

This product is no longer marketed in New Zealand and this data sheet may not be up to date. A more up-to-date data sheet for a product with the same active ingredient may be available on the Medsafe website.

Data Sheet

ISOTANE

Isotretinoin 5 mg, 10 mg and 20 mg capsules

Presentation

ISOTANE 5: Capsule with a yellow paste fill and a bicoloured reddish brown/cream opaque gelatin shell bearing the logo "15" in black ink, contains 5mg of isotretinoin.

ISOTANE 10: Capsule with a yellow paste fill and a reddish brown opaque gelatin shell bearing the logo "10" in black ink, contains 10mg of isotretinoin.

ISOTANE 20: Capsule with a yellow paste fill and a bicoloured reddish brown/cream opaque gelatin shell bearing the logo "20" in black ink, contains 20mg of isotretinoin.

Uses

Actions

Isotretinoin is a retinoid with a specific antiseborrheic action for oral treatment of severe cystic acne and conglobate acne resistant to other forms of treatment.

Isotretinoin, the active ingredient of Isotane, is a synthetic stereoisomer of all-trans retinoic acid (tretinoin), an active substance which has proved effective in topical treatment of acne vulgaris.

Administered orally, isotretinoin has a marked effect in severe forms of acne which have proved insufficiently responsive to previous treatment. The mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with dose-related suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Pharmacokinetics

Time-related blood concentrations can be predicted on the basis of linear pharmacokinetics.

Absorption:

Peak plasma concentrations (C_{max}) of approximately 310 ng/ml have been achieved in healthy volunteers and in patients with cystic acne one to four hours (t_{max}) after administration of 80-100mg isotretinoin.

Taking isotretinoin with food increases bioavailability up to twofold relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication. Furthermore, there is an overall decrease in fluctuations in systemic availability when isotretinoin is ingested with food.

Distribution:

Isotretinoin is extensively bound to plasma proteins (99.9%) with the result that the free active fraction of the substance is less than 0.1% of the total over a wide range of therapeutic concentrations. Albumin appears to be the major binding protein.

The volume of distribution of isotretinoin is not known in humans since it is not available as an intravenous preparation.

Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities.

Owing to its lipophilicity, there is a high probability that isotretinoin is secreted into the breast milk. It is therefore contraindicated in nursing mothers.

Steady state blood concentrations ($C_{\min,ss}$) of isotretinoin in patients with severe acne treated with 40 mg b.i.d. ranged from 120-200 ng/ml; the concentration of 4-oxo-isotretinoin in these patients was

2-5 times higher than the isotretinoin concentrations. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum.

Metabolism:

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid), and 4-oxo-tretinoin. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state that are 2.5 times higher than those of the parent compound. Other minor metabolites have been detected but are not completely identified, which also includes glucuronide conjugates.

Isotretinoin metabolites have shown biological activity in several in-vitro tests. Thus the observed clinical profile in patients could be the result of the pharmacological activity of isotretinoin and its metabolites.

Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (= interconverted), the metabolism of tretinoin is linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerization.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man.

In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. CYP2C8, CYP2C9, CYP2B6, and possibly CYP3A4 appear to have the greatest contributions in the metabolism of isotretinoin to 4-oxo-isotretinoin. CYP2C9, CYP2B6, and possibly CYP2C8, CYP3A4, CYP2A6, and CYP2E1 contribute to the metabolism of isotretinoin. CYP 26 is also known to metabolize retinoids.

Elimination:

After oral administration of radiolabeled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

Indications

Severe forms of nodulo-cystic acne which are resistant to therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk. Isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if isotretinoin is used during pregnancy.

Dosage and Administration

Patient response to isotretinoin is dose-related and varies from case to case. This necessitates adapting the dosage to individual needs according to severity of the clinical picture and side effects. With a dosage of between 0.1 and 1.0mg per kg daily over 12-16 weeks, it is generally possible to achieve a considerable improvement or complete healing. The daily dose is taken with meals, low doses once daily and higher amounts as a single dose or in several doses spread over the day.

Initial Treatment

As a rule, therapy is started with 0.5 mg/kg daily and maintained for 2 to 4 weeks until the patient's response is clear. Initially, the acne may be aggravated for a short period.

Follow-up Treatment (Maintenance Dose)

In patients who respond well to isotretinoin, treatment should be continued with a dosage of 0.5 mg/kg daily. With patients who show signs of intolerance during the initial therapy, the daily dosage should be reduced to 0.1-0.2 mg/kg. Where response to the initial dosage is slight, and in particularly severe cases, the daily dosage may be increased to 1.0 mg/kg provided the medicine is well tolerated. The maintenance dose is administered for a period of 12 weeks after which the first stage of therapy is generally terminated. After discontinuation of treatment, often a further improvement is observed which may last from a few weeks to several months and there should therefore be an interval of at least eight weeks before restarting treatment. In the event of recurrence of the acne, treatment should be resumed on the above lines, bearing in mind that recurrences may respond to a lower dosage.

