AUSTRALIAN PRODUCT INFORMATION – VESANOID (TRETINOIN) CAPSULES

1 NAME OF THE MEDICINE

Tretinoin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VESANOID capsule contains 10mg of tretinoin. Excipients of known effect: soya bean products.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

VESANOID is available as oval, soft gelatin capsules containing 10 mg of tretinoin; 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 (daunorubicin and cytosine arabinoside (ARA-C) or equivalent therapies) may be treated with VESANOID. Following complete remission, consolidation full-dose chemotherapy should be employed. A loss of responsiveness to VESANOID has been reported among patients maintained on VESANOID. The median time to relapse for patients maintained on VESANOID is 4 to 6 months.

4.2 DOSE AND METHOD OF ADMINISTRATION

A total daily dose of 45 mg/m^2 body surface area, divided in two equal doses, is recommended for oral administration to APL patients. This is approximately 8 capsules per patient per day. Data on the correct dose for paediatric, geriatric, renally and hepatically impaired patients are limited. A dose of 45 mg/m^2 may be given, and a dose reduction should be considered if severe toxicity occurs. Dose reduction should be particularly considered for children with intractable headache. Treatment should be continued for 30 to 120 days except when the disease progresses; 84% of responding patients achieve CR by 90 days. After complete remission, a standard course of consolidation chemotherapy should be initiated immediately; for example, three 7-day courses of daunorubicin and cytosine arabinoside, in 5 to 6 week intervals. This treatment is subject to change with improvements in medical practice.

4.3 CONTRAINDICATIONS

Tretinoin is highly teratogenic; it is strictly contraindicated in pregnancy. 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. Breast-feeding should be discontinued if therapy with VESANOID is initiated.

VESANOID is contraindicated for use in patients with known hypersensitivity to VESANOID or any of its components.

The use of VESANOID in combination with Vitamin A is contraindicated (see 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 VESANOID (RA-APL syndrome). This syndrome is characterised by fever, dyspnoea, shortness of breath, acute respiratory distress, pulmonary infiltrates, hyperleukocytosis, hypotension, pleural and pericardial effusions, oedema, weight gain, hepatic, renal and multiorgan failure. Untreated, this syndrome can be fatal. The RA-APL syndrome may occur with and without leukocytosis. Prevention of RAS may be achieved by administration of full dose chemotherapy in combination with VESANOID, if significant elevation of leukocyte count is observed. The role of corticosteroids in preventing RAS is not established.

The current recommendations for treating hyperleukocytosis with or without RAS are as follows:

- immediate treatment with a combination of VESANOID and full-dose chemotherapy for patients presenting with a WBC count of $> 5 \times 10^9$/L at any time,
- addition of full-dose chemotherapy to VESANOID therapy in the case of rapidly evolving leukocytosis in a leukopenic patient (WBC $< 5 \times 10^9$/L) at diagnosis/initiation of treatment. Rapidly evolving leukocytosis is defined as a WBC count of $\geq 6 \times 10^9$/L at any time from day 1 to day 6 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 3 days or until resolution of the symptoms) if the patient presents early clinical signs of the syndrome.

There is a risk of thrombosis (both venous and arterial), which may involve any organ system, during the first month of treatment. Therefore, caution should be exercised when treating patients with antifibrinolytic agents (see 4.5 Interactions with other medicines and other forms of interactions).

VESANOID 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. Current treatment guidelines for APL should be consulted before use of VESANOID.

Supportive care appropriate for patients with acute promyelocytic leukaemia (e.g. prophylaxis for bleeding and prompt therapy for infection) should be maintained during therapy with VESANOID. The patient's haematologic profile, coagulation profile, liver function, 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 tretinoin. 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.

VESANOID 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 4.5 Interactions with other medicines and other forms of interactions).

Micro-dosed progesterone preparations ("minipill") may be an inadequate method of contraception during treatment with VESANOID (see 4.6 Fertility, pregnancy and lactation Use in pregnancy – Pregnancy Category X).

Use in hepatic impairment

The requirement for dosage adjustment in patients with liver dysfunction has not been investigated.

Use in renal impairment

The requirement for dosage adjustment in patients with kidney dysfunction has not been investigated.

Use in the elderly

There are limited clinical data on the use of VESANOID in the elderly.

Paediatric use

There are limited clinical data on the use of VESANOID in children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs affecting the hepatic cytochrome P450 enzyme system function may interact with VESANOID, leading to a change of blood levels. 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 tretinoin. Particular care is advised when combining these agents with orally administered tretinoin.

