AUSTRALIAN PRODUCT INFORMATION – ZETIN (acitretin) CAPSULES

1 NAME OF THE MEDICINE

Acitretin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZETIN (acitretin) is a retinoid for the oral treatment of severe cases of psoriasis and disorders of keratinisation. It is available in 10 and 25 mg capsules.

For full list of excipients, see section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

ZETIN hard gelatin capsule is intended for oral administration.

ZETIN 10 mg capsule: Hard gelatin capsule containing a yellow powder with a white to off-white body and a brown cap printed in black with “A10” on the capsule body.

ZETIN 25 mg capsule: Hard gelatin capsule containing a yellow powder with a yellow to light yellow body and a brown cap printed in black with “A25” on the capsule body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZETIN (acitretin) may be used for the treatment of:

- Severe intractable psoriasis in all its forms
- Severe forms of disorders of keratinisation such as:
    - hyperkeratosis palmaris et plantaris
    - pustulosis palmaris et plantaris
    - ichthyosis
    - keratosis follicularis (Darier's disease)
    - lichen planus affecting the skin or the mucosae
    - pityriasis rubra pilaris

4.2 DOSE AND METHOD OF ADMINISTRATION

ZETIN should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.

Adults

Because there are differences in the absorption and rate of metabolism of acitretin, the dosage must be individually adjusted. The capsules should be taken preferably once daily with meals, or with milk.

An initial dosage of 25 mg or 30 mg for about two to four weeks may give satisfactory therapeutic results.

The maintenance dose must be based on clinical efficacy and tolerance. In general, a daily dosage of 25 - 50 mg taken for a further six to eight weeks achieves optimal therapeutic results.

Therapy can be terminated in patients with psoriasis whose lesions have resolved sufficiently. Relapses should be treated as described above.

In disorders of keratinisation, a continuous maintenance is mostly needed with the dose at the lowest possible level. This may be less than 20 mg and should not exceed 50 mg daily.

Children

In view of possible severe side effects associated with long-term treatment, the risk should be carefully weighed against the therapeutic benefit. Acitretin should be used only when all alternative therapies have provided inadequate. The dosage should be established on a weight basis. The daily dosage is about 0.5 mg/kg. Higher doses up to 1 mg/kg or 35 mg daily may be necessary in some cases for limited periods. Maintenance doses should be kept as low as possible in view of possible long term adverse effects.

Combined Treatment

When ZETIN is used in combination with other types of therapy, it may be possible, depending on the patient's individual response, to reduce the dosage of ZETIN (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Standard topical treatments can generally be continued and do not interfere with ZETIN.

4.3 CONTRAINDICATIONS

ZETIN (acitretin) is strictly contraindicated in:

- Pregnant women
- Women of childbearing potential unless all of the other conditions of the Pregnancy Prevention Program are met

ZETIN (acitretin) is highly teratogenic and must not be used by patients who are pregnant or who intend to become pregnant during therapy or for 3 years after cessation of therapy.

ZETIN is also contraindicated in people who are hypersensitive to acitretin or other ingredients in ZETIN or to other retinoids.

Women of childbearing potential must not receive blood from patients being treated with acitretin. Donation of blood by a patient being treated with acitretin is prohibited during and for three years after completion of treatment with acitretin.

ZETIN (acitretin) is contraindicated while breast feeding.

ZETIN (acitretin) is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values.

Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated.

An increased risk of hepatitis has been reported to result from combined use of methotrexate and Tigason® (active ingredient: etretinate). Consequently, the combination of methotrexate with acitretin is also contraindicated.

Concomitant administration of acitretin and vitamin A or other retinoids is contraindicated due to the risk of hypervitaminosis A.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Pregnancy Prevention Program

This medicinal product is TERATOGENIC.