A cumulative dose of 120 mg/kg per treatment has been documented to increase remission rates and prevent relapse. The therapy duration in individual patients therefore varies as a function of the daily dose. Complete remission of the acne is often achieved by a therapy course of 16-24 weeks. In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of a longer therapy duration.

Special Dosage Instruction

Patients with Renal Impairment

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day) and afterwards individually adjusted according to tolerability.

Contraindications

Isotretinoin is contraindicated in: pregnancy (in women who are pregnant or who may become pregnant while undergoing treatment; see section on pregnancy), hepatic insufficiency, pre-existing hypervitaminosis A, patients with excessively elevated blood lipid values, known hypersensitivity to Isotane and any of its components .

Warnings

It is recommended that clinically significant serum triglyceride elevations be controlled, since levels in excess of 800 mg/dL are sometimes associated with acute pancreatitis, which is known to be potentially fatal (see Adverse Effects). Hence, isotretinoin should be discontinued if uncontrolled hypertriglyceridaemia or symptoms of pancreatitis occur.

Precautions

Prescribers should inform the individual patient of the risks associated with use of isotretinoin. Patients should understand the need for rigorous follow-up preferably on a monthly basis.

Isotretinoin should only be prescribed by doctors who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with isotretinoin therapy (see Pregnancy, Nursing Mothers).

Depression, psychosis and rarely, suicidal ideation and attempts have been reported in patients treated with isotretinoin (see Adverse Effects). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Although no mechanism of action for these events has been

established, discontinuation of therapy may be insufficient and further evaluation by a psychiatrist may be necessary.

Donation of blood by patients should be avoided during and within 1 month after cessation of isotretinoin treatment to prevent an accidental exposure.

Liver function should be checked before and 1 month after the start of treatment, and subsequently at 3 month intervals. Transitory and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, when transaminase levels exceed the normal levels, reduction of the dose or discontinuation of treatment may be necessary.

Serum lipids (fasting value) should also be checked, before and one month after the start of therapy, and also at the end of treatment. The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may also resolve in response to dietary measures.

Bone changes, including premature epiphyseal closure, have occurred after several years of administration at high doses for treating disorders of keratinization. Therefore, a careful evaluation of the risk/benefit ratio should be carried out in every patient.

Myalgia and arthralgia may occur and may be associated with reduced tolerance to vigorous exercise (see Adverse effects). Isolated instances of raised serum CPK values have been reported in patients receiving isotretinoin, particularly those undertaking vigorous physical activity.

Aggressive dermabrasion should be avoided in patients on isotretinoin and for a period of 5-6 months after treatment because of the risk of hypertrophic scarring in atypical areas. Wax epilation should be avoided during therapy and at least for a period of 6 months thereafter due to the possibility of scarring or dermatitis.

Decreased night vision has occurred during isotretinoin therapy and in rare instances has persisted after discontinuation of therapy (see Adverse effects). Because the onset in some patients was sudden, 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.

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of isotretinoin considered.

Rare cases of benign intracranial hypertension (pseudotumor cerebri) have been reported, some of which involved concomitant use of tetracyclines (see Interactions).

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Anaphylactic reactions have been rarely reported and only after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Precautions for Special Patient Groups

In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with isotretinoin, more frequent checks of serum values for lipids (see Warnings) and/ or blood glucose may be necessary.

In known or suspected diabetics, frequent determination of blood glucose levels is recommended. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

Pregnancy, Nursing Mothers

Isotretinoin is highly teratogenic. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral isotretinoin in any amount even for short periods. Potentially all exposed fetuses can be affected.

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

- She must have severe acne resistant to standard therapies.
- She must be reliable in understanding and carrying out instructions.
- She must be informed by her doctor of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin.
- She must be warned of the possibility of contraception failure.
- She must confirm that she has understood the precautions.
- She must be capable of complying with the mandatory effective contraceptive measures.
- She must use effective contraception without any interruption for 1 month before beginning isotretinoin therapy, during therapy and for 1 month following discontinuation of therapy. At least one and preferably two complementary forms of contraception including a barrier method should be used. Microdosed progesterone preparations (minipills) may be an inadequate method of contraception during isotretinoin therapy.
- She must have a negative result from a reliable pregnancy test within 11 days prior to the start of therapy. Pregnancy testing should be performed before, during (monthly testing is strongly recommended) and 5 weeks after the end of treatment.
- She must start isotretinoin therapy only on the 2nd or 3rd day of the next normal menstrual period.
- In the event of relapse treatment she must also use the same uninterrupted and effective contraceptive measures 1 month prior to, during, and for 1 month after isotretinoin therapy and the same reliable pregnancy evaluations should be followed.
- She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.

Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity must be advised to use effective contraceptive measures while taking isotretinoin, following the above guidelines.

Should pregnancy occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe malformation of the foetus (involving in particular the central nervous system, the heart and the large blood vessels). There is also an increased risk of spontaneous abortion. If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy.

Major human foetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphism, thymus gland abnormalities, parathyroid gland abnormalities and cerebellar malformation.

Nursing mothers

As isotretinoin is highly lipophilic, the passage of isotretinoin into human milk is very likely. Because of the potential for adverse effects, the use of isotretinoin should be avoided in nursing mothers.

Male patients

The available data suggest that the level of maternal exposure from the semen of patients receiving isotretinoin, is not of sufficient magnitude to be associated with the teratogenic effect of isotretinoin.

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

Adverse Effects

Most of the side effects of isotretinoin are dose-related. With the recommended dosage, the risk/benefit ratio is generally acceptable considering the severity of the disease.

Symptoms Associated with Hypervitaminosis A

The following symptoms are the most frequently reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips, the nasal mucosa (epistaxis), the pharynx (hoarseness), the eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).

Other symptoms reported include drying of the vagina and anus.

Skin and Appendages Disorders

Exanthema, pruritus, facial erythema/dermatitis, sweating, pyogenic granuloma, paronychia, nail dystrophy, increased formation of granulation tissue, persistent hair thinning, reversible alopecia, acne fulminans, hirsutism, hyperpigmentation, photosensitivity, photoallergic reactions, skin fragility. Acne flare occurs at the start of treatment and persists for several weeks.

Musculo-Skeletal System Disorders

Myalgia (muscle pain) with or without elevated serum CPK values (see Precautions), arthralgia (joint pain), hyperostosis, arthritis, calcification of ligaments and tendon and other bone changes, tendinitis.

Psychiatric and Central Nervous System Disorders

Behavioural disorders, depression (see Precautions), headache, increased intracranial pressure (pseudotumor cerebri), seizures.

Sensory Disorders

Isolated cases of visual disturbances, photophobia, dark-adaptation disturbances (decreased night vision), rarely colour vision disturbances (reversible upon discontinuation), lenticular cataract, keratitis, impaired hearing at certain frequencies.

Gastro-Intestinal System Disorders

Nausea, inflammatory bowel disease such as colitis, ileitis, and haemorrhage have been reported to occur. Patients treated with isotretinoin, especially those with high triglyceride levels, are at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (see Warnings).

Liver and Biliary System Disorders

Transitory and reversible increases in liver transaminases, some cases of hepatitis. In many such cases the changes have been within the normal range and values have returned to baseline levels during treatment. In other cases, however, it has been necessary to reduce the dose or discontinue treatment with isotretinoin.

Respiratory System Disorders

Bronchospasm has been rarely reported; sometimes in patients with a pre-history of asthma.

Disorders of the blood

Decrease in white blood cell count, disorders of red blood cell parameters (such as decrease in red blood cell count and haematocrit, elevation of sedimentation rate), increase or decrease in platelet count.

Laboratory Findings

Increase in serum triglyceride and cholesterol levels, decrease in HDL hyperuricemia. Rare cases of elevated blood glucose have been reported, and new cases of diabetes have been diagnosed (see Precautions).

Resistance Mechanism Disorders

Local or systemic infections due to Gram positive microorganisms (*Staphylococcus aureus*).

Miscellaneous Reactions

Lymphadenopathy, haematuria, and proteinuria, vasculitis (for example Wegener's granulomatosis, allergic vasculitis), allergic responses, systemic hypersensitivity, glomerulonephritis.

Interactions

Concurrent therapy with isotretinoin and vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified.

Rare cases of benign intracranial hypertension 'pseudotumor cerebri' have been reported, some of which involved concomitant use of tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see Precautions).

Overdosage

Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Such symptoms are reversible. Nevertheless, evacuation of the stomach may be indicated in the first few hours after overdose.

Pharmaceutical Precautions

Store below 25°C.

Protect from light and moisture.

Medicine Classification

Prescription Medicine.

Package Quantities

Capsules 5mg: 100s (This strength is not currently marketed in New Zealand)

Capsules 10mg: 100s

Capsules 20mg: 100s

Further Information

Nil.

Name and Address

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone: 09-579-2792

Date of Preparation

2 February 2009