In 13 patients who had received daily doses of tretinoin for 4 consecutive weeks, administration of ketoconazole (400 to 1200 mg oral dose) 1 hour prior to the administration of the tretinoin dose on day 29 led to a 72% increase (218 ± 224 vs 375 ± 285 ng·h/mL) in tretinoin mean plasma AUC. The precise cytochrome P450 enzymes involved in these interactions have not been specified; CYP3A4, 2C8 and 2E have been implicated in various preliminary reports. Similar effects have been demonstrated with the related azole drugs fluconazole and liarozole. In patients receiving VESANOID therapy, concomitant use of potent inhibitors or inducers of the cytochrome P450 enzyme system should be avoided if possible.

Antifibrinolytic agents such as tranexamic acid, aminocaproic acid and aprotinin: Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with VESANOID and anti-fibrinolytic agents. Therefore, caution should be exercised when administering VESANOID concomitantly with these agents.

Tetracyclines: Systemic treatment with retinoids may cause elevation of intracranial pressure/pseudotumour cerebri. Since tetracyclines may also cause elevation of intracranial pressure/pseudotumour cerebri, patients treated with VESANOID and tetracyclines at the same time might be at a greater risk of experiencing this condition.

Vitamin A: As with other retinoids, VESANOID must not be administered in combination with Vitamin A because the combination may cause or exacerbate symptoms of hypervitaminosis A.

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

Effects on fertility

Effects on fertility and reproductive performance have not yet been investigated in adequate nonclinical studies. In a 6-week toxicology study in dogs, minimal to marked testicular degeneration, with increased numbers of immature spermatozoa, were observed at ≥ 2 mg/kg/day (about 3 times the equivalent human dose based on AUC).

Use in pregnancy – Pregnancy Category X

Pregnancy: VESANOID 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 VESANOID in any amount even for short periods.

Potentially, all exposed foetuses can be affected. Therapy with VESANOID 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 one month after treatment with VESANOID,

- she is capable of complying with the mandatory contraception measures,
- it is absolutely essential that every woman of child-bearing potential who is to undergo treatment with VESANOID uses effective contraception for four weeks before, during and for one month after discontinuation of treatment with VESANOID,
- 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. Pregnancy tests must be performed at monthly intervals during therapy.

Should pregnancy occur, in spite of these precautions, during treatment with VESANOID or up to one month after its discontinuation, there is a high risk of severe malformation of the foetus particularly if VESANOID was taken 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.

Use in lactation

Breast-feeding should be discontinued if therapy with VESANOID is initiated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The ability to drive or operate machinery may be impaired in patients treated with VESANOID, particularly if they experience dizziness or severe headache.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In patients treated with the recommended daily doses of tretinoin, the following undesirable effects frequently occur: xeroderma, mouth dryness, cheilitis, rash, oedema, nausea, vomiting and bone pain. Also headache, elevation in serum triglycerides, cholesterol, transaminases (ALT, AST) and creatinine may occur. Occasional cases of hypercalcaemia have been reported.

In addition, the following undesirable effects have been reported at a frequency of greater than 5% in APL patients during clinical trials. These effects were judged by clinical investigators to be possibly or probably related to drug treatment.

- *dermatological effects*: erythema, pruritus, increased sweating, cellulitis, alopecia, dry mucosa (e.g. nose, conjunctiva - with or without inflammatory symptoms), skin exfoliation, dermal bleeding, xerophthalmia, dermatitis, hair loss, genital ulceration has been reported infrequently;
- *gastrointestinal effects*: abdominal pain, diarrhoea, constipation, blisters in the mouth, stomach upset, decreased appetite, pancreatitis;
- *cardiovascular effects*: cardiac arrhythmia, flushing, cases of thrombosis (both venous and arterial) involving various sites including cerebrovascular accident, myocardial infarction and renal infarction (uncommon) have also been reported (see 4.4 Special warnings and precautions for use), myocarditis, pericarditis;
- *respiratory effects*: coughing, pleural effusion, nasal congestion, dyspnoea, pharyngitis, respiratory insufficiency or distress, rales and wheezing;
- *central nervous system effects*: dizziness, confusion, intracranial hypertension/pseudotumour cerebri (mainly in children), anxiety, depression, paraesthesias, insomnia;
- *neurosensory effects*: vision and hearing disorders;
- *other effect*s: fever, shivering, fatigue, malaise, weight changes, back and musculoskeletal pain, chest pain, bleeding disorders, pneumonia, infection and septicaemia, generalised weakness and lethargy.