Acitretin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Program are met:

- She has severe forms of psoriasis (erythrodermic psoriasis, local or generalized pustular psoriasis) or severe keratinization disorders (congenital ichthyosis, pityriasis rubra pilaris, Darier's disease, other disorders of keratinization which may be resistant to other therapies) (see 4.1 THERAPEUTIC INDICATIONS).
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 3 years after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

- Even if she has amenorrhea she must follow all the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment (see 4.6 FERTILITY, PREGNANCY AND LACTATION)
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of acitretin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 3 years after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with acitretin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the foetus. This risk persists until the product has been completely eliminated, which is within 3 years following the end of treatment.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 3 years after stopping treatment with acitretin, even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing

According to local practice, medically supervised pregnancy tests are recommended to be performed, as follows:

Prior to starting therapy

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with acitretin.

Follow-up visits

Follow-up visits should be arranged at regular intervals, ideally monthly. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

Women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of acitretin should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of acitretin should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male Patients

For male patients treated with acitretin, available data, based on the level of maternal exposure from the semen and seminal fluid indicate a minimal, if any, risk of teratogenic effects.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 3 years following discontinuation of acitretin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to acitretin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of acitretin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Psychiatric disorders

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including acitretin. 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.

Use in diabetes

In diabetics, retinoids can either improve or worsen glucose tolerance. Blood sugar levels must therefore be checked more frequently than usual in the early stages of treatment.

Pseudotumour cerebri

Acitretin and other retinoids administered orally have been associated with cases of pseudotumour cerebri (benign intracranial hypertension). Early signs and symptoms include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these signs and symptoms should be examined for papilloedema and, if present, should discontinue acitretin immediately and be referred for neurologic evaluation and care.

Hyperostosis

In clinical trials with acitretin, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column. Of 262 patients treated with acitretin, 7% had pre-existing abnormalities of the spine, which showed new changes or progression of pre-existing findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, and narrowing and destruction of a cervical disc space. These existing abnormalities may be in some part attributable to the underlying psoriasis and/or the patient's age. No bone changes were seen in patients who had normal pre-treatment X-rays. A substantially higher incidence of hyperostosis has been observed with oral administration of other retinoids also involving patients without pre-existing abnormalities of the spine. Maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic lesions and in extraskeletal calcification, as has been observed in long-term systemic treatment with retinoids.

In adults receiving long-term treatment with acitretin, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If such disorders arise, the continuation of therapy should be discussed with the patient on the basis of a careful risk/benefit analysis.

General

Patients should be advised that a transient increase in psoriasis is sometimes seen during the initial treatment period.

Patients with severe headache, nausea, vomiting, and visual disturbances should discontinue acitretin immediately and be referred for neurologic evaluation and care.

Patients should be advised that they may experience decreased tolerance to contact lenses during the initial treatment period.

Donation of blood by a patient being treated with acitretin is prohibited during and for three years after completion of treatment with acitretin.

It should be emphasized that, at the present time, not all the consequences of life-long administration of acitretin are known.

For male patients treated with acitretin, available data, based on the level of maternal exposure from the semen and seminal fluid indicate a minimal, if any, risk of teratogenic effects.

Use in hepatic impairment

Elevated transaminase and alkaline phosphatase levels have been noted in a number of patients receiving acitretin. Several cases of hepatitis have been noted in association with etretinate.

Hepatic function should be monitored before and every one to two weeks for the first two months after starting treatment with acitretin and then every three months during treatment. If pathological values for hepatic function are found, monitoring should be repeated at weekly intervals. If hepatotoxicity is suspected during acitretin treatment, the drug must be discontinued and the aetiology further investigated. In such cases it is advisable to continue monitoring hepatic function for at least 3 months.

Use in renal impairment

See section 5.2 PHARMACOKINETIC PROPERTIES – Special populations.

Paediatric use

Skeletal changes in premature epiphysial ossification are seen in young animals treated with etretinate. These effects have not been observed in man but only a limited number of children have been studied. Because of the uncertain effects of acitretin on growth and skeletal development, the drug should only be used in those under 18 in the following situations: life-threatening circumstances where other therapy cannot be used or is not effective; and in severe forms of the disorder for which there is no alternative therapy. Growth parameters and bone development must be closely monitored in all patients on long-term therapy, by regular measurement and X-ray.

