Vesanoid®
Tretinoin

Category
Antineoplastic agent, Retinoid for cancer treatment

1. COMPOSITION AND PHARMACEUTICAL FORM
Active substance: 1 soft capsule contains 10 mg of all-trans retinoic acid (ATRA, tretinoin).

Galenical form: soft capsules, 10 mg.

Excipients: Capsule contents: yellow beeswax, hydrogenated soybean oil, partially hydrogenated soybean oil, soybean oil.
Capsule shell: gelatin, glycerol, karion 83 (sorbitol, mannitol, starch), titanium dioxide, iron oxide yellow, iron oxide red.

2. PROPERTIES AND EFFECTS
All-trans retinoic acid is a natural metabolite of retinol and belongs to the class of retinoids, comprising natural and synthetic analogs. *In vitro* studies with all-trans retinoic acid have demonstrated induction of differentiation and inhibition of cell proliferation in transformed hemopoietic cell lines, including human myeloid leukemia cell lines. The mechanism of action in acute promyelocytic leukemia (APL) is not known, may be due to an alteration in binding of all-trans retinoic acid to a nuclear retinoic acid receptor (RAR) given that the α-receptor of retinoic acid is altered by fusion with a protein called PML.

3. PHARMACOKINETICS
All-trans retinoic acid is an endogenous metabolite of vitamin A and is normally present in plasma. Oral doses of all-trans retinoic acid are well absorbed and maximum plasma concentrations in normal volunteers are attained after 3 hours. There is a large inter-patient and intra-patient variation in absorption of all-trans retinoic acid. In plasma, all-trans retinoic acid is extensively 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 and all-trans retinoic acid is not retained in body tissues.

Renal excretion of metabolites formed by oxidation and glucuronidation is a major route (60%) of elimination. All-trans retinoic acid is isomerized to 13-cis retinoic acid and oxidized to 4-oxo-metabolites. These metabolites have longer half-lives than all-trans retinoic acid and may show some accumulation.

During continuous dosing a marked decrease in plasma concentration can occur, possibly due to cytochrome P450 enzyme induction which increases clearance and decreases bioavailability after oral doses.

At present, there are no data in terms of interaction between all-trans retinoic acid and daunorubicin.

Pharmacokinetics in special situations

The requirement for dosage adjustment in patients with kidney or liver dysfunction has not been investigated. As a precautionary measure, the dose should be decreased to 25 mg/m^2/day (see section 5).

4. INDICATIONS AND USAGE

Vesanoid is indicated for induction of remission in acute promyelocytic leukemia (APL; FAB classification AML-M3). Previously untreated patients as well as patients who relapse after standard chemotherapy (anthracycline and cytosine arabinoside or equivalent therapies) or patients who are refractory to any chemotherapy may be treated with all-trans retinoic acid. The association of chemotherapy to all-trans retinoic acid increases the duration of survival, reduces the risk of relapse compared to chemotherapy alone. Maintenance therapy is still under investigation, however a loss of responsiveness to all-trans retinoic acid has been reported among patients maintained on all-trans retinoic acid alone.

5. DOSAGE AND ADMINISTRATION

A total daily dose of 45 mg/m^2 body surface divided in two equal doses is recommended for oral administration to APL patients. This is approximately 8 capsules per adult dose. It is recommended that pediatric patients be treated with 45 mg/m^2 unless severe toxicity becomes apparent. Dose reduction should be particularly considered for children with intractable headache.

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

Due to the lack of extensive information in case of renal and/or hepatic insufficiency, the dose should be decreased to 25 mg/m^2 as a precautionary measure.

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

If there has been a remission with all-trans retinoic acid alone, it is not necessary to modify doses of all-trans retinoic acid if all-trans retinoic acid is used with chemotherapy.

The effect of food on the bioavailability of all-trans retinoic acid 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 all-trans retinoic acid be administered with a meal or shortly thereafter.

6. CONTRAINDICATIONS

Vesanoid is contraindicated for use in patients with known hypersensitivity to all-trans retinoic acid or any of its components.

