Drug Monograph

A - Drug Name

tretinoin (ATRA)

SYNONYM(S): ATRA; All-trans Retinoic Acid

COMMON TRADE NAME(S): Vesanoid®

back to top

B - Mechanism of Action and Pharmacokinetics

Tretinoin is an endogenous metabolite of retinol (vitamin A). It induces terminal differentiation and inhibits cell proliferation in transformed hemopoietic precursor cell lines, including human myeloid lines. Acute Promyelocytic Leukemia (APL) is associated with a specific translocation between chromosomes 15 and 17 (region of retinoic acid receptor - α). The translocation appears to inhibit differentiation and lead to carcinogenesis; tretinoin may overcome this when used in high doses. Tretinoin induces remissions in 64-100% of APL patients, with time to remission usually between 8 and 119 days of therapy (Gillis 1995). Acquired resistance during therapy is common especially with prolonged dosing (4-6 months) possibly due to induction of metabolism or increased expression of cellular retinoic acid binding proteins.

Absorption	Oral: well absorbed with 50% bioavailability. Absorption is affected by biliary pH and fatty composition. Effect of food on tretinoin absorption is unclear but increases bioavailability of retinoids as a class. Hence, tretinoin should be administered with food. Peak plasma concentrations are reached within 1-2 hours. Pharmacokinetics (AUC, peak plasma concentration) initially increase in a higher than dose proportional manner. Prolonged dosing leads to a significant decrease in AUC and plasma levels.
Distribution	Rapidly and extensively distributed into tissues

	Cross blood brain barrier?	No
	PPB	>95% (mainly to albumin)
Metabolism	Primarily by hepatic cytochrome P450 (e.g. CYP3A4, CYP2C8, CYP2E). Metabolites are glucuronidated and excreted in bile and urine. Tretinoin induces its own metabolism, with lower plasma level and AUC after 2-6 weeks of continuous treatment with an increase in urinary excretion of 4-oxo metabolites.	
	Active metabolites	Several, including 13-cis isomer
	Inactive metabolites	Many
Elimination	Feces	31% within 6 days
	Urine	63 % within 72 hours
	Half-life	0.7 hours (range 0.5 - 2 h)

back to top

C - Indications and Status

Health Canada Approvals:

- For the induction of remission in acute promyelocytic leukemia (either de novo or after relapse following cytotoxic chemotherapy). Consolidation chemotherapy should be given after complete remission.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Ear pain (23%)	E

	Hearing impaired (6%) (irreversible in <1%)	E
Cardiovascular	Arrhythmia (23%)	E
	Arterial thromboembolism (3%)	E
	Cardiotoxicity (6%)	E
	Flushing (23%)	I E
	Hypertension (11%)	E
	Hypotension (14%)	E
	Pericarditis (3%)	E D
	Tachycardia	E
	Venous thromboembolism	E
Dermatological	Alopecia (14%)	E
	Dry skin (77%) (including mucosal dryness)	E
	Erythema nodosum (rare)	
	Nail disorder	E D
	Other (Sweet's syndrome- rare)	E
	Photosensitivity (rare)	I E
	Rash (54%)	E
Gastrointestinal	Abdominal distension (11%)	E
	Abdominal pain (31%)	E
	Anorexia, weight loss (17%)	E
	Constipation (17%)	E
	Diarrhea (23%)	E
	Dyspepsia (14%)	E
	Mucositis (26%)	E
	Nausea, vomiting (57%)	I E
	Weight gain (23%)	E
General	Edema (52%)	E
	Fatigue (66%)	E
	Hypothermia (3%)	I E
	Other (25%) (retinoic acid syndrome)	I E
Hematological	Basophilia (severe-rare)	E
	Disseminated intravascular coagulation (26%)	E
	Hemorrhage (60%)	E