In view of possible severe adverse effects associated with long-term treatment, the risk should be carefully weighed against the therapeutic benefit. Acitretin should be used only when alternative therapies have been exhausted.

Use in the elderly

See section 5.2 PHARMACOKINETIC PROPERTIES – Special populations.

Effects on laboratory tests

Lipids

Blood lipid determinations should be performed before acitretin is administered and again at intervals of one to two weeks until the lipid response to the drug is established, which is usually within four to eight weeks. Approximately 65% of patients receiving acitretin during clinical trials experienced an elevation in triglycerides. Approximately 30% developed a decrease in high density lipoproteins (HDL). The mean cholesterol level of the study population rose slightly with time but never exceeded the normal range, although some individual patients did exceed the normal range. These effects of acitretin were reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridaemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions.

Hypertriglyceridaemia and lowered HDL may increase a patient's cardiovascular risk status. Therefore, every attempt should be made to control significant elevations of triglycerides or HDL decreases by reduction of weight or restriction of dietary fat and alcohol intake while continuing acitretin therapy. Acitretin treatment should be discontinued in case of uncontrolled levels of hypertriglyceridemia or if symptoms of pancreatitis occur.

Serum cholesterol and serum triglycerides (fasting values) must be monitored, before starting treatment, one month after the commencement and then every 3 months during treatment, especially in high-risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism) and during long-term treatment. During treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these conditions persist.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Preliminary studies indicated that acitretin does not interfere with the actions of oestrogen-progesterone oral contraceptives. In a study of ten healthy male volunteers, acitretin did not interfere with the hypoprothrombinemic effect of the coumarin-type anticoagulant, phenprocoumon. Progestogen-only oral contraceptives (“Minipills”) should be avoided as a contraceptive measure because their efficacy may be reduced by retinoid treatment.

Concomitant administration of vitamin A and other retinoids must be avoided because of the risk of hypervitaminosis A. (see 4.3 CONTRAINDICATIONS).

Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction.

Methotrexate, tetracyclines (see 4.3 CONTRAINDICATIONS).

In a study of twelve healthy male subjects, the concomitant administration of digoxin and acitretin did not alter the pharmacokinetics of either drug. In a study of ten healthy men, the concomitant administration of cimetidine and acitretin did not alter the pharmacokinetics of either drug.

Further interactions between acitretin and other substances (e.g. digoxin, cimetidine, combined estrogen/progestogen oral contraceptives) have not been observed so far.

In concurrent treatment with phenytoin, it must be remembered that acitretin partially reduces the protein binding of phenytoin.

Concomitant administration of alcohol may cause increased levels of etretinate, which is much slower than acitretin to be eliminated from the body. Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol. In a 2-way crossover study, all 10 subjects formed etretinate with concurrent ingestion of a single 100 mg oral dose of acitretin during a 3 hour period of ethanol ingestion (total ethanol ~1.4 g/kg body weight). A mean peak etretinate concentration of 59 ng/mL (range: 22 - 105 ng/mL) was observed and extrapolation of AUC values indicated that the formation of etretinate in this study was comparable to a single 5 mg oral dose of etretinate. Ethanol must not be ingested during treatment with acitretin by women of childbearing age, as clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol. This result was also observed *in vitro*. The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible. Ethanol should be avoided for two months after cessation of acitretin therapy.

NOTE:

In a study with healthy volunteers, concurrent intake of a single dose of acitretin together with ethanol led to the formation of etretinate. This was already observed *in vitro*. In recent investigations, the formation of etretinate has also been observed in certain patients treated with acitretin. Until this phenomenon has been fully explained, the pharmacokinetic behaviour of etretinate must be taken into account. Therefore, since the elimination half-life of etretinate is approximately 120 days, contraceptive measures must be taken for 3 years after completion of acitretin treatment.

