SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Isotretinoin 5 mg
capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 5 mg of isotretinoin.

Excipients with known effect

Soya-bean oil, refined 66.40 mg

Soya-bean oil, partly hydrogenated 3.850 mg

Sorbitol, liquid (non-crystallising) (E420) 4.995 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule,
soft

Faint pinkish/cream to cream coloured oval, soft-gelatin capsules, containing a yellow/orange, opaque, viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

The prescriber must consider that there is no other appropriate effective treatment before initiation of isotretinoin therapy.

4.2 Posology and method of administration

Posology

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:
Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose- related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with renal impairment
In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

Paediatric Population
Isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children less than 12 years of age due to a lack of data on efficacy and safety.

Patients with intolerance
In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

Method of administration
For oral use.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding
(see section
4.6).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

Isotretinoin is contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients listed in section 6.1. Isotretinoin 5 mg Capsules contain soya oil and partially hydrogenated soya oil.

Therefore, Isotretinoin 5 mg capsules are contraindicated in patients allergic to peanut or soya.

Isotretinoin is also contraindicated in patients

- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- Receiving concomitant treatment with tetracyclines (see section 4.5)

4.4 Special warnings and precautions for use

Teratogenic effects
Isotretinoin is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects
Isotretinoin is strictly contraindicated in:
-Pregnant women
-Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC

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

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy (see section 4.1).
- 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 1 month 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 of 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 1 month after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

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 1 month after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with isotretinoin, 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 fetus. This risk persists until the product has been completely eliminated, which is within one month 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 child-bearing 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 1 month after stopping treatment with isotretinoin, 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 with a minimum sensitivity of 25 mIU/mL 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 isotretinoin.

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

1 month after stopping treatment, women should undergo a final pregnancy test.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of isotretinoin 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 isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

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.

For those patients that are considered by the prescriber to have compelling reasons to indicate that there is no risk of pregnancy, once stable on isotretinoin (after the first 1-3 months), the prescription duration may be for longer than 30 days (up to 12 weeks).

Male patients
The available data suggest that the level of maternal exposure from the semen of the patients receiving isotretinoin, is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin. 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 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8).

Patients, and where appropriate, parents or carers, must be counselled about the risk of psychiatric adverse events with isotretinoin prior to prescription of isotretinoin, and preferably prior to any referral that might include consideration of isotretinoin treatment.

All patients should have an assessment of their mental health before starting treatment with isotretinoin and be assessed regularly during treatment for developing or worsening psychiatric disorders. Particular care needs to be taken in patients with a history of depression. Patients should be referred for appropriate psychiatric treatment if necessary. Discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Awareness by family or friends may be useful to detect mental health deterioration.

Sexual disorders

Isotretinoin use may be associated with sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of isotretinoin.

Patients, and where appropriate, parents or carers, must be counselled about the risk of sexual dysfunction with isotretinoin prior to the prescribing decision, and ideally prior to any referral that might include consideration of isotretinoin treatment. The age and maturity of the patient should be taken into account in choosing the most

appropriate counselling approach, including giving the option to discuss without parents or carers present where appropriate.

All patients should be asked about the presence of symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin, and monitored for the development of new sexual disorders during treatment.

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

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

Furthermore, the educational material reinforces the warnings about the risks of isotretinoin, including possible risks to mental health and sexual function.

Skin and subcutaneous tissue disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.5).

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with isotretinoin

treatment (see section 4.8).

Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms.

If signs and symptoms suggestive of these reactions appear, isotretinoin should be withdrawn immediately and an alternative treatment considered (as appropriate).
If the patient has developed a severe cutaneous adverse reaction such as SJS, TEN, or AGEP or with the use of isotretinoin, treatment with isotretinoin must not be restarted in this patient at any time.

Allergic reactions
Anaphylactic reactions have been rarely reported, in some cases 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.

Eye disorders
Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Cases of dry eyes not resolving after discontinuation of therapy have been reported. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculoskeletal and connective tissue disorders
Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8). In some cases, this may progress to potentially life threatening rhabdomyolysis.

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

Sacroiliitis has been reported in patients exposed to isotretinoin. To differentiate sacroiliitis from other causes of back pain, in patients with clinical signs of sacroiliitis, further evaluation may be needed including imaging modalities such as MRI. In cases reported post-marketing, sacroiliitis improved after discontinuation of isotretinoin and appropriate treatment.

Benign intracranial hypertension

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see section 4.3 and section 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders
Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient 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, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency
Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2).

Lipid Metabolism
Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800 mg/dL or 9 mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders

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.
Fructose intolerance
Isotretinoin 5 mg capsules contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

High Risk Patients
In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4).

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3 and 4.4). Women of childbearing potential should comply with the Pregnancy Prevention Programme and use effective contraception one month before treatment, during treatment and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with isotretinoin or within one month following treatment, there is a great risk of very severe and serious malformation of the foetus.

