PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]JAMP Tretinoin

Tretinoin capsules

Capsules, 10 mg, oral

Antineoplastic agents, Retinoids for cancer treatment

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RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS	07/2023
7 WARNINGS AND PRECAUTIONS, Cardiovascular	07/2023
7 WARNINGS AND PRECAUTIONS, Psychiatric	07/2023

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JAMP Tretinoin (tretinoin, also known as all-trans retinoic acid [ATRA]) is indicated for:

- induction of remission in acute promyelocytic leukemia (APL; FAB classification AML-M3).

Previously untreated patients, as well as patients who relapsed after, or were refractory to standard chemotherapy (daunomycin and cytosine arabinoside or equivalent therapies) may be treated with JAMP Tretinoin.

1.1 Pediatrics

Pediatrics: There is limited safety and efficacy information on the use of tretinoin in pediatric patients (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: There is limited safety and efficacy information on the use of tretinoin in elderly patients compared to younger adult patients (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Tretinoin is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Tretinoin is highly teratogenic; therefore, it is contraindicated during pregnancy and in nursing mothers. Tretinoin must not be used by women of child-bearing potential unless effective contraception is practiced for at least one month before beginning therapy, during therapy and at least one month following discontinuation of therapy (see 7.1.1 Pregnant women).

The use of tretinoin in combination with vitamin A, tetracyclines and other retinoids is contraindicated (See 9 DRUG INTERACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Teratogenic effect: Tretinoin is highly teratogenic. Its use is contraindicated in pregnant women. Tretinoin must not be used by women of child-bearing potential unless effective contraception is practiced for at least one month before beginning therapy, during therapy and at least one month following discontinuation of therapy (see 2 CONTRAINDICATION and 7.1.1 Pregnant women).

Should pregnancy occur, in spite of all precautions, during treatment with tretinoin or within one month after its discontinuation, there is a high risk of severe malformation of the fetus, particularly when tretinoin was given during the first trimester of pregnancy (See 7.1.1 Pregnant women).

Differentiation Syndrome (formerly known as Retinoic Acid Syndrome): Differentiation syndrome has been reported in many APL patients treated with tretinoin (approximately 26% in some clinical trials) or in association with arsenic trioxide and may be fatal.

Differentiation syndrome may occur with severe symptoms such as fever, dyspnea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, peripheral edema, weight gain and may progress into pulmonary, hepatic, renal and multi-organ failure (See 7 WARNINGS AND PRECAUTIONS, General).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Due to limited information on patients with hepatic and/or renal insufficiency, the dose should be decreased to 25 mg/m^2 as a precautionary measure.
- Rule out pregnancy prior to administration. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1.1 Pregnant Women.

4.2 Recommended Dose and Dosage

Adjustment Recommended Dose

A total daily dose of 45 mg/m^2 body surface divided in two equal doses is recommended for oral administration to APL patients, including pediatric and geriatric patients. This is approximately 8 capsules per adult dose.

Treatment should be continued for 30 to 90 days until complete remission has been achieved.

After completion of remission, a course of consolidation chemotherapy including anthracycline and cytosine arabinoside should be initiated immediately; for example, three courses in 5 to 6 weeks intervals.

If there has been a remission with tretinoin alone, it is not necessary to modify the dose of tretinoin if tretinoin is used with chemotherapy.

Dosage Adjustment

- In cases of moderate and severe differentiation syndrome, temporary interruption of tretinoin therapy should be considered (see 7 WARNINGS AND PRECAUTIONS, General). The treatment with tretinoin may need to be withheld during the initial acute symptomatic period but may be resumed when symptoms resolve.

- If intracranial hypertension/pseudotumor cerebri occur, a dose reduction of tretinoin is recommended (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

- Dose reduction should be particularly considered for children with intractable headache (see 7.1.3 Pediatrics).

The decision to interrupt or continue therapy should be based on an evaluation of the benefit of the treatment versus the severity of the side effects.

Pediatrics: There is limited safety and efficacy information on the use of tretinoin in children. For children the same treatment regimen as for adults is applicable. The optimal pediatric dose of tretinoin has not yet been established. In an attempt to reduce tretinoin related toxicity, the daily dose administered in children can be reduced to 25 mg/m^2.

Renal and Hepatic Impairment: The pharmacokinetics of tretinoin in patients with compromised kidney or liver function have not been studied (see 10.3 Pharmacokinetics). The need for dosage adjustment in patients with renal or hepatic impairment is unknown; however, a reduction of dose to 25 mg/m^2 is recommended as a precautionary measure.

4.4 Administration

The capsules should be swallowed whole with water. They should not be chewed. It is recommended to take the capsules with a meal or shortly thereafter.

4.5 Missed Dose

If a dose is missed, it should be taken within 6 hours of the initially missed dose. If 6 hours have passed since the initially missed dose, the dose should be omitted, and the regular dosing schedule should be continued.