There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, phenprocoumon, oral contraceptives or glyburide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Full patient information as specified in the Pregnancy Prevention Program about the tetratogenic risk and the strict pregnancy prevention measures should be given by the physician to all patients, both male and female.

Acitretin should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.

See Section 4.6 USE IN PREGNANCY for further information.

Use in pregnancy (Category X)

Acitretin must not be used by females who are pregnant or who may become pregnant while undergoing treatment. Acitretin is highly teratogenic. Its use is contraindicated in pregnant women and women who might become pregnant during or within 3 years of the cessation of treatment. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage. Foetal exposure to acitretin always involves a risk of congenital malformation.

Acitretin is contraindicated in women of childbearing potential unless the patient meets all of the following conditions:

- has severe psoriasis or disorder of keratinisation
- is unresponsive to or intolerant of standard non-teratogenic therapies
- is reliable in understanding and carrying out instructions
- is capable of complying with the mandatory contraceptive measures
- it is absolutely essential that every woman of childbearing potential who is to undergo treatment with acitretin uses effective contraception (preferably 2 complementary methods) without interruption for four weeks before, during and for 3 years after the discontinuation of treatment with acitretin. Primary contraceptive method is a combination hormonal contraceptive product or an intrauterine device and it is recommended that a condom or diaphragm (cap) is also used. Low dose progesterone-only products (minipills) are not recommended due to indications of possible interference with their contraceptive effect.
- has received both oral and written warnings of the hazards of foetal exposure to acitretin and the risk of possible contraception failure and the possible consequences if pregnancy occurs during the course of treatment with acitretin or within 3 years of discontinuing therapy and has acknowledged her understanding of these warnings.
- has had a negative serum or urine pregnancy test (minimum sensitivity of 25mlU/mL) must be obtained up to three days before the first dose is given. During therapy, pregnancy tests should be arranged at 28-day intervals. A negative pregnancy test not older than 3 days is mandatory before prescription is made at these visits. After stopping therapy, pregnancy tests should be performed at 1-3 monthly intervals for a period of 3 years after the last dose is given.
- will begin therapy only on the second or third day of the next normal menstrual period.
- must avoid alcohol consumption (in food, drinks and medicine) during treatment and for 2 months after stopping treatment.

It is recommended that a prescription should not be issued until a report of a negative pregnancy test has been obtained and the patient has begun her menstrual period. It is also recommended that additional pregnancy tests are performed at monthly intervals during therapy and at 1-3 monthly intervals after stopping therapy. Acitretin is a metabolite of etretinate. Major human foetal abnormalities related to etretinate administration have been reported, including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray. Fatalities related to some of these malformations have been reported.

It is absolutely essential that every woman of childbearing potential who is to undergo treatment with acitretin uses effective contraception (preferably 2 complementary methods) must be used for at least one month before beginning acitretin therapy, throughout therapy and for three years following discontinuation of therapy. The same effective and uninterrupted contraceptive measures must be taken every time therapy is repeated, however long the intervening period may have been, and must be continued for 3 years afterwards.

The formation of etretinate has been observed in certain patients treated with acitretin. Until this phenomenon has been fully explained, the pharmacokinetic behaviour of etretinate must be taken into account. Since the elimination half-life of etretinate is approximately 120 days, contraceptive measures must be taken for three years following discontinuation of therapy even where there has been a history of infertility, unless due to hysterectomy.

Women who have taken Tigason® (etretinate) must continue to follow the contraceptive recommendations for Tigason®.

Should pregnancy occur, in spite of these precautions, there is a high risk of severe malformation of the foetus (e.g. craniofacial defects, cardiac and vascular or CNS malformations, skeletal and thymic defects) and the incidence of spontaneous abortion is increased. The risk applies especially during treatment with acitretin and 2 months after treatment. For up to 3 years after acitretin discontinuation, the risk is lower (particularly in women who have not consumed alcohol) but cannot be entirely excluded (due to possible formation of etretinate).

