NEW ZEALAND DATA SHEET

VESANOID® 10mg liquid filled capsule

Tretinoin

1 PRODUCT NAME

VESANOID® 10mg liquid filled capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

All-trans retinoic acid (tretinoin, ATRA) 10mg per capsule.

Excipients with known effect:

Soybean oil.

Sorbitol.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Dose and method of administration

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

Special populations

Renal and Hepatic impairment: 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.

Paediatric population

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.

Method of administration

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.

4.3 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 4.6).

The use of all-trans retinoic acid in combination with vitamin A is contraindicated (see Section 4.5).

4.4 Special warnings and precautions for use

Hyperleukocytosis and Retinoid Acid Syndrome (RAS)

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.

Risk of thrombosis

There is a risk of thrombosis (both venous and arterial) which may involve any organ system, during the first month of treatment (see Section 4.8). 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 4.5).

Intracranial hypertension/pseudotumor cerebri

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 4.5).

Patients with APL

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.

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.

Women of childbearing age

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

4.5 Interaction with other medicines and other forms of interaction

Inducers/Inhibitors of Hepatic P450 enzymes

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. 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 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 Section 4.4).

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 4.4).

Contraindicated associated therapy (see Section 4.3)

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.

***Antifungal agents such as posaconazole, voriconazole, ketoconazole and itraconazole*:**

As all-trans retinoic acid (ATRA) is metabolised by the hepatic cytochrome P450 enzymes, notably CYP3A4, concomitant administration with strong inhibitors of CYP3A4, including posaconazole, may lead to increased exposure to tretinoin resulting in an increased toxicity (especially hypercalcaemia). Serum calcium levels should be monitored and, if needed, appropriate dose adjustments of tretinoin should be considered during the treatment with CYP3A4 inhibitors like posaconazole, and during the following days after treatment.

4.6 Fertility, pregnancy and lactation

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 (also see Section 4.4).
- 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.

Breastfeeding

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

Fertility

There are no data available in humans.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile

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 (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 hyperhistaminemia)
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, pseudotumor 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 (formerly known as retinoic acid syndrome) may be fatal and is characterised by fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural and pericardial effusions, hypotension, edema, weight gain, hepatic, renal and multi-organ failure. Retinoic acid syndrome is frequently associated with hyperleukocytosis. For prevention and treatment of retinoic acid syndrome see Section 4.4.

Leukocytosis/hyperleukocytosis are frequent adverse effects associated with all-trans retinoic acid therapy of APL and may be accompanied by differentiation syndrome. However, most cases of leukocytosis/hyperleukocytosis are not associated with a differentiation syndrome.

Teratogenicity: See Section 4.6.

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 pseudotumor cerebri (see Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Retinoids for cancer treatment, ATC code: L01XF01

Mechanism of action

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.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

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.

Biotransformation

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.

Elimination

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.

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 Section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of 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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years. This medicine should not be used after the expiry date shown on the outer pack.

6.4 Special precautions for storage
Keep the bottle tightly closed; protect capsules from light; store below 30°C.

6.5 Nature and contents of container
Bottles of 100 capsules.

6.6 Special precautions for disposal
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription medicine.

8 SPONSOR
Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL
21 April 1994

10 DATE OF REVISION OF THE TEXT
31 March 2026

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Addition of safety information regarding interaction with antifungal agents such as posaconazole, voriconazole, ketoconazole and itraconazole.
4.8 and 4.9	Update to link for reporting adverse reactions and addition of wording for overdose