5 OVERDOSAGE

In cases of overdose with tretinoin, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear. There is no specific treatment in the case of an overdose, however, it is important that the patient is treated in a special hematological unit.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Capsule 10 mg	Butylated hydroxyanisole, edetate disodium, gelatin, glycerin, hydrogenated vegetable oil type I, hydrogenated vegetable oil type II, non-crystallizing sorbitol solution, medium-chain triglycerides (as Captex 355), red ferric oxide, soybean oil, titanium dioxide, yellow wax, Phosal 53 MCT and purified water. The capsules may include traces of ascorbyl palmitate, caprylic / capric triglycerides, oleic acid, phosphatidycholine, sunflower seed oil glyceride and tocopherol. The capsule ink-printing contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

JAMP Tretinoin capsules are available in bottles of 100. The soft gelatin capsules are pink, oval, printed with 'T10' and filled with a yellow to orange, opaque, viscous suspension.

7 WARNINGS AND PRECAUTIONS

General

Differentiation Syndrome (formerly known as Retinoic Acid Syndrome): During clinical trials hyperleukocytosis has been frequently observed, sometimes associated with the "differentiation syndrome" (DS). DS has been reported in many acute promyelocytic leukaemia patients treated with tretinoin (about 26% in some clinical trials) or in association with arsenic trioxide and may be fatal. Early recognition and treatment of DS is therefore of paramount importance. If symptoms of DS become apparent, treatment with a short course of high doses of corticosteroids (i.e., dexamethasone) should be initiated immediately particularly in patients where the syndrome is suspected but hyperleukocytosis is not observed.

During clinical trials hyperleukocytosis has been frequently observed (75%), sometimes associated with the DS.

For those patients experiencing hyperleukocytosis when they receive tretinoin alone, the DS can be prevented by addition of a full-dose anthracycline-based chemotherapy to the tretinoin regimen based on the white blood cell (WBC) count. The current therapeutic treatment recommendations are the following:

- Immediate treatment of patients with a WBC count of > 5 x 10^9/L at diagnosis or at any time with a combination of tretinoin and chemotherapy.
- Addition of full-dose chemotherapy to tretinoin therapy in patients with a WBC of < 5 x 10^9/L at day 0 of the treatment with tretinoin and if WBC counts become:
- ≥ 6 x 10^9/L at any time from day 1 to day 6 of treatment

and/or ≥ 10 x 10^9/L at any time from day 7 to day 10 of treatment

and/or ≥ 15x 10^9/L at any time from day 11 to day 28 of treatment

- Treatment with dexamethasone (10 mg every 12 hours for up to maximum 3 days or until resolution of the symptoms), if the patient presents early clinical signs of the syndrome.
- In cases of moderate and severe DS, temporary interruption of tretinoin therapy should be considered.

Mortality and morbidity are reduced by following these treatment recommendations in patients with this syndrome.

Supportive care appropriate for patients with acute promyelocytic leukemia, e.g., prophylaxis for bleeding and prompt treatment of infections, should be maintained during therapy with tretinoin.

An increased body mass index (BMI) has been identified as a predictor factor for DS. Therefore, patients with increased BMI should be closely monitored during therapy especially in terms of respiratory functions, diuresis, and creatinine levels.

Cardiovascular

Thrombosis

There is a risk of thrombosis (both venous and arterial) which may involve any organ system during the first month of treatment (See 8 ADVERSE REACTIONS). Therefore, caution should be exercised when treating patients with the combination of tretinoin and antifibrinolytic agents such as tranexamic acid, aminocaproic acid or aprotinin (See 9.1 Serious Drug Interactions).

Myocarditis

Myocarditis was reported in APL patients treated with tretinoin and was commonly observed in patients experiencing DS. The most common symptoms of myocarditis included chest pain, dyspnea, fatigue, palpitations, and syncope. Additionally, increased troponin and creatinine kinase values, changes in electrocardiogram with ST-segment elevation, decreased left ventricular ejection fraction, increased wall thickness and pericardial effusion were observed. In patients experiencing myocarditis, symptoms most often occurred within the first days of induction treatment, but in some patients, symptoms occurred only after 3 weeks of treatment. In all cases, urgent treatment is required as myocarditis may be fatal. Possible treatment options are similar to the treatment of the DS and include glucocorticoid therapy and temporary interruption of tretinoin therapy.

Driving and Operating Machinery

The ability to drive or operate machinery might be impaired in patients treated with tretinoin, particularly if they are experiencing dizziness or severe headache.

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Hyperleukocytosis

Patients experiencing hyperleukocytosis should be treated with full-dose anthracycline-based chemotherapy. Immediate treatment of patients with white blood cell (WBC) count of ≥ 5 x 10^9/L at diagnosis or during any time of therapy is recommended.

In terms of combination therapy of tretinoin with arsenic trioxide, the use of hydroxyurea should

be considered for treatment of leukocytosis to keep WBC<10.000/mcL.

Hepatic/Biliary/Pancreatic

The pharmacokinetics of tretinoin in patients with compromised liver function have not been studied. As with other retinoids, the need for dosage adjustments in patients with hepatic impairment is unknown, however, a reduction of dose to 25 mg/m^2 is recommended as a precautionary measure.