Post-Marketing Experience

Dermatological effects: Sweet's Syndrome has been reported uncommonly. Erythema nodosum has been reported rarely.

Musculo-skeletal system: Myositis has been reported rarely.

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.

Reproductive system and breast disorders: Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia.

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

Based on the information presently available, these undesirable effects do not represent a permanent or irreversible hazard, but it may be advisable to interrupt or discontinue the therapy, depending on the alternative options available to the patient.

The long-term safety of tretinoin has not been established in clinical trials.

Symptoms of the "Retinoic Acid Syndrome" in APL patients have been frequently reported and may be life threatening unless treated (see 4.4 Special warnings and precautions for use).

VESANOID is teratogenic (see 4.4 Special warnings and precautions for use Use in pregnancy – Pregnancy Category X, Use in lactation).

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 an increased incidence of pseudotumour cerebri.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Cases of acute overdosage with tretinoin have not been reported. Cases of overdose would be expected to show largely reversible effects characteristic of hypervitaminosis A. The recommended dose 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 hematological unit.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tretinoin is a natural metabolite of retinol and belongs to the class of compounds known as retinoids, which are structurally related to Vitamin A and comprise natural and synthetic analogs. In vitro studies with tretinoin have demonstrated induction of differentiation and

inhibition of cell proliferation in transformed haemopoietic cell lines, including human myeloid leukaemia cell lines.

The majority of acute promyelocytic leukaemia (APL) cases are associated with a non-random chromosomal abnormality characterised by balanced and reciprocal translocations between the long arms of chromosomes 15 and 17 [t(15;17)(q22;q21)]. The gene encoding the retinoic acid receptor-alpha (RAR-α) is located on chromosome 17. A promyelocytic leukaemia gene (PML), that appears to code for a transcription factor, is located on chromosome 15. The 15;17 translocation fuses the genes for PML and RAR-α, resulting in the synthesis of a chimeric fusion transcript, PML/RAR-α. In rare cases, alternative fusion genes to PML may be found. In addition to the APL causing chromosomal translocation, additional chromosomal abnormalities have been described in approximately 25% of patients with APL. The PML/RAR-α fusion protein appears to inhibit the differentiation of myeloid cells, resulting in leukaemogenesis, an effect which may be overcome by the use of high doses of tretinoin. Orally administered tretinoin induces a high rate of molecular and clinical remission (CR) in patients with t(15;17) APL. Patients who fail to respond to tretinoin therapy may have APL caused by a rare genotype.

Relapse (secondary acquired resistance) to tretinoin may have a pharmacokinetic component (see below) but more recent evidence points to molecular disturbances in APL cells as the predominant factor. The detection of the PML/RAR-α fusion protein by reverse transcriptase polymerase chain reaction (RT-PCR) in the presence of clinical (morphological) remission after treatment is indicative of minimal residual disease and therefore the prognosis is one of ultimate clinical relapse.

Clinical trials

APL is a rare disease thus making clinical trials difficult which contributes to the lack of clinical data. VESANOID has been investigated in 140 APL patients entered into four open-label, uncontrolled studies: three single investigator studies and one compassionate plea study conducted by the US National Cancer Institute (NCI) with 56 physicians participating. The overall frequency of induction into CR (complete remission) ranged from 62% to 90% in single investigator studies whereas response rates were lower in the compassionate trial population (47%). The two main reasons for this lower response rate were a high early death rate in this much sicker patient group and a high proportion of patients resistant to VESANOID treatment. The median time to CR as analysed by survival methodology ranged from 41 to 69 days with the longest time being 109 days with 84% of the responding patients achieving CR by 90 days.

5.2 PHARMACOKINETIC PROPERTIES

Tretinoin is an endogenous metabolite of Vitamin A and is normally present in plasma. The physiological levels of tretinoin appear largely independent of a normal dietary range of intake of Vitamin A (in contrast to blood levels of some other retinol metabolites) but exhibit a diurnal pattern, may decrease with fasting, surgical caloric restriction or disease (but not APL) and may increase with excessive intake of liver or Vitamin A supplements. The

physiological, diurnal levels of tretinoin in one detailed study in female, healthy subjects (C_{max} 5.3 ± 0.93 nmol/L [1.6 ± 0.28 ng/mL], C_{min} 3.3 ± 0.48 nmol/L [0.99 ± 0.14 ng/mL]; mean ± SD; N=35 women, 18-40 years) are representative. One study indicates that physiological tretinoin levels in healthy men are significantly lower (about 25%) than in women.

