VESANOID®

(all-trans retinoic acid / tretinoin)
Prescribing Information

INDICATIONS AND CLINICAL USE

'Vesanoid' (all-trans retinoic acid) may be used for the 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 all-trans retinoic acid. Upon achievement of complete remission, full-dose consolidation chemotherapy should be employed. Among patients maintained on all-trans retinoic acid, a loss of responsiveness to all-trans retinoic acid, has been reported, with a median time to relapse of 4-6 months.

CONTRAINDICATIONS

'Vesanoid' (all-trans retinoic acid) is highly teratogenic; therefore, it is contraindicated during pregnancy and in nursing mothers. 'Vesanoid' 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. 'Vesanoid' is contraindicated in patients with a known hypersensitivity to all-trans retinoic acid or related compounds. The use of all-trans retinoic acid in combination with vitamin A is contraindicated (see PRECAUTIONS, Drug Interactions).

WARNINGS

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

Pregnancy: All-trans retinoic acid 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 all-trans retinoic acid, irrespective of the dose or duration of the treatment. Potentially all exposed fetuses can be affected. Therapy with all-trans retinoic acid should only be started in female patients if each of the following conditions is met:

- The patient is suffering from life threatening malignancies. She is informed by her physicians of the hazards of becoming pregnant during and within one month after treatment with all-trans retinoic acid.
- She is willing to comply with the mandatory contraception measures.
- Every woman of child-bearing potential who is to undergo treatment with all-trans retinoic acid uses effective contraception for four weeks before, during and for one month after discontinuation of treatment with all-trans retinoic acid.
- Therapy should not begin until the second or third day of the next normal menstrual period.
- 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 all-trans retinoic acid or within 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.

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

Nursing Mothers: Nursing should be discontinued if therapy with all-trans retinoic acid is initiated.

"RETINOIC ACID SYNDROME": In many patients (20-25%) with acute promyelocytic leukemia (APL) treated with 'Vesanoid' (all-trans retinoic acid), a syndrome may occur characterized by some or all of the following symptoms: fever, dyspnea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, edema, weight gain, hepatic, renal and multi-organ failure (Retinoic Acid Syndrome). RAS is frequently associated with hyperleukocytosis and may be fatal. If symptoms of the "Retinoic Acid Syndrome" 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.

PRECAUTIONS

DRUG 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. There are no data to suggest that co-use with these medications increase 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 cytosine arabinoside. 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 WARNINGS). 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 WARNINGS).

CONTRAINDICATED DRUG ASSOCIATIONS (see Contraindications)
Vitamin A: As with other retinoids, all-trans retinoic acid must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.

RENAL AND HEPATIC IMPAIRMENT
The pharmacokinetics of all-trans retinoic acid in patients with compromised kidney or liver function have not been studied. As with other retinoids, the need for dosage adjustments 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.

ADVERSE REACTIONS

Symptoms of the "Retinoic Acid Syndrome" in APL have been frequently reported and may be life threatening unless treated (see WARNINGS). The safety profile of 'Vesanoid' (all-trans retinoic acid) has been evaluated retrospectively in a small number of patients.
In persons treated with the recommended daily doses of 'Vesanoid', the following adverse events were observed frequently (in about ¼ of the patients or more) 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.

The following adverse events, considered remotely, possibly or probably related to drug treatment have been reported in less than ¼ of all APL patients treated with 'Vesanoid' in the clinical trials:

Autonomic Nervous System: tachycardia, hypertension, hypotension, flushing, pallor, red extremeties.
Body as a Whole: generalized pain, abdominal distension, post traumatic pain, chest discomfort, hypothermia.
Cardiovascular System: cardiac failure, cyanosis, heart enlarged, arrhythmias. Cases of thrombosis (both venous and arterial) involving various sites (e.g. cerebrovascular accident, myocardial infarctions, renal infarct) have been reported uncommonly.
Central and Peripheral Nervous System: dizziness, confusion, intracranial hypertension, light headed feeling, flank pain, numbness of extremeties, abnormal gait, leg weakness, neurologic reaction, inguinal pain, visual field defects, hyporeflexia, paresthesia.
Dermatological: pruritus, increased sweating, alopecia, dry scalp, nasal dryness, nail disorder, photosensitivity reaction, xerophthalmia, erythemia.
Gastrointestinal: abdominal pain, diarrhea, constipation, blisters in the mouth, stomach upset, dysphagia, buccal mucosa ulceration, stomatitis, flatulence, ulcer, pancreatitis, diminished appetite.
Metabolic and Nutritional Disorders: weight changes, edema of extremities, acidosis, gout, dehydration, fluid overload, moonface, elevation in serum creatinine.
Musculoskeletal: musculoskeletal pain.
Platelet, Bleeding & Clotting: disseminated intravascular coagulation (DIC), nosebleed and other bleeding disorders, thrombosis.
Psychiatric: generalized weakness, anxiety, lethargy, depression, malaise, insomnia, anorexia, agitation, forgetfulness.
Resistance Mechanism Disorders: infection, septicemia, moniliasis.
Respiratory System: pleural effusion, nasal congestion, pharyngitis, rale, respiratory insufficiency, asthma-like syndrome, pneumonia, respiratory distress, tachypnea, pharynx irritation, pulmonary infiltration, hypoxia, sinusitis, bronchial asthma.
Special Senses: blurred vision, visual disturbance, photophobia, conjunctivitis, decreased vision, changes in visual acuity, ear fullness, earache, ear buzzing.
Urinary System: dysuria, kidney failure, urinary tract infection, micturition frequency, renal insufficiency, cystitis.
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.

POST-MARKETING EXPERIENCE:
Metabolic and Nutritional Disorders: Occasional cases of hypercalcemia have been reported.
Dermatological: Sweet's syndrome has been reported uncommonly. Erythema nodosum has been reported rarely.
Hematologic: 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.
Musculoskeletal: Myositis has been reported rarely.
Others: Vasculitis, predominantly involving the skin has been reported rarely. 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 tretinoin, particularly increased pseudotumor cerebri.

DOSAGE AND ADMINISTRATION

A total daily dose of 45 mg/m2 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. It is recommended that pediatric patients be treated with 45mg/m2 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. 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-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 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
In cases 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.

AVAILABILITY OF DOSAGE FORMS

'Vesanoid' (all-trans retinoic acid) capsules are available in bottles of 100 capsules.