Monitoring and Laboratory Tests

Because hypercalcaemia may occur during therapy, serum calcium levels should be monitored. The patient's hematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

Neurologic

Tretinoin may cause intracranial hypertension/pseudotumor cerebri. The concomitant use of other agents known to cause intracranial hypertension/pseudotumor cerebri such as tetracyclines might increase the risk of this condition (See 9 DRUG INTERACTIONS).

Psychiatric

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including tretinoin. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

Renal

The pharmacokinetics of tretinoin in patients with compromised kidney function have not been studied. As with other retinoids, the need for dosage adjustments in patients with renal impairment is unknown, however, a reduction of dose to 25 mg/m^2 is recommended as a precautionary measure.

Reproductive Health: Female and Male Potential

Micro-dosed progestogen preparations ("minipill") may be an inadequate method of contraception during treatment with tretinoin. Information about mandatory contraception during treatment of women of child- bearing potential has to be considered. See 7.1.1 Pregnant women**.**

- **Teratogenic Risk**

Tretinoin is highly teratogenic. See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1.1 Pregnant women .

Skin

Cases of Sweet's syndrome or acute febrile neutrophilic dermatitis have been reported in patients treated with tretinoin and responded to corticosteroid treatment.

7.1 Special Populations

7.1.1 Pregnant women

Tretinoin is highly teratogenic. Its use is contraindicated in pregnant women and women who might become pregnant during or within one month of the cessation of treatment.

There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking tretinoin, irrespective of the dose or duration of the treatment. Potentially all exposed fetuses can be affected. Therapy with tretinoin should only be started in a female patient if each of the following conditions is met:

- She is informed by her physicians of the hazards concerning pregnancy during and within one month after treatment with tretinoin.
- She is willing to comply with the mandatory contraception measures.
- Every woman of child-bearing potential who is to undergo treatment with tretinoin uses effective contraception for four weeks before, during and for one month after discontinuation of treatment with tretinoin.
- A negative pregnancy test result must be obtained within the two weeks before commencement of treatment. It is advisable to perform additional pregnancy tests at monthly intervals during therapy.

Should pregnancy occur, in spite of these precautions, during treatment with tretinoin or within one month after its discontinuation, there is a high risk of severe malformation of the fetus particularly when tretinoin was given during the first trimester of pregnancy.

All these measures should be considered in relationship to the severity of the disease and the urgency of the treatment.

There is no experience about the extent of exposure in pregnancy during clinical trials.

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. Because of its teratogenic effects, nursing should be discontinued if therapy with tretinoin is initiated. Tretinoin is contraindicated in nursing mothers (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

There is limited safety and efficacy information on the use of tretinoin in pediatric patients.

Pseudotumor cerebri (See 8 ADVERSE REACTIONS) has a higher incidence in pediatric patients than in adults. Clinical trial data show a decreased incidence of pseudotumor cerebri with the use of a lower tretinoin dose, without compromising the outcome results. Therefore, a dose reduction to 25 mg/m^2 should be considered for children with toxicity symptoms, such as intractable headache (See 4.2 Recommended Dose and Dosage Adjustment).

7.1.4 Geriatrics

There is limited safety and efficacy information on the use of tretinoin in elderly patients compared to younger adult patients. Elderly patients seemed at least as responsive to therapy as did younger patients, but rates of response and survival were lower in this age setting owing to a higher incidence of early deaths and deaths in remission when conventional treatment with tretinoin and chemotherapy was used.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Differentiation syndrome has been frequently reported in APL patients treated with tretinoin or in association with arsenic trioxide and may be fatal (see 7 WARNINGS AND PRECAUTIONS, General).

The most frequently observed adverse reactions in persons treated with the recommended daily doses of tretinoin capsules (in $\geq$ 25% of the patients) were signs and symptoms of the hypervitaminosis A syndrome (including xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain). Headache, fever, shivering, fatigue, back pain, chest pain, dyspnea, coughing, abdominal pain, dermal bleeding, and elevation in serum triglycerides, cholesterol and transaminases may also be observed.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may therefore not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety profile of tretinoin capsules has been evaluated retrospectively in a small number of patients.

The following adverse events, considered remotely, possibly or probably related to drug treatment have been reported in more than 25% of all APL patients treated with tretinoin capsules in the clinical trials:

Table 2 – Adverse Reactions ($\geq$ 25%) in APL Patients Treated with tretinoin capsules in Clinical Trials

ADR Preferred Term (MedDRA) System Organ Class	Frequency
Gastrointestinal disorders	
Nausea	57.1%
Vomiting	54.3%
Cheilitis	30.0%
Abdominal pain	28.6%
General disorders and administration site conditions	

Pyrexia	82.9%
Chills	62.9%
Fatigue	57.1%
Edema	28.6%
Musculoskeletal and connective tissue disorders	
Back pain	40.0%
Bone pain	40.0%
Chest pain	28.6%
Nervous system disorders	
Headache	85.7%
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	60.0%
Cough	31.4%
Skin and subcutaneous tissue disorders	
Xeroderma	48.6%
Lip dry	45.7%
Rash	40.0%
Skin haemorrhage	31.4%

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events, considered remotely, possibly or probably related to drug treatment have been reported in less than 25% of all APL patients treated with tretinoin capsules in the clinical trials:

Cardiac disorders:

cardiac failure, cyanosis, heart enlarged, arrhythmias.

