

DRUG NAME: Tretinoin**SYNONYM(S):** All-trans retinoic acid, ATRA**COMMON TRADE NAME(S):** VESANOID®**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.¹ 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.^{1,2} Tretinoin induces remissions in 64-100% of APL patients, with time to remission usually between 8 and 119 days of therapy.¹ 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.^{3,4}

PHARMACOKINETICS:

Interpatient variability	considerable interpatient and inpatient variability in AUC; moderate variability in the time to peak plasma concentration after oral administration ⁴	
Oral Absorption	Well absorbed with 50% bioavailability. ³ Absorption is affected by biliary pH and fatty composition. ⁴ 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 ⁵	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. ^{3,4}	
	cross blood brain barrier?	not detected in CSF ^{1,3}
	volume of distribution	no information found
	plasma protein binding	> 95%
Metabolism	Primarily by hepatic cytochrome P450. ³ Tretinoin may induce its own metabolism, with lower plasma level and AUC after 2-6 weeks of continuous treatment. ^{2,5}	
	active metabolite(s)	several ³
	inactive metabolite(s)	many ³
Excretion	fecal and renal excretion	
	urine ⁵	63% within 72 h
	feces ⁵	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 ⁶	

Adapted from reference² unless specified otherwise.

USES:**Primary uses:**

*Leukemia, acute promyelocytic⁷⁻¹⁰

Other uses:

Kaposi's sarcoma, AIDS-related^{11,12}
Myelodysplastic syndrome¹³

*Health Canada Therapeutic Products Programme approved indication

SPECIAL PRECAUTIONS:**Contraindications:**

- history of hypersensitivity reaction to tretinoin or related compounds (e.g., acitretin, isotretinoin, vitamin A)⁵
- during pregnancy, as well as in nursing mothers¹⁴
- concurrent therapy with vitamin A; symptoms of hypervitaminosis A may be aggravated¹⁴

Caution:

- Ability to drive or operate machinery might be impaired in patients receiving tretinoin, particularly if they are experiencing dizziness or severe headache.¹⁴
- Tretinoin is highly teratogenic; women of childbearing potential who may become pregnant within one month of stopping tretinoin should not take tretinoin without effective birth control. Note: micro-dosed progesterone preparations (also known as "minipill") may be an inadequate method of contraception during treatment with tretinoin.¹⁴ See **Pregnancy** section and **Drug Interactions**.
- Concurrent use of tetracycline and other agents known to cause intracranial hypertension/pseudotumour cerebri should be avoided during tretinoin treatment¹⁴ See **Side Effects** and **Drug Interactions**.

Special populations: Children may experience increased toxicity with tretinoin, particularly pseudotumour cerebri.¹⁴

Carcinogenicity: Short-term animal studies showed increased hepatic adenomas and carcinomas.⁵

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.⁵

Fertility: Animal studies showed increased fetal resorption, testicular degeneration and increased numbers of immature spermatozoa.⁵

Pregnancy: FDA Pregnancy Category D.⁵ 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^{2,5}:

- Inform patient of the risks and hazards of pregnancy during and within one month after therapy is stopped.¹⁴
- A negative pregnancy test result must be obtained within two weeks before treatment is started. Monthly pregnancy testing is recommended during therapy. Therapy should not begin until the second or third day of the next normal menstrual period.¹⁴
- Use effective contraception at least one month prior to starting tretinoin, during therapy, and then continue at least one month after tretinoin is stopped.¹⁴