Use in lactation.

Acitretin must not be given to nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Decreased night vision has been reported with acitretin therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects are seen in most patients receiving acitretin. However, they usually disappear when the dosage is reduced or the drug withdrawn. An initial worsening of the disease symptoms is sometimes seen.

Most of the adverse effects occurring in association with systemic retinoids, including acitretin, resemble those of excessive vitamin A intake.

During treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these conditions persist.

Skin and Appendages

Very Common: Dry skin or lips, pruritus, erythema, rash, scaling particularly on palms and soles, skin fragility, thinning of skin, sticky skin, alopecia, nail fragility, paronychia.

Common: Bullous eruption, abnormal hair texture, dermatitis.

Uncommon: Photosensitivity reactions.

Rare: Retinoid dermatitis (occasionally provoking psoriatic lesions), urticaria.

Frequency Not Known: Pyogenic granuloma, madarosis, angioedema, exfoliative dermatitis.

Ocular

Very Common: Dry eyes, eye irritation, intolerance of contact lenses, xerophthalmia, conjunctivitis.

Common: Blurred vision, impaired night vision.

Rare: Keratitis, corneal erosions or ulcerations, abrasion and irregularities leading to corneal opacities, papilloedema.

Special Senses Other

Common: Tinnitus, taste perversion.

Uncommon: Deafness.

Respiratory

Very Common: Drying of and inflammation of mucous membranes e.g. epistaxis, rhinitis.

Not Known: Dysphonia

Thoracic and mediastinal

Frequency unknown: Dysphonia

Cardiovascular

Common: Flushing.

Musculoskeletal

Common: Arthalgia, arthritis, muscle, joint and bone pain. In chronic hypervitaminosis A syndrome, demineralisation and rarefaction of bone, cortical hyperostosis, periosteal calcification, premature epiphyseal closures (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric Use). In long-term treatment, irreversible hyperostosis and extra-skeletal calcification e.g. spinal hyperostosis and calcification of spinal ligaments resulting in spinal cord compression (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hyperostosis), myalgia in the case of marked CK elevation.

Rare: Elevated serum creatine kinase (CK).

Very Rare: Exostosis (maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic lesions and in extraskeletal calcification, as has been observed in long-term systemic treatment with retinoids) (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Neurological and Psychiatric

Common: Headache, fatigue, depression, somnolence.

Uncommon: Lassitude, vertigo, dizziness, disturbance of consciousness, abnormal thinking, emotional lability, aggressive feelings.

Rare: Pseudotumour cerebri (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Pseudotumour Cerebri), peripheral neuropathy.

Endocrine

Rare: Gynaecomastia.

Metabolic and nutritional

Very Common: Elevated serum cholesterol and triglycerides (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in hepatic impairment).

Rare: Oedema, thirst.

Liver and Biliary System

Very Common: Elevated serum transaminases and alkaline phosphatase (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on laboratory tests).

Uncommon: Jaundice, hepatitis.

Gastrointestinal

Very Common: Cheilitis, rhagades of corner of mouth, thirst, dry mouth.

Common: Stomatitis, gingivitis, gastro-intestinal disorders (e.g. abdominal pain, diarrhoea, nausea, vomiting).

Uncommon: Gastritis, heartburn, inflammatory bowel disorders.

Rare: Pancreatitis, hepatitis, icterus.

Frequency Not Known: Dysgeusia, rectal haemorrhage.

Genitourinary

Rare: Metrorrhagia.

Immunological

Uncommon: Vulvovaginitis due to *Candida albicans*.

Not Known: Type I hypersensitivity

Reproductive system and breast disorders

Frequency Not Known: Erectile dysfunction

General Disorders and Administration Site Conditions

Common: Peripheral oedema.