Eye disorders:

blurred vision, visual disturbance, photophobia, conjunctivitis, decreased vision, changes in visual acuity

Ear and labyrinth disorders:

ear fullness, earache, ear buzzing

Gastrointestinal disorders:

abdominal pain, diarrhea, constipation, blisters in the mouth, stomach upset, dysphagia, buccal mucosa ulceration, stomatitis, flatulence, ulcer, pancreatitis, diminished appetite

General disorders and administration site conditions:

generalized pain, abdominal distension, post traumatic pain, chest discomfort, hypothermia

Immune system disorders:

infection, septicemia, moniliasis

Metabolism and nutrition disorders:

weight changes, edema of extremities, acidosis, gout, dehydration, fluid overload, moonface, elevation in serum creatinine

Musculoskeletal and connective tissue disorders:

musculoskeletal pain

Nervous system disorders:

tachycardia, hypertension, hypotension, pallor, red extremities, dizziness, confusion, intracranial hypertension, lightheaded feeling, flank pain, numbness of extremities, abnormal gait, leg weakness, neurologic reaction, inguinal pain, visual field defects, hyporeflexia, paresthesia

Psychiatric disorders:

generalized weakness, anxiety, lethargy, depression, malaise, insomnia, anorexia, agitation, forgetfulness, confusion state

Renal and urinary disorders:

dysuria, kidney failure, urinary tract infection, micturition frequency, renal insufficiency, cystitis

Respiratory, thoracic and mediastinal disorders:

pleural effusion, nasal congestion, pharyngitis, rale, respiratory insufficiency, asthma-like syndrome, pneumonia, respiratory distress, tachypnea, pharynx irritation, pulmonary infiltration, hypoxia, sinusitis, bronchial asthma

Skin and subcutaneous tissue disorders:

pruritus, increased sweating, alopecia, dry scalp, nasal dryness, nail disorder, photosensitivity reaction, xerophthalmia, erythema

Vascular disorders: flushing, thrombosis (both venous and arterial) involving various sites (e.g., cerebrovascular accident, myocardial infarctions, renal infarct)

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

There is limited safety information on the use of tretinoin in children. There have been some reports of increased toxicity in children treated with tretinoin, particularly increased intracranial hypertension/ pseudotumor cerebri.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other

Quantitative Data Clinical Trial Findings

Clinical Chemistry
Blood triglyceride increased, blood creatinine increased, blood cholesterol increased, transaminases increased

Post Market Findings

Clinical Chemistry
Histamine level increased

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders: Thrombocytosis, marked basophilia with or without symptomatic hyperhistaminemia (mainly in patients with the rare APL variant associated with basophilic differentiation), leukocytosis

Cardiac disorders: Myocarditis, pericarditis

Infections and infestations: Necrotizing fasciitis

Metabolism and Nutrition Disorders: Hypercalcemia

Musculoskeletal and connective tissue disorders: Myositis, bone pain

Skin and subcutaneous tissue disorders: Sweet's syndrome, erythema nodosum

Vascular disorders: Vasculitis predominantly involving the skin

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Tretinoin must not be administered in combination with vitamin A or other retinoids because symptoms of hypervitaminosis A could be aggravated (See 2 CONTRAINDICATIONS).
- Antifibrinolytic agents such as tranexamic acid, aminocaproic acid, and aprotinin: cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with tretinoin and antifibrinolytic agents. Therefore, caution should be exercised when administering tretinoin concomitantly with these agents (See 7 WARNINGS AND PRECAUTIONS).
- Agents known to cause intracranial hypertension/pseudotumor cerebri such as tetracyclines: Tretinoin may cause intracranial hypertension/pseudotumor cerebri. Concomitant administration of tretinoin and agents known to cause intracranial hypertension/pseudotumor cerebri as well might increase the risk of this condition (See 7 WARNINGS AND PRECAUTIONS).
- Post-marketing experience shows that coadministration, in particular of orally administered antimycotics of the imidazole and triazole type, can increase the toxicity of tretinoin (See 9.2 Drug-Interactions Overview).

9.2 Drug-Interactions Overview

As tretinoin is metabolized by the hepatic P450 system, there is the potential for alteration of pharmacokinetic parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and ciclosporin.