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is $\geq 5\%$ higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
auditory/hearing	ototoxicity (19-25%) ^{11,12}
blood/bone marrow febrile neutropenia	basophilia (severe, rare) ^{15,16} ; see paragraph following Side Effects table
	hyperleukocytosis (75%)
cardiovascular (general)	pericarditis (6%) ⁸
	edema (> 25%)
coagulation	thrombosis/embolism (8%) ⁸ ; see paragraph following Side Effects table
constitutional symptoms	fatigue (> 25%)
	fever (> 25%)
	shivering (> 25%)
	weight gain (32%) ⁸
dermatology/skin	cheilitis (24-65%) ¹
	mucosal and skin dryness (24-65%) ¹
	photosensitivity (rare)
	pruritus/rash (24-65%) ¹
gastrointestinal	<i>emetogenic potential: rare</i> ¹⁷
	gastritis (rare) ¹
	nausea/vomiting (51%) ⁸
hemorrhage	dermal bleeding (> 25%)
hepatic	elevated bilirubin (16%) ⁸
	elevated hepatic enzymes (> 25%)
lymphatics	cervical/tonsillar lymphadenopathy (10%) ⁸
metabolic/laboratory	hypercalcemia (rare) ^{1,18}
	hypercholesterolemia (> 25%)
	hyperhistaminemia (rare)
	hyperlipidemia (rare) ¹
	hypertriglyceridemia (> 25%)
ocular/visual	visual disturbance, photophobia, conjunctivitis (rare)
pain	abdominal pain (> 25%)
	arthralgia (20-30%) ¹
	back pain (> 25%)
	bone pain (20-30%) ¹
	chest pain (> 25%)
	headache (29-90%) ¹ ; see paragraph following Side Effects table
pulmonary	coughing (> 25%)
	dyspnea (> 25%)
	nasal congestion (24-65%) ¹
renal/genitourinary	increased serum creatinine (20-56%) ¹
sexual/reproductive function	penile or scrotal ulceration (rare) ^{1,19}
syndromes	hypervitaminosis A (25%) ¹⁴ ; see paragraph following Side Effects table
	pseudotumour cerebri (rare) ^{20,21} ; see paragraph following Side Effects table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	retinoic acid syndrome (25%) ^{1,4} ; see paragraph following Side Effects table ¹
	Sweet's syndrome (rare) ^{22,23} ; see paragraph following Side Effects table

Adapted from reference² unless specified otherwise.

Headache occurring several hours after tretinoin ingestion is the most common side effect.²⁴ It differs from that associated with pseudotumour 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-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

Signs and symptoms of **hypervitaminosis A syndrome** have been observed in about 25% of patients receiving recommended daily doses of tretinoin, including xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain. The concurrent use of vitamin A with tretinoin may aggravate the symptoms of hypervitaminosis A and should be avoided.¹⁴

Pseudotumour cerebri, also known as benign or idiopathic intracranial hypertension, 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.⁴ The onset of symptoms is about 3-17 days of tretinoin therapy.^{21,25} Pseudotumour cerebri is more common in children than in adults and may be due to their increased sensitivity to the CNS effects of tretinoin.¹ The cause and appropriate management of pseudotumour 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} [The concomitant use of other drugs known to cause intracranial hypertension/pseudotumour cerebri \(e.g., tetracyclines\) may increase risk of this condition; avoid if possible.](#)¹⁴

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.^{2,4,26} The earliest manifestations of the syndrome are dyspnea, rales, fever and/or unexplained weight gain.⁴ Although the syndrome may occur without concomitant hyperleukocytosis, the risk may be increased if rapidly evolving hyperleukocytosis occurs during tretinoin therapy.^{5,26} 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^{2,26}:

- 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.

Thrombosis (both venous and arterial) is a risk during the first month of treatment and may involve any organ system. Fatal thrombotic complications have been reported rarely in patients treated concurrently with tretinoin and antifibrinolytic agents such as tranexamic acid, aminocaproic acid, and aprotinin; caution is advised.¹⁴

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 ^{2,3,28}	increased tretinoin AUC	inhibits tretinoin metabolism	avoid concurrent therapy outside clinical trials
progestogen (low dose) ²	decreased contraceptive efficacy of progestogens	unknown	avoid concurrent therapy
tetracyclines ²	may increase intracranial pressure (resulting in intracranial hypertension/pseudotumour cerebri) ¹⁴	additive	avoid concurrent therapy
vitamin A ²	may increase tretinoin toxicity (symptoms of hypervitaminosis A may be aggravated) ¹⁴	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.²

SUPPLY AND STORAGE:

Oral: Xediton Pharmaceuticals Inc. (for CHEPLAPHARM Arzneimittel GmbH) supplies tretinoin as 10 mg capsules. Store at room temperature. Protect from light. Keep bottle tightly closed.¹⁴

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

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

Oral:

45 mg/m²/day PO in 2 divided doses

Round dose to the nearest 10 mg.

Administer with food.²

Duration of therapy:

Treatment should be continued for 30 days after complete remission or for a maximum of 90 days, whichever occurs first.⁵

Dosage in renal failure:

25 mg/m² /day is recommended as a precautionary measure, as studies have not been done in patients with renal dysfunction²

Dosage in hepatic failure:

25 mg/m² /day is recommended as a precautionary measure, as studies have not been done in patients with hepatic dysfunction²

Dosage in dialysis:

no information found

Children:

Oral: 45 mg/m²/day PO in 2 divided doses¹⁰
 Round dose to the nearest 10 mg.
 Administer with food.²

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