All-trans retinoic acid is teratogenic. It is therefore contraindicated in pregnancy and nursing mothers (see section 8).

The use of all-trans retinoic acid in combination with vitamin A is contraindicated (see section10).

7. PRECAUTIONS

During clinical trials hyperleukocytosis has been frequently observed (75%), sometimes associated with the “differentiation syndrome” (DS), formerly known as “retinoic acid syndrome”. DS has been reported in many APL patients (up to 26% in some clinical trials) treated with all-trans retinoic acid.

DS is characterized by fever, dyspnea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, edema, weight gain, hepatic, renal and multi-organ failure.

DS is frequently associated with hyperleukocytosis and may be fatal.

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

Immediate treatment of patients presenting with a WBC count of > 5 x 10^9/l at diagnosis or at any time with a combination of all-trans retinoic acid and chemotherapy.

Addition of full-dose chemotherapy to all-trans retinoic acid therapy in patients with a WBC of < 5 x 10^9/l at day 0 of the treatment with all-trans retinoic acid 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
≥ 15 x 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 all-trans retinoic acid therapy should be considered.

There is a risk of thrombosis (both venous and arterial) which may involve any organ system, during the first month of treatment (see section 9). Therefore, caution should be exercised when treating patients with the combination of Vesanoid and anti-fibrinolytic agents, such as tranexamic acid, aminocaproic acid or aprotinin (see section 10). Because hypercalcemia may occur during therapy, serum calcium levels should be monitored.

All-trans retinoic acid 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 section 10).

All-trans retinoic acid should be administered only to patients with APL under the strict supervision of a physician who is experienced in the treatment of hematological/oncological diseases.

Supportive care appropriate for patients with acute promyelocytic leukemia for example prophylaxis for bleeding and prompt therapy for infection, should be maintained during therapy with all-trans retinoic acid. The patient's hematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

Psychiatric disorders
Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including all-trans retinoic acid. 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.

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

Micro-dosed progestogen preparations ("minipill") are an inadequate method of contraception during treatment with all-trans retinoic acid.

8. PREGNANCY, NURSING MOTHERS

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

Pregnancy: All-trans retinoic acid is teratogenic. Its use is contraindicated in pregnant women and women who might become pregnant during or within one month of the cessation of treatment, unless the benefit of all-trans retinoic acid treatment outweighs the risk of foetal abnormalities due to the severity of the patient's condition and the urgency of treatment. There is an extremely high risk for any exposed foetus that a deformed infant will result if pregnancy occurs while taking all-trans retinoic acid, irrespective of the dose or duration of the treatment. Therapy with all-trans retinoic acid should only be started in a female patient of child-bearing age if each of the following conditions is met:

The patient is informed by her physician of the hazards of becoming pregnant during and for one month after treatment with all-trans retinoic acid.

The patient is willing to comply with the mandatory contraception measures. It is absolutely essential that every woman of child-bearing potential who is to undergo treatment with all-trans retinoic acid uses effective contraception during and for one month after discontinuation of treatment with all-trans retinoic acid.

Pregnancy tests must be performed at monthly intervals during therapy.

In spite of these precautions, should pregnancy occur during treatment with all-trans retinoic acid or up to one month after its discontinuation, there is a high risk of severe malformation of the fetus, particularly when all-trans retinoic acid was given during the first trimester of pregnancy.

Lactation: Breastfeeding must be discontinued if therapy with all-trans retinoic acid is initiated.

9. UNDESIRABLE EFFECTS

In patients treated with the recommended daily doses of all-trans retinoic acid the most frequent undesirable effects consist of the signs and symptoms of the hypervitaminosis A syndrome (as for other retinoids).

<u>Tabulated list of adverse reactions</u>

The adverse reactions listed in the table below have been reported in pivotal clinical studies and during the post-marketing period.