There are no data on a possible pharmacokinetic interaction between tretinoin and daunorubicin and cytosine arabinoside.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Vitamin A or other retinoids	T	Aggravated symptoms of hypervitaminosis A	Combination is contraindicated. Serious side effects due to hypervitaminosis A are expected.
Tetracyclines and other agents known to cause intracranial hypertension/pseudo-tumour cerebri	T	Increased risk for the occurrence of intracranial hypertension/pseu-dotumour cerebri	This combination should be avoided to reduce the risk for this serious side effect.
Antifibrinolytic agents such as tranexamic acid, aminocaproic acid and aprotinin	C	Fatal thrombotic events during concomitant treatment.	There is a risk for thrombosis during treatment with tretinoin. Concomitant use of antifibrinolytic agents can aggravate these thrombotic events and should be avoided.
Imidazole or triazole antimycotics	C	Increased toxicity of tretinoin due to inhibition of its metabolism.	In case treatment with imidazole or triazole antimycotics is urgently needed, clinicians should be aware of signs and symptoms indicative of tretinoin toxicity.
Cytochrome P450 inducers such as rifampicin, glucocorticoids, phenobarbital and pentobarbital	T	Decreased tretinoin plasma levels due to increased metabolism.	Clinical relevance is currently not known. However, since the therapeutic efficacy of tretinoin may be reduced due to low plasma concentrations, concomitant use with CYP450 inducers should be avoided.
Cytochrome P450 inhibitors such as ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and ciclosporin	CT	Increased tretinoin plasma levels due to decreased metabolism.	In case of imidazole and triazole antimycotics (see above), this interaction has already been identified to cause tretinoin toxicity. In a clinical trial, ketoconazole was successfully used to increase tretinoin plasma levels by countering its self-induced metabolism. Therefore, clinical effects caused by this interaction largely vary and clinicians should be aware of signs and symptoms indicative of tretinoin toxicity.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

The effect of food on the bioavailability of tretinoin has not been characterized. Since the bioavailability of retinoids, as a class, is known to increase in the presence of food, it is recommended that tretinoin be administered with a meal or shortly thereafter.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tretinoin is a natural metabolite of retinol and belongs to the class of compounds known as retinoids, which are structurally related to vitamin A and comprise natural and synthetic analogs.

Acute promyelocytic leukemia (APL) is associated with a non-random chromosomal abnormality characterized by balanced and reciprocal translocations between the long arms of chromosomes 15 and 17 [t(15;17)(q22;q21)]. The gene encoding the retinoic acid receptor-alpha (RAR-α) is located on chromosome 17. A previously unidentified gene, PML, that may act as a transcription factor, is located on chromosome 15. The 15;17 translocation fuses the genes for PML and RAR-α, resulting in the synthesis of two reciprocal fusion transcripts, PML/RAR-α (found in all patients) and RAR-α/PML (found in about 2/3 of patients). PML/RAR-α may inhibit the differentiation of myeloid cells, resulting in carcinogenesis, an effect which may be overcome by the use of high doses of tretinoin.

10.2 Pharmacodynamics

In vitro studies with tretinoin have demonstrated induction of differentiation and inhibition of cell proliferation in transformed hemopoietic cell lines, including human myeloid leukemia cell lines.

10.3 Pharmacokinetics

Table 4 – Summary of Tretinoin Pharmacokinetic Parameters in the Adult Patient Population

	C_{max}	T_{max}	$t_{½}$ (h)	Active metabolites
Single dose mean	0.03 - 2.5 mcg/ml	~ 90 min	0.71 h	4-hydroxy-tretinoin, 4-oxo-tretinoin (less effective than tretinoin)

Absorption:

Tretinoin is an endogenous metabolite of vitamin A and is normally present in plasma at concentrations of 2 to 4 ng/mL. After oral administration, tretinoin is absorbed by the digestive tract. It is transported directly via the portal system rather than through the lymphatics and thus absorption does not require specific transport mechanisms. Maximum plasma concentrations of tretinoin were reached within one to two hours in APL patients. Maximum plasma concentrations in healthy volunteers are attained after 3 hours. There is a large inter-patient and intra-patient variation in plasma levels of tretinoin.

Distribution:

Tretinoin is highly lipophilic with more than 95% of total drug concentration bound to plasma proteins. Following peak levels, plasma concentrations decline with a mean elimination half-life of 0.7 hours. Plasma concentrations return to endogenous levels following a single 40 mg dose after 7 to 12 hours. No accumulation is seen after multiple doses.

Metabolism:

Tretinoin is primarily metabolized by liver enzymes and is converted to the 13-cis isomer. During continuous administration, a marked decrease in plasma concentration can occur, possibly due to cytochrome P450 enzyme induction which increases clearance and decreases bioavailability after oral doses. Among patients maintained on tretinoin, a loss of responsiveness to tretinoin has been reported, with a median time to relapse of 4-6 months. Oxidation by P450 isoenzymes leads to the corresponding 4-hydroxy and 4-oxo- compounds.

Elimination:

Following an oral single dose administration, plasma concentrations of tretinoin declined mono-exponentially with a mean elimination half-life of 0.71 hours. Endogenous levels (2 to 4 ng/mL) were reached 7 to 12 hours after dosing.

After glucuronidation, the 4-hydroxy and 4-oxo-compounds are excreted in the urine and bile. Following a single dose of radiolabelled tretinoin, about 30% of the total radioactivity was recovered in the feces and about 60% in the urine. Nearly the entire dose was excreted within 3 to 6 days.

