Data Sheet

Vesanoid®
Tretinoin 10mg capsules
Differentiation inducing agent

Composition

Active ingredient
All-trans retinoic acid (tretinoin).
Capsules 10 mg.

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

Appearance
Vesanoid soft gelatin capsules are oval, approximately 10mm in length and 7mm in diameter. One half of each capsule is opaque orange-yellow and the other half opaque reddish-brown.

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 haemopoietic cell lines, including human myeloid leukaemia cell lines. The mechanism of action in acute promyelocytic leukaemia (APL) is not known but 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.

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 isomerised to 13-cis retinoic acid and oxidised 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 P-450 enzyme induction which increases clearance and decreases bioavailability after oral doses.

At present, there are no data in terms of interaction between ATRA 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 will be decreased to 25 mg/m$^2$/day (see Dosage and Administration).

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**Indications and Usage**

Vesanoid should be used for induction of remission in acute promyelocytic leukaemia (APL; FAB classification AML-M3). Previously untreated patients as well as patients who relapse after or are refractory to standard chemotherapy (anthracycline and cytosine arabinoside or equivalent therapies) may be treated with tretinoin. Following complete remission, consolidation full-dose chemotherapy should be employed. The addition of chemotherapy to tretinoin improves the chance of longer survival as this combination reduces the risk of relapse as compared to chemotherapy alone. Maintenance therapy is still under investigation, however a loss of responsiveness to tretinoin has been reported among patients maintained on tretinoin alone.

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**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 paediatric 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 will 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 ATRA alone, it is not necessary to modify doses of ATRA if ATRA is used with chemotherapy.

The effect of food on the bioavailability of all-trans retinoic acid has not been characterised. 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.

### 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 Pregnancy, Nursing Mothers).

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

### Precautions

During clinical trials hyperleukocytosis has been frequently observed (75%), sometimes associated with the “Retinoic Acid Syndrome” (RAS). RAS has been reported in many APL patients (up to 25% in some clinical trials) treated with all-trans retinoic acid.

RAS is characterised by fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, oedema, weight gain, hepatic, renal and multi-organ failure.

RAS is frequently associated with hyperleukocytosis and may be fatal.

For those patients experiencing hyperleukocytosis when they receive all-trans retinoic acid alone, the RAS 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 $> 5 \times 10^9/l$ at diagnosis or at any time with a combination of all-trans retinoic acid and chemotherapy.

- Addition of full-dose chemotherapy to ATRA therapy in patients with a WBC of $< 5 \times 10^9/l$ at day 0 of the treatment with ATRA and if WBC counts become:

  $\geq 6 \times 10^9/l$ at any time from day 1 to day 6 of treatment
  and/or $\geq 10 \times 10^9/l$ at any time from day 7 to day 10 of treatment
  and/or $\geq 15 \times 10^9/l$ 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 RAS, 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 Undesirable Effects). 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 Interactions).

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 Interactions).

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 haematological/oncological diseases.

Supportive care appropriate for patients with acute promyelocytic leukaemia, for example prophylaxis for bleeding and prompt therapy for infection, should be maintained during therapy with tretinoin. The patient’s haematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

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 progesterone preparations (“minipill”) may be an inadequate method of contraception during treatment with all-trans retinoic acid.

**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 female patients of child-bearing age if each of the following conditions is met:

• She is informed by her physician of the hazards of becoming pregnant during and one month after treatment with all-trans retinoic acid.
• She 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 foetus, particularly when all-trans retinoic acid was given during the first trimester of pregnancy.

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

### Undesirable Effects

In patients treated with the recommended daily doses of all-trans retinoic acid the most frequent undesirable effects are consistent with the signs and symptoms of the hypervitaminosis A syndrome, which all-trans retinoic acid shares with other retinoids.

**Skin:** dryness, erythema and rash, pruritus, sweating, hair loss. Genital ulceration and Sweet’s syndrome have been reported uncommonly. Erythema nodosum has been reported rarely.

**Mucous membranes:** cheilitis, dryness of mouth, nose, conjunctiva and other mucous membranes, without or with inflammatory symptoms.

**Central nervous system:** headache, intracranial hypertension/pseudotumor cerebri (mainly in children), fever, shivering, dizziness, confusion, anxiety, depression, paraesthesias, insomnia, malaise.

**Neuro-sensory system:** vision and hearing disorders.

**Musculo-skeletal system:** bone pain, chest pain. Myositis has been reported rarely.

**Gastrointestinal tract:** nausea, vomiting, abdominal pain, constipation, diarrhoea, diminished appetite, pancreatitis.

**Metabolic, hepatic and renal dysfunctions:** elevation in serum triglycerides, cholesterol, transaminases (ALAT, ASAT), creatinine. Occasional cases of hypercalcaemia have been reported.

**Respiratory system:** dyspnoea, respiratory insufficiency, pleural effusion, asthma-like syndrome.

**Cardiovascular system:** arrhythmias, flushing, oedema. Cases of thrombosis (both venous and arterial) involving various sites (e.g. cerebrovascular accident, myocardial infarction, renal infarct) have been reported uncommonly (see Precautions).

**Haematologic:** Thrombocytosis has been reported rarely. Marked basophilia with or without symptomatic hyperhistaminemia has been reported rarely, mainly in patients with the rare APL variant associated with basophilic differentiation.

**Others:** Vasculitis, predominantly involving the skin, has been reported rarely.
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.

“Retinoic acid 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 Precautions).

Teratogenicity: See Pregnancy, Nursing Mothers.

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 pseudotumor cerebri.

### Interactions

As all-trans retinoid acid is metabolised 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. There are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of all-trans retinoic acid. There are no data on a possible pharmacokinetic interaction between all-trans retinoic acid and daunorubicin and AraC.

**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 anti-fibrinolytic agents. Therefore, caution should be exercised when administering all-trans retinoic acid concomitantly with these agents (see Precautions).

**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 Precautions).

**Contraindicated associated therapy (see Contraindications)**

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

### Overdosage

In case of overdosage with all-trans retinoic acid, reversible signs of hypervitaminosis A (headache, nausea, vomiting, mucocutaneous symptoms) can appear. The recommended dose in acute promyelocytic leukaemia is one-quarter of the maximum tolerated dose in solid tumour 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 haematological unit.

**Special Remarks**

**Storage**

Keep the bottle tightly closed; protect capsules from light; store below 30°C.

This medicine should not be used after the expiry date shown on the outer pack.

**Medicine Classification**

Prescription medicine.

**Packs**

Bottles of 100 capsules.

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