	Leukocytosis (75%) (hyperleukocytosis)	I E
	Thrombocytosis (rare)	E
Hepatobiliary	↑ LFTs (60%)	E
	Pancreatitis (rare)	E
Infection	Infection (58%)	E
Metabolic / Endocrine	Acidosis (3%)	E
	↑ Ca (rare)	E
	Hyperlipidemia (60%) (increased cholesterol and triglycerides)	E
	Hyperuricemia	E
Musculoskeletal	Musculoskeletal pain (77%)	E
	Myositis (rare)	E
Nervous System	Anxiety (17%)	E
	Confusion (11%)	E
	Depression (14%)	E D
	Dizziness (20%)	E
	Headache (86%)	I E
	Insomnia (14%)	E
	Other (9%) (pseudotumour cerebri)	E
	Paresthesia (17%)	E
Ophthalmic	Conjunctivitis (rare)	E
	Other (17%) (visual disturbance)	E
	Photophobia (rare)	E
Renal	Nephrotoxicity (11%)	E D
Respiratory	Bronchospasm	E
	Cough, dyspnea (60%)	E
	Lung infiltrate (6%)	E
	Pleural effusion (20%)	E
Vascular	Vasculitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Hypervitaminosis A syndrome is seen in at least 25% of patients, with rash, dry skin and mucosa, edema, nausea, vomiting, bone pain. **Headache** occurring several hours after tretinoin ingestion is the most common side effect. It differs from that associated with pseudotumour cerebri in that it is often transient, mild in intensity and well-controlled with mild analgesics. Patients usually develop tolerance with continued tretinoin therapy.

Retinoic acid syndrome (RAS) occurs in 20-25% of patients, and is characterized by some or all of the following symptoms: fever, dyspnea, hypotension, bone pain, weight gain, edema, respiratory distress, pulmonary infiltrates, hyperleukocytosis, pleural or pericardial effusion, congestive heart failure, hepatic / renal failure, multi-organ failure and may be fatal. Due to the severity and poor prognosis of the syndrome once the full-blown signs have been developed, prophylaxis or early treatment with chemotherapy, corticosteroids or temporary interruption is required (section E)

Basophilia/ Hyperhistaminemia: Basophilia-associated hyperhistaminemia has been rarely reported in patients with rare basophilic variants of APL. The severity of symptoms depends on the level of plasma histamine. Severe symptoms include tachycardia, shock due to vasodilatation, gastric and duodenal ulceration. Prophylactic H_2 or H_1 antagonist has been used to prevent symptoms mediated via H_2 and H_1 receptors.

Pseudotumour cerebri syndrome: 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. Symptoms include severe headache which may be aggravated by analgesic or narcotic overuse, nausea and vomiting, papilledema, retinal hemorrhages, visual changes (e.g., intermittent visual loss), and ophthalmoplegia. Cases reported onset of symptoms from 3-17 days to 6 months of tretinoin therapy. Pseudotumour cerebri is more common in children than in adults and may be due to their increased sensitivity to the CNS effects of tretinoin. The cause and appropriate management of pseudotumour cerebri have not been established, but the risk is increased with other drugs known to cause pseudotumour cerebri such as tetracyclines. Narcotic analgesics, corticosteroids, 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.

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 (e.g., myositis, fasciitis). 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.

back to top

E - Dosing

Refer to protocol by which patient is being treated. Consolidation chemotherapy should be considered after complete response to tretinoin as well as during therapy depending on white cell count.

Adults:

Oral: 45 mg/m^2/day (Round dose to the nearest 10 mg) in 2 divided doses.
Continue for 30 days to a maximum of 90 days until complete remission and then give consolidation chemotherapy (anthracycline + cytarabine).

Dosage with Toxicity:

Baseline WBC x 10^9 /L		**During Treatment WBC x 10^9 /L**	**Action**
> 5	AND	At any time	Add anthracycline-based chemotherapy.
< 5	AND	≥ 6, day 1 - day 6 OR ≥ 10, day 7 – day 10 OR ≥15, day 11 – day 28	Add full-dose anthracycline-based chemotherapy

Retinoic Acid Syndrome and Toxicity:

- For patients with early signs of the syndrome any time during tretinoin therapy, start dexamethasone 10 mg IV every 12 hours for at least 3 days until symptom resolution.
- Consider temporary interruption of tretinoin with moderate or severe retinoic acid syndrome
- Reduce dose in the event of intractable headaches

Dosage with Hepatic Impairment:

Reduced dose of 25 mg/m^2/day is recommended as a precautionary measure, as studies have not been done in patients with hepatic impairment. Consider withholding tretinoin in patients with serum transaminase concentrations greater than 5 x ULN. (AHFS 2013)

Dosage with Renal Impairment:

Reduced dose of 25 mg/m^2/day is recommended as a precautionary measure, as studies have not been done in patients with renal impairment.