Special Populations and Conditions:

Multiple Doses: Multiple oral doses of tretinoin were associated with a significant (about 2-fold) decrease in both the peak plasma levels and the AUC levels, after 2-6 weeks of treatment. These changes were associated with a 10-fold increase in urinary excretion of 4-oxo all-trans retinoic acid glucuronide.

The administration of ketoconazole, an inhibitor of the P450 enzyme system, after multiple doses of tretinoin resulted in a greater mean plasma tretinoin AUC than after the administration of tretinoin alone.

Pediatrics*:* A phase I trial of tretinoin administered orally twice a day for treatment courses of 28 days was performed in pediatrics. Cohorts of at least 3 patients were entered at successive tretinoin dose levels (from 45 to 80 mg/m^2/day, with a twice a day dosing regimen) until dose-limiting toxicity was consistently observed. Twenty-one patients with a median age of 14 years and various types of tumours including 2 patients with APL were entered into the trial.

Pharmacokinetics were determined in eighteen patients on day one and in seven patients on day 1 and day 28. Time to peak plasma concentrations was between 1 and 4 hours after dosing. Peak plasma concentrations of tretinoin of 0.59, 0.62 and 1.64 mcM (180, 190 and 490 ng/mL) were observed following doses of 22.5, 30 and 40 mg/m^2. AUC values for these doses were 1.29, 1.13 and 3.35 mcM (387, 339 and 1005 ng.h/mL), respectively. Peak plasma concentrations and AUC values did not appear to increase in proportion to dose. A greater than three-fold increase in AUC was observed following a 30% increase in dose (30 to 40 mg/m^2). The average terminal half-life was 0.7 hours. The AUC on day 1 was significantly greater than the AUC on day 28 (mean decrease 78% ± 30 SD). Quantifiable concentrations of 4-oxo metabolites of tretinoin were not observed.

Hepatic Insufficiency: The pharmacokinetics of tretinoin in patients with compromised liver function have not been studied. As a precautionary measure, the dose will be decreased to 25 mg/m^2/day (See 4.1 Dosing Considerations).

Renal Insufficiency: The pharmacokinetics of tretinoin in patients with compromised kidney function have not been studied. As a precautionary measure, the dose will be decreased to 25 mg/m^2/day (See 4.1 Dosing Considerations).

11 STORAGE, STABILITY AND DISPOSAL

Keep the bottle tightly closed and store at 20°C to 25°C; excursions permitted to 15°C and 30°C. Store away from heat and direct light.

12 SPECIAL HANDLING INSTRUCTIONS

Broken capsules should be disposed of without touching or wearing rubber gloves to avoid exposure to the drug.

PART II: SCIENTIFIC INFORMATION

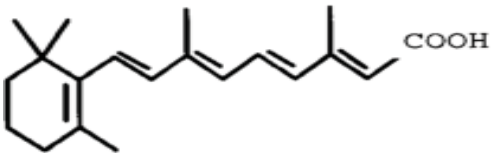
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tretinoin (also known as all-trans retinoic acid)

Chemical name: 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8-all-trans tetraenoic acid

Molecular formula and molecular mass: $C_{20}H_{28}O_2$ 300.44 g/mol

Structural formula: 

Physicochemical properties: Yellow to light-orange crystalline powder with very low solubility in water. Slightly soluble in alcohol and in chloroform. It is very sensitive to light and oxygen.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.2 Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-sequence, two-period, crossover, single dose (1 x 10 mg) comparative bioavailability study of JAMP Tretinoin (JAMP Pharma Corporation), and PrVESANOID® (CHEPLAPHARM Arzneimittel GmbH) was conducted in 34 healthy, adult male subjects under fed conditions. A summary of the comparative bioavailability data from the 34 subjects who completed the study is presented in following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Tretinoin (1 x 10 mg) From baseline corrected data Geometric Mean Arithmetic Mean (%CV)				
Parameter	TEST[1]	REFERENCE[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	210.44 228.21 (42.37)	196.76 218.14 (45.47)	107.0	93.7 - 122.1
AUC_I (ng·h/mL)	217.79 232.99 (41.25)	212.71[3] 235.70 (45.03)	102.3	90.1 - 116.3
C_{max} (ng/mL)	80.63 91.38 (48.74)	76.55 88.75 (55.89)	105.4	87.5 - 126.8
T_{max}[4] (h)	3.83 (1.33-8.00)	4.00 (1.67-12.00)		
t½ [5] (h)	0.99 (86.58)	1.31 (195.58)		

[1] JAMP Tretinoin (tretinoin) capsules, 10 mg (JAMP Pharma Corporation).
[2] PrVESANOID® (tretinoin) capsules, 10 mg (CHELAPHARM Arzneimittel GmbH).
[3] n=33
[4] Expressed as the median (range) only.
[5] Expressed as the arithmetic mean (%CV) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Symptoms of acute toxicity in LD_{50} studies in mice and rats included sedation, hair loss, respiratory depression, blood encrusted eyes, swollen eyelids, changes in skin texture, cachexia, diuresis, diarrhea and salivation. The 10 days LD_{50} values were between 2,200 to 2,600 mg/kg and 2,000 mg/kg for mice and rats, respectively.