Investigations

Very Common: Liver function test abnormal (transient, usually reversible elevation of transaminases and alkaline phosphatases). Lipids abnormal (during treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients and during long-term treatment. An associated risk of atherogenesis cannot be ruled out if these conditions persist).

Children

There have been occasional reports of bone changes in children, including premature epiphyseal closure, skeletal hyperostosis and extraosseous calcification after long-term treatment with etretinate, these effects may be expected with acitretin. In children, growth parameters and bone development must be closely monitored.

Diabetics

Retinoids can either improve or worsen glucose tolerance.

Post Market

Very rare cases of Capillary Leak Syndrome / retinoic acid syndrome have been reported from worldwide post marketing experience

Very rare cases of exfoliative dermatitis have been reported from world-wide post marketing experience

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

In the event of acute overdosage, ZETIN must be withdrawn at once. Symptoms of overdose are identical to an acute hypervitaminosis A, i.e. headache and vertigo. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg.

Treatment

Treatment of overdose should consist of general supportive measures.

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

ZETIN (acitretin) reverses the epidermal proliferation and increased keratinisation seen both in chemically induced epithelial tumours in animals and in hyperkeratotic disorders in man.

Vitamin A (retinol and its esters) can beneficially influence hyperkeratotic changes in the skin or metaplasias of the mucous membranes.

Clinical trials

Use of acitretin in psoriatic patients results in improvement manifested by a decrease in scale, erythema and thickness of lesions, and decreased inflammation in the epidermis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Acitretin reaches peak plasma concentration 1 - 5 hours after ingestion of the medicine. Bioavailability of orally administered acitretin is best when the medicine is taken together with food. Bioavailability of a single dose is approximately 60%, but this may vary considerably from one patient to another (36 - 95%).

After administration of a single 50 mg oral dose of acitretin to 18 healthy subjects, maximum plasma concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in 2 to 5 hours (mean 3.5 hours). The oral absorption of acitretin is linear and proportional with increasing doses from 25 to 100 mg. Following multiple doses, acitretin plasma concentrations reached steady-state conditions within two weeks and accumulation was 0.5 to 2.6-fold higher than after a single dose. In patients with psoriasis, mean steady-state trough concentrations of acitretin increased in a proportional manner and ranged between 6 and 7 ng/mL, 11 and 14 ng/mL, and 19 and 25 ng/mL over an eight-week period at daily oral doses of 10 mg, 25 mg and 50 mg, respectively. In this same study, acitretin plasma concentrations were non-measurable (< 4-6 ng/mL) in all patients where blood samples were drawn three weeks after cessation of therapy.

Distribution

Acitretin is highly lipophilic and penetrates readily into body tissues. Protein binding of acitretin exceeds 99%. In animal studies, acitretin passed the placental barrier in quantities sufficient to produce foetal malformations. Due to its lipophilic nature, it can be assumed that acitretin passes into breast milk in considerable quantities.

Metabolism

Acitretin is metabolised by isomerisation into its 13-*cis* isomer (*cis* acitretin), by glucuronidation and cleavage of the side chain. Both acitretin and its 13-*cis* isomer are eliminated from the body primarily by metabolism to chain-shortened breakdown products and conjugates that are ultimately excreted in the faeces (35 - 45%) and urine (48 - 61%). The formation of the 13-*cis* isomer relative to parent

compound is not altered by dose or fed/fasted conditions of oral administration of acitretin. The elimination of the 13-*cis* isomer is essentially parallel to that of acitretin after multiple doses.

There was no detectable formation of etretinate when a single 100 mg oral dose of acitretin was administered without concurrent ethanol ingestion. Although the formation of etretinate without concurrent ethanol ingestion cannot be excluded, only 7.5% of 240 evaluated psoriatic patients on acitretin therapy (5 - 60 mg/day) in controlled and uncontrolled clinical trials were found to have measurable etretinate concentrations (5 ng/mL). Of these patients, the last measurable etretinate concentration was observed at two months after cessation of acitretin therapy.