Adverse reactions are presented by MedDRA System Organ Class and frequency (very common (≥ 1/10)). Adverse reactions reported during the post-marketing period are also included in the table under the frequency category "not known" (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction(s)
Infections and infestations	Not known	Necrotising fasciitis
Blood and lymphatic system disorders	Not known	Thrombocytosis, leukocytosis, basophilia (with or without symptomatic hyperhistaminemia)
	Very common	Decreased appetite

Metabolism and nutrition disorders	Not known	Hypercalcemia
Psychiatric disorders	Very common	Confusional state, anxiety, depression, insomnia
Nervous system disorders	Very common	Headache, intracranial pressure increased, pseudotumour cerebri, dizziness, paraesthesia
	Not known	Cerebrovascular accident
Eye disorders	Very common	Visual disturbances, conjunctival disorders
Ear and labyrinth disorders	Very common	Hearing impaired
Cardiac disorders	Very common	Arrhythmia
	Not known	Myocardial infarction, myocarditis, pericarditis
Vascular disorders	Very common	Flushing
	Not known	Arterial thrombosis, venous thrombosis involving various sites (e.g. cerebrovascular accident, myocardial infarction, renal infarct), vasculitis
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory failure, nasal dryness, asthma
Gastrointestinal disorders	Very common	Dry mouth, nausea, vomiting, abdominal pain, diarrhea, constipation, pancreatitis, cheilitis
Skin and subcutaneous tissue disorders	Very common	Erythema, rash, pruritus, alopecia, hyperhidrosis
	Not known	Erythema nodosum, acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders	Very common	Bone pain
	Not known	Myositis
Renal and urinary disorders	Not known	Renal infarct
Reproductive system and breast disorders	Not known	Genital ulceration
General disorders and administration site conditions	Very common	Chest pain, chills, malaise
Investigations	Very common	Blood triglyceride increased, blood creatinine increased, blood cholesterol increased, transaminases increased
	Not known	Histamine level increased

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.

Description of selected adverse reactions

Differentiation syndrome in APL patients: The signs, symptoms and manifestations of this potentially fatal syndrome, as well as its prevention and therapy have been described above (see section 7).

Teratogenicity: see section 8.

Pediatric population
There is limited safety information on the use of all-trans retinoic acid in children. There have been some reports of increased toxicity in children treated with all-trans retinoic acid, particularly increased pseudotumor cerebri.

10. INTERACTIONS

As all-trans retinoid acid is metabolized by the hepatic P450 system, there is the potential for alteration of pharmacokinetics 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 cyclosporine. Post-marketing experience shows that co-administration, in particular of orally administered antimycotics of the imidazole and triazole type, can increase the toxicity of all-trans retinoic acid. Particular care is advised when combining these agents with orally administered all-trans retinoic acid. There are no data on a possible pharmacokinetic interaction between all-trans retinoic acid and daunorubicin or cytarabine.

Antifibrinolytic agents such as tranexamic acid, aminocaproic acid and aprotinin: Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with all-trans retinoic acid and antifibrinolytic agents. Therefore, caution should be exercised when administering all-trans retinoic acid concomitantly with these agents (see section 7).

Agents known to cause intracranial hypertension/pseudotumor cerebri such as tetracyclines: All-trans retinoic acid may cause intracranial hypertension/pseudotumor cerebri. Concomitant administration of all-trans retinoic acid and agents known to cause intracranial hypertension/pseudotumor cerebri as well might increase the risk of this condition (see section 7).

Contra-indicated drug associations (see section 6)

Vitamin A: As other retinoids, all-trans retinoic acid must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.

11. OVERDOSAGE

In case of overdose with all-trans retinoic acid, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear. The recommended dose in acute promyelocytic leukemia is one quarter of the maximum tolerated dose in solid tumor patients and below the maximum tolerated dose in children.

There is no specific treatment in the case of an overdose, however, it is important that the patient be treated in a special hematological unit.

12. SPECIAL REMARKS

Stability
The shelf-life is 3 years.

13. STORAGE

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture. Keep the bottle in the outer carton to protect the capsules from light.

This medicine should not be used after the expiration date (EXP) shown on the outer pack.

14. PACKS
Bottles of 100 capsules, 10 mg.
Medicine: Keep out of reach and sight of children

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