In subchronic (up to 13 weeks) and chronic (up to 440 days) toxicity studies in rats, symptoms were dose-related (up to 50 mg/kg/day) and included increased serum alkaline phosphatase, reduced body weight, testicular degeneration, bone fractures, increased liver weight and decrease in red blood cells.

Carcinogenicity: In carcinogenicity studies in mice, tretinoin had different effects on the incidence of chemically induced tumors. Tretinoin was either tumor-enhancing, tumor-inhibiting or had no effect at all. Tretinoin alone was shown to have no carcinogenic effects.

Genotoxicity: Tretinoin did not show genotoxic effects in the preclinical studies.

Reproductive and Developmental Toxicology: Tretinoin showed embryotoxic and teratogenic effects in several studies involving different species such as rats, mice, hamsters, rabbits and monkeys. Effects were shown to be dose-dependent and included malformations and fetal resorption.

In one study conducted in rats with doses up to 5 mg/kg p.o., no effects on the fertility or reproductive capacity of male and female adult rats were shown. However, survival of their offspring was reduced.

17 SUPPORTING PRODUCT MONOGRAPH

1. VESANOID (tretinoin capsules, 10 mg) Submission Control No: 263752, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. November 18, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]JAMP Tretinoin

Tretinoin Capsules

Read this carefully before you start taking JAMP Tretinoin and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about JAMP Tretinoin.

Serious Warnings and Precautions

Female Patients: Pregnancy

- Do not take JAMP Tretinoin if you are pregnant, may become pregnant during or within one month after treatment. It may harm your unborn baby and cause birth defects.
- If you are able to get pregnant:
- Use effective birth control for at least 1 month before treatment, during treatment and for at least 1 month after your last dose. Ask your healthcare professional about methods of birth control available to you. Some types of birth control might not work as well during treatment with JAMP Tretinoin.
- Do not take JAMP Tretinoin if you are breastfeeding.
- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Your healthcare professional will do a pregnancy test within 2 weeks before you start taking JAMP Tretinoin. This test must show that you are not pregnant. More pregnancy tests might be done monthly during treatment.
- Get your blood monitored regularly and keep all of your scheduled doctor's appointments.

Differentiation Syndrome and Hyperleukocytosis:

- JAMP Tretinoin may cause hyperleukocytosis and differentiation syndrome. Symptoms include fever, shortness of breath, lung problems, low blood pressure, swelling and weight gain. This may lead to lung, liver, renal and multi-organ failure.
- Your healthcare professional will monitor you for signs and symptoms of hyperleukocytosis and differentiation syndrome. They might treat you with other medicines in addition with JAMP Tretinoin.

What is JAMP Tretinoin used for?

- JAMP Tretinoin is used to treat adults and children (13 years and older) with a type of blood cancer called acute promyelocytic leukemia (APL).
- JAMP Tretinoin can be used in patients with APL:
    - who have never been treated for APL before, or
    - where other current cancer treatments do not work, or
    - where the APL has come back even after previous cancer treatment.

How does JAMP Tretinoin work?

JAMP Tretinoin helps stop the growth of abnormal blood cells which occur in APL.

What are the ingredients in JAMP Tretinoin?

Medicinal ingredients: Tretinoin (all-trans retinoic acid)

Non-medicinal ingredients: Butylated hydroxyanisole, edetate disodium, gelatin, glycerin, hydrogenated vegetable oil type I, hydrogenated vegetable oil type II, non-crystallizing sorbitol solution, medium-chain triglycerides (as Captex 355), red ferric oxide, soybean oil, titanium dioxide, yellow wax, Phosal 53 MCT and purified water.

The capsules may include traces of ascorbyl palmitate, caprylic / capric triglycerides, oleic acid, phosphatidycholine, sunflower seed oil glyceride and tocopherol. The capsule ink-printing contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

JAMP Tretinoin comes in the following dosage forms:

Capsules, 10 mg

Do not use JAMP Tretinoin if:

- you are allergic to tretinoin or to any ingredient in this medicine or container
- you are pregnant or breastfeeding
- you are taking Vitamin A, tetracyclines or other retinoids
- you are 0 - 12 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JAMP Tretinoin. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney problems
- have ever had any mental health problems like depression
- have skin problems
- are pregnant, plan on getting pregnant, or are breastfeeding
- have an increased body mass index (BMI)

Other warnings you should know about:

Blood clots: JAMP Tretinoin may cause **thrombosis** (blood clots) during the first month of treatment.

Brain problems: JAMP Tretinoin may cause **intracranial hypertension or pseudotumor cerebri** (build of pressure around the brain). This is more common in children.

Heart problems: JAMP Tretinoin may cause heart problems, including myocarditis (inflammation of the heart muscle and lining around the heart). This can cause a heart attack which may lead to death. Your healthcare professional will decide the best treatment options for you.