Oral doses of VESANOID are well absorbed and maximum plasma concentrations in normal volunteers are attained after 3-4 hours but may be earlier (after 1-3 hours) in patients with APL. There is a large interpatient and intrapatient variation in absorption of VESANOID. In plasma, tretinoin is extensively bound to plasma proteins. Plasma concentrations decline with a mean elimination half-life of about 0.7 hours and return to endogenous levels following a single dose after 7-12 hours. No accumulation is seen after multiple doses and tretinoin is not retained in body tissues. Renal excretion of metabolites formed by oxidation and glucuronidation is a major route (60%) of elimination. Tretinoin is isomerised to 13-cis-retinoic acid (isotretinoin) and 9-cis-retinoic acid and oxidised to 4-oxo-metabolites. These metabolites have longer half-lives than tretinoin.

During multiple doses a marked decrease in plasma concentration can occur, possibly due to cytochrome P450 enzyme induction, which increases clearance and decreases bioavailability after oral doses. A therapeutic dose of 45 mg/m^2 per day VESANOID in equal divided doses given to 13 healthy men and women for 15 days yielded a C_{max} of 1693 ± 717 nmol/L [508 ± 215 ng/mL] for the first dose on Day 1 and 1253 ± 1180 nmol/L [376 ± 354 ng/mL] on Day 15; the $AUC_{0-\infty}$ decreased by 31.8%. Increasing the dose 2 fold or administration of cytochrome P450 inhibitors, such as ketoconazole, does not persistently overcome the reduced plasma levels accompanying continuous treatment but a break in treatment of 7 days briefly restores first dose conditions. Pharmacokinetic data from several small studies in a variety of cancer patients and with VESANOID doses ranging from 12.5 mg/m^2 to > 300 mg/m^2 suggest a weak relationship between dose and Cmax and a dominant effect of interpatient variability. The therapeutic studies which established the efficacy of VESANOID induction treatment in APL were conducted with continuous treatment and the recommended dose of 45 mg/m^2 per day in equal divided doses. When taken with food, the oral absorption of tretinoin is expected to increase, as has been observed with other retinoids. The influence of food on the bioavailability of VESANOID has not been investigated.

Pharmacokinetics in special populations

Paediatric patients.

Limited pharmacokinetic data are available for administration of oral VESANOID to children covering single doses ranging from 7 mg/m^2 to 40 mg/m^2 in patients with APL or a variety of other tumours. No striking differences from adult pharmacokinetics are apparent.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tretinoin did not reveal any genotoxic potential in a series of assays for gene mutations (Ames test, chinese hamster lung cells). A two-fold increase in the sister chromatid exchange (SCE) has been demonstrated in human diploid fibroblasts, but other chromosome aberration assays (human lymphocytes *in vitro*, mouse micronucleus test *in vivo*) did not show a clastogenic or aneuploidogenic effect.

Carcinogenicity

No long-term carcinogenicity studies with tretinoin have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsule contents are yellow beeswax, hydrogenated soya oil, partially hydrogenated soya oil, and soya oil. The capsule shell contains gelatin, glycerol, Karion 83 (ARTG PI: 1854), titanium dioxide, iron oxide yellow and iron oxide red, purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

Bottles of 100.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

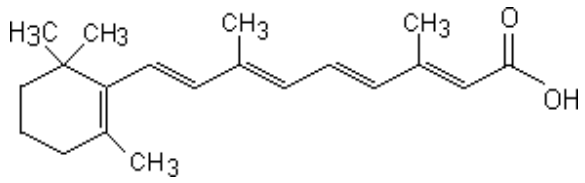
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemically, tretinoin is 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8-all-trans-retinoic acid. The molecular formula is $C_{20}H_{28}O_2$. The molecular weight is 300.4. Tretinoin is a yellow to light orange powder with very low solubility in water. It is very

sensitive to light and oxygen. Tretinoin (all-trans retinoic acid; ATRA) is a well known chemical substance described in all international pharmacopoeia.

Chemical structure



CAS number:

302-79-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

01 November 1995

10 DATE OF REVISION

28 April 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Minor editorial change (to P450) and new subsection to add information regarding interaction with antifungal agents such as posaconazole, voriconazole, ketoconazole and itraconazole.