Vesanoid®

Tretinoin

Category

Antineoplastic agent, Retinoid for cancer treatment

1. PRODUCT DESCRIPTION

Active ingredient: Each 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 (maize)), 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 analogues. *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, 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 healthy 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.

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

All-*trans* retinoic acid is metabolised by CYP26A1 besides CYP3A4. Compounds that inhibit CYP26A1, such as ketoconazole, could result in an increase of all-*trans* retinoic acid exposure. Clinical evidence is still lacking on the relative involvement of this enzyme to the overall metabolism of all-*trans* retinoic acid.

Renal excretion of metabolites formed by oxidation and glucuronidation is a major route (60%) of elimination, while 30% is excreted in the faeces. 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.

Pharmacokinetics in special clinical 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 leukaemia (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 into two equal doses is recommended for oral administration to adult and elderly APL patients. This is approximately 8 capsules per patient per day (one capsule contains 10 mg all-*trans* retinoic acid). It is recommended to treat paediatric patients 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 weeks 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 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.

6. CONTRAINDICATIONS

Vesanoid is contraindicated for use in patients with known hypersensitivity to all-*trans* retinoic acid, other retinoids, soya, peanut or to any of the excipients listed in section 1.

All-*trans* retinoic acid is teratogenic. It is therefore contraindicated in pregnancy and in nursing mothers, unless the benefit of all-*trans* retinoic acid treatment outweighs the risks (see section 8).

The use of all-*trans* retinoic acid in combination with vitamin A, tetracyclines and retinoids is contraindicated (see section 10).

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 25% in some clinical trials) treated with all-*trans* retinoic acid.

DS is characterised by fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, oedema, 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 antifibrinolytic agents, such as tranexamic acid, aminocaproic acid or aprotinin (see section 10).

All-*trans* retinoic acid may cause intracranial hypertension/pseudotumour cerebri. The concomitant use of other agents known to cause intracranial hypertension/pseudotumour 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 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 all-*trans* retinoic acid. The patient's haematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

Psychiatric symptoms

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") may be an inadequate method of contraception during treatment with all-*trans* retinoic acid.

Vesanoid contains sorbitol; therefore, patients with rare hereditary problems of fructose intolerance should not take Vesanoid.

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 childbearing age if each of the following conditions is met:

- The patient is informed by the physician of the risks concerning pregnancy 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 childbearing 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: 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 with the signs and symptoms of the hypervitaminosis A syndrome (as for other retinoids).

Tabulated list of adverse reactions

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 hyperhistaminaemia)
Metabolism and nutrition disorders	Very common	Decreased appetite
	Not known	Hypercalcaemia
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, diarrhoea, 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.

Paediatric 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 pseudotumour cerebri.

10. 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 ciclosporin. Increased toxicity of all-*trans* retinoic acid (e.g. pseudotumour cerebri, hypercalcaemia) was reported when azole antifungals (e.g. fluconazole, voriconazole, posaconazole) were administered. This appears to be the result of a pharmacokinetic interaction mainly involving CYP3A4. Combination with other strong CYP3A4 inhibitors (protease inhibitors or macrolides, e.g. clarithromycin), may also trigger all-*trans* retinoic acid toxicity. A dose reduction of all-*trans* retinoic acid should be considered if necessary.

There are no data on a possible pharmacokinetic interaction between all-*trans* retinoic acid and daunorubicin, idarubicin 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/pseudotumour cerebri such as tetracyclines: All-*trans* retinoic acid may cause intracranial hypertension/pseudotumour cerebri. Concomitant administration of all-*trans* retinoic acid and agents known to cause intracranial hypertension/pseudotumour cerebri as well might increase the risk of this condition (see section 7).

Contraindicated 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 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.

12. 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.

13. PACKS

Bottles of 100 capsules, 10 mg.

Medicine: keep out of reach of children

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