Dosage in dialysis:</i>	no information found

Children:

Oral: 45 mg/m²/day PO in 2 divided doses¹¹
Round dose to the nearest 10 mg.
Administer with food.³

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