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

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

Breast-feeding

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mother's milk, the use of isotretinoin is contraindicated during breast-feeding (see section 4.3).

Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

4.7 Effects on ability to drive and use machines

Isotretinoin could potentially have an influence on the ability to drive and use machines.

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 and section 4.8). 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 machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

4.8 Undesirable effects

Summary of safety profile

Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped. The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips (cheilitis), the nasal mucosa (epistaxis) and the eyes (conjunctivitis).

Tabulated list of adverse reactions

The incidence of the adverse reactions calculated from pooled clinical trial data involving 824 patients and from post-marketing data are presented in the table below. The adverse reactions are listed below by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and SOC, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions in patients treated with isotretinoin

System Organ Class	Very Common	Common	Rare	Very Rare	Not known*
Infections				Gram positive (mucocutaneous) bacterial infection	

Blood and lymphatic system disorders	Thrombocytopenia, anaemia, thrombocytosis, red blood cell sedimentation rate increased	Neutropenia		Lymphadenopathy	
Immune system disorders			Anaphylactic reactions, hypersensitivity, allergic skin reaction		
Metabolism and nutrition disorders				Diabetes mellitus, hyperuricaemia	
Psychiatric disorders			Aggressive tendencies, anxiety, mood alterations.	Psychotic disorder, abnormal behaviour	Depression, depression aggravated, suicide, suicide attempt, suicidal ideation
Nervous system disorders		Headache		Benign intracranial hypertension, convulsions, drowsiness, dizziness	
Eye disorders	Blepharitis, conjunctivitis, dry eye, eye irritation			Papilloedema (as sign of benign intracranial hypertension), cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, photophobia, visual disturbances, blurred vision.	
Ear and labyrinth disorders				Hearing impaired	
Vascular disorders				Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)	
Respiratory, thoracic and mediastinal disorders		Nasopharyngitis, epistaxis, nasal dryness		Bronchospasm (particularly in patients with asthma), hoarseness	
Gastrointestinal disorders				Inflammatory bowel disease, colitis, ileitis, pancreatitis, gastrointestinal haemorrhage, haemorrhagic diarrhoea, nausea dry throat (see section 4.4)	Anal fissure
Hepatobiliary disorders	Transaminase increased (see section			Hepatitis	

	4.4)				
Skin and subcutaneous tissues disorders	Pruritus, rash erythematous, dermatitis, cheilitis, dry skin, localised exfoliation, skin fragility (risk of frictional trauma)		Alopecia	Acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP)
Musculo-skeletal and connective tissue disorders	Arthralgia, myalgia, back pain (particularly in children and adolescent patients)			Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis	Rhabdomyolysis, Sacroiliitis
Renal and urinary disorders				Glomerulonephritis	Urethritis
Reproductive system and breast disorders					Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia, vulvovaginal dryness, orgasm abnormal, genital hypoaesthesia
General disorders and administration site conditions				Granulation tissue (increased formation of), malaise	
Investigations	Blood triglycerides increased, high density lipoprotein decreased	Blood cholesterol increased, blood glucose increased, haematuria, proteinuria		Blood creatine phosphokinase increased	

* cannot be estimated from the available data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoid for treatment of acne.

ATC code:
D10BA01

Mechanism of action

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact 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 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.

Clinical efficacy and safety

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2 Pharmacokinetic properties

Absorptio
n

The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distributio n

Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9 %). The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. 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. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Biotransformation

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. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites include glucuronide conjugates. 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.

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

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. Isotretinoin and its metabolites do not significantly affect CYP activity.

Eliminatio n

After oral administration of radiolabelled 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.

Hepatic impairment

Since isotretinoin is contraindicated in patients with hepatic impairment, limited information on the kinetics of isotretinoin is available in this patient population.

Renal impairment

Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

5.3 Preclinical safety data

Acute toxicity

The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

Chronic toxicity

A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1–2 weeks.

Teratogenicity

Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age (see section 4.3, section 4.4, and section 4.6).

Mutagenicity

Isotretinoin has not been shown to be mutagenic in *in vitro* or *in vivo* animal tests.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:
Soya-bean oil, refined
all-rac-α-Tocopherol
Disodium edetate
Butylhydroxyanisole (E 320)
Soya-bean oil, partially hydrogenated
Hydrogenated vegetable oil
Beeswax, yellow

Capsule shell:
Gelatin
Glycerol
Sorbitol, liquid (non-crystallising) (E 420)
Purified water
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

AL/PVC/PVDC blisters.

10, 15, 20, 30, 50 and 60 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Return any unused Isotretinon 5 mg capsules to the Pharmacist.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,
Unit G4,
Riverside Industrial
Estate, Riverside Way,
Dartford,
DA1 5BS,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0043

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/01/2008

10 DATE OF REVISION OF THE TEXT

27/04/2026