Animal studies confirm the possibility that, in the rat at least, metabolism of acitretin to etretinate in the absence of alcohol can occur.

Excretion

Multiple-dose studies in patients aged 21-70 years showed an elimination half-life of approximately 50 hours for acitretin and 60 hours for its main metabolite in plasma, *cis* acitretin, which is also a teratogen. From the longest elimination half-life observed in these patients for acitretin (96 hours) and *cis* acitretin (123 hours), and assuming linear kinetics, it can be predicted that more than 99% of the drug is eliminated within 36 days after cessation of long-term therapy. Furthermore, plasma concentrations of acitretin and *cis* acitretin dropped below the sensitivity limit of the assay (< 6 ng/mL) within 36 days following cessation of treatment. Acitretin is excreted entirely in the form of its metabolites, in approximately equal parts via the kidneys and the bile.

Special Populations

Plasma concentrations of acitretin were significantly lower in end stage renal failure subjects (*n* = 6) when compared to age-matched controls following single 50 mg oral doses. However, acitretin was not removed by haemodialysis in these subjects.

In a multiple-dose study in healthy young (*n* = 6) and elderly (*n* = 8) subjects, increased acitretin plasma concentrations were seen in elderly subjects although the elimination half-life did not change.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Acitretin has been shown to be embryotoxic and/or teratogenic in mice, rats and rabbits at doses approximately 3, 15 and 0.5 times the maximum recommended therapeutic dose, respectively.

Carcinogenicity

Carcinogenicity studies carried out with acitretin showed an increase in the frequency of blood vessel tumours (haemangiomas and haemangiosarcomas) in male mice.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each ZETIN capsule contains acitretin as the active ingredient. In addition, each capsule contains the following inactive ingredients: maltodextrin, sodium ascorbate, microcrystalline cellulose, gelatin, sodium lauryl sulfate, purified water, black printing ink (shellac glaze, iron oxide black (E172), propylene glycol (E1520)) and the colourants iron oxide red (E172), iron oxide yellow (E172) and titanium dioxide.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

Store below 25°C. Protect from light and moisture.

The product is sensitive to moisture, therefore, store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

ZETIN 10 mg capsule: Blister pack (PVC/PVDC/Aluminium foil) of 60 and 100 capsules (AUST R 196005)

ZETIN 25 mg capsule: Blister pack (PVC/PVDC/Aluminium foil) of 60 and 100 capsules (AUST R 196004)

Not all strengths and/or pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

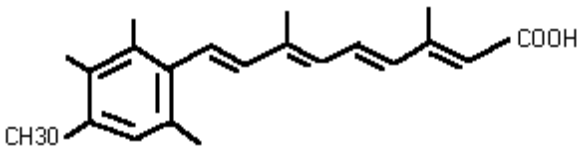
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Acitretin is a metabolite of etretinate and is related to both retinoic acid and retinol (Vitamin A). Acitretin is a green-yellow crystalline powder. It is virtually insoluble in water (< 0.1 mg/100 mL). The pKa is approximately 5. It is present in the capsules as a spray-dried powder.

Acitretin



Molecular Formula: $C_{21}H_{26}O_3$.

Molecular Weight: 326.44.

CAS number

CAS Registry Number: 55079-83-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine.

8 SPONSOR

Douglas Pharmaceuticals Australia Pty Ltd

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Cremorne Victoria 3121

Distributed by Arrow Pharmaceuticals Pty Ltd on behalf of Oraderm Pharmaceuticals Pty Ltd

15-17 Chapel Street

Cremorne Victoria 3121

www.oraderm.com.au

9 DATE OF FIRST APPROVAL

23 May 2013

10 DATE OF REVISION

16 December 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Precaution – Addition of discontinuation advice in case of additional advice of uncontrolled levels of hypertriglyceridemia or if symptoms of pancreatitis occur. Include advice on monitoring serum cholesterol and serum triglycerides (fasting values).