Mental health problems: JAMP Tretinoin may cause depression, aggression, anxiety and

mood changes. You may not notice these problems. It is important to tell your friends and family that JAMP Tretinoin can cause these mental problems. They could tell you if they notice these problems. Your healthcare professional will also monitor you for signs of these mental health problems.

Skin problems: JAMP Tretinoin may cause skin problems like Sweet's syndrome, which is a type of rash.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They might do blood tests to check:

- Your calcium levels
- Blood health
- Blood fat levels
- Liver and kidney health
- Lung health

Driving and using machines: JAMP Tretinoin can cause dizziness or serious headache. Before you drive or do tasks that require special attention, wait until you know how you respond to JAMP Tretinoin.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking the following medicines with JAMP Tretinoin cause serious problems:

- Vitamin A or vitamin A related compounds: This can cause overdose levels of vitamin A.
- Medicines to treat blood clots, such as tranexamic acid, aminocaproic acid, and aprotinin. These can cause deadly blood clot related problems.
- Medicines that can cause build-up of pressure around the brain like tetracyclines (a type of antibiotic, used to treat bacterial infections). Taking JAMP Tretinoin with these medicines might increase the risk of this problem.
- Imidazole and triazole type of medicines, like ketoconazole. These are used to treat fungal infections.

The following may also interact with JAMP Tretinoin:

- Medicines used to treat bacterial infections (antibiotics), like rifampin, erythromycin
- Medicines typically used to treat epilepsy (seizures) and insomnia like phenobarbital, pentobarbital
- Medicines used to treat stomach ulcers like cimetidine
- Medicines used to treat high blood pressure like verapamil, diltiazem
- Medicines used to treat arthritis like ciclosporin
- Medicines containing progestogen, like some types of birth control pills (minipill)
- Glucocorticoids (steroid hormones) used to treat inflammation and autoimmune diseases

How to take JAMP Tretinoin:

- Take exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Do not change your dose or stop taking it unless your healthcare professional tells you to.
- Swallow capsules whole with water. Do not chew the tablets.
- Take with a meal or shortly after a meal.

Usual dose:

- Your healthcare professional will decide on the best dosage for you based on your size and condition.
- Your healthcare professional may have you do other treatments if you respond to JAMP Tretinoin.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
    - experience serious side effects, or
    - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much JAMP Tretinoin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of JAMP Tretinoin:

- Take the missed dose as soon as possible if it has been within 6 hours of your missed dose.
- Skip the missed dose if it has been 6 hours or more since your missed dose. Take your next dose at the usual time.
- Continue taking your capsules according to your usual schedule.

What are possible side effects from using JAMP Tretinoin?

These are not all the possible side effects you may have when taking JAMP Tretinoin. If you experience any side effects not listed here, tell your healthcare professional.

- dry skin
- dry mouth and lips
- swelling of the mouth and lips
- rash
- swelling
- nausea, vomiting
- headache
- shivering
- tiredness
- back, chest, bone or stomachpain
- coughing

JAMP Tretinoin can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Differentiation Syndrome: fever, difficulty breathing, shortness of breath, lightheadedness, dizziness or a faint feeling, unusual swelling, weight gain, difficulty in urination, yellowing of the skin or eyes			X
Flushing: severe flushing may include general swelling, rash, itchiness		X	
Heart problems (disorders affecting your heart muscle, heart lining, valves or rhythm)**:** Chest pain, or chest discomfort, high blood pressure, irregular heart rhythm, shortness of breath, fainting, swelling of the legs, ankles and feet, weakness, tiredness		X	
Hypervitaminosis A (too much vitamin A in the body): dry skin, lip and mouth dryness, lip inflammation, rash, swelling, nausea, vomiting, bone pain, headache, fever, shivering, tiredness, back pain, chest pain, shortness of breath, coughing, stomach pain, bleeding into the skin, hair loss, vision changes		X	
Infections (blood, fungal, respiratory): fever and chills, nausea, vomiting, diarrhea, generally feeling unwell, itching, burning, soreness, irritation, whitish-grey cottage cheese-like discharge from vagina, thick white patches in the mouth, tongue or on the throat, chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, sweating, shortness of breath, runny or stuffy nose, body aches, headache, sneezing		X	
Intercranial hypertension / pseudotumor cerebri (pressure			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
around the brain): headache, nausea, ear buzzing, dizziness		X	
Mental health problems: depression (feelings of sadness, irritability, unusual tiredness, trouble concentrating, change in normal sleep patterns and loss of appetite with possible weight loss), agitation, anxiety, mood changes, forgetfulness, feeling of weakness		X	
Skin problems, including Sweet's syndrome: rash, itchy, red skin when exposed to sunlight		X	
Thrombosis (clot in a blood vessel): swelling and pain in one part of the body			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Keep the bottle tightly closed, store at 20°C to 25°C.
- Store away from heat and direct light.
- Wear rubber gloves when touching and throwing away broken capsules.

If you want more information about JAMP Tretinoin:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.jamppharma.com); or by calling 1-866-399- 9091.

This leaflet was prepared by:

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