Dosage in the elderly:

No adjustment is required.

Children:

Few studies or data are available. Same dosage as for adults. There appears to be an increased risk of pseudotumour cerebri.

back to top

F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Should be administered with food.
- Tretinoin capsules should not be opened.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Store at room temperature (15-30°C); protect from heat and direct light.

back to top

G - Special Precautions

Contraindications:

- patients with a history of hypersensitivity reaction to tretinoin or related compounds (e.g. acitretin, isotretinoin, vitamin A)
- patients taking vitamin A

Other Warnings/Precautions:

- Use with caution with antifibrinolytic agents (as fatal thrombosis may occur) and with tetracyclines

- Overdose may result in symptoms of hypervitaminosis A; no specific antidote is available but patients should be closely monitored.
- Patients who are drowsy or who have headaches may have reduced ability to operate heavy machinery or motor vehicles.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Yes
  Tretinoin is **highly teratogenic** with a high risk of severe malformations; therefore, it is **contraindicated** i**n pregnancy and in women who might become pregnant during or within one month of treatment cessation**. All patients of childbearing potential should use effective contraception at least 4 weeks prior to treatment, during and for at least 1 month after treatment cessation. Therapy should not begin until the second or third day of the next normal menstrual period and a pregnancy test should be negative within 2 weeks before starting treatment (Refer to product monograph for full details). Low dose progesterone contraceptives should not be used.
- Lactation: Contraindicated
- Fertility effects: Yes

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs inducing P450 (rifampicin, glucocorticoids, Phenobarbital, etc)	↓ blood levels of tretinoin	Induces tretinoin metabolism	Avoid concurrent therapy or use with caution
Ketoconazole and drugs inhibiting p450 (cimetidine, erythromycin, cyclosporine, etc)	↑ tretinoin AUC	Inhibits tretinoin metabolism	Avoid concurrent therapy
Progesterone (low dose)	↓ contraceptive efficacy of progestogens	Unknown	Avoid concurrent therapy; use alternative methods for contraception
Tetracyclines	May ↑ intracranial blood	Additive	Avoid concurrent

	pressure/ pseudotumour cerebri		therapy
Vitamin A	May ↑ Tretinoin toxicity	Additive	CONTRAINDICATED
Antifibrinolytic agents (e.g. tranexamic acid, aminocaproic acid, aprotinin)	↑ risk of thrombosis	Additive	Avoid concomitant use or use with caution
Hydroxyurea	Massive cell lysis and marrow necrosis	Synergistic (tretinoin induces cells to enter S phase; hydroxyurea cytotoxic to S phase cells)	Avoid concomitant use

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Pregnancy test in patients of childbearing potential	Baseline (within 2 weeks before treatment starts) and at each month
Renal function tests	Baseline and regular
Liver function tests	Baseline and regular
CBC & coagulation	Baseline and frequent (weekly for the first month)
Clinical toxicity assessment (including skin, headache, bleeding, infection, Retinoic Acid Syndrome).	

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Cholesterol and triglycerides	Baseline and regular

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- tretinoin (ATRA)

back to top

K - References

Gillis JC, Goa KL. Tretinoin. A review of its pharmacodynamic and pharmacokinetic properties and use in the management of acute promyelocytic leukemia. Drugs 1995; 50(5):897-923.

Koike T, Tatewaki W, Aoki A, et al. Brief report: severe symptoms of hyperhistaminemia after the treatment of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). N Engl J Med 1992;327(6):385-7.

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists, p. 1226-30.

Shimamoto Y, Suga K, Yamaguchi M, et al. Prophylaxis of symptoms of hyperhistaminemia after the treatment of acute promyelocytic leukemia with all-trans retinoic acid. Acta Haematol 1994;92(2):109-12. Tretinoin drug monograph. BCCA Cancer Drug Manual, February 2014.

Product monograph: Vesanoid (tretinoin). Xediton Pharmaceuticals. October 3, 2013.

Tretinoin drug monograph. BCCA Cancer Drug Manual, February 2014.

Yeh YC, Tang HF, Fang IM. Pseudotumor cerebri caused by all-trans-retinoic acid treatment for acute promyelocytic leukemia. Jpn J Ophthalmol. 2006 May-Jun;50(3):295-6.

June 2019 Updated emetic risk category.

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top