SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acitretin 25 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard of Acitretin 25 mg contains 25 mg acitretin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Acitretin 25 mg consists of a yellow to light yellow body and a brown cap, printed in black with “A25” on the capsule body and filled with a yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Extensive and severe refractory forms of psoriasis;
- Pustulous psoriasis of the hands and feet;
- Severe congenital ichthyosis and ichthyosiform dermatitis;
- Lichen ruber planus of skin and mucous membranes;
- Other severe and refractory forms of dermatitis characterised by dyskeratosis and/or hyperkeratosis.

4.2 Posology and method of administration

Acitretin should only be prescribed by doctors, who have experience in treatment with systemic retinoids and who are aware of the teratogenic risk associated with acitretin (see sections 4.4 and 4.6).

The dosage is based on the clinical appearance of the disorder and the tolerability of the product. The treating physician must determine the dosage individually for each patient. The following information can serve as a guide.

This product is available in two strengths:

Acitretin 10 mg capsules

Acitretin 25 mg capsules

Adults

An initial daily dose of 25 or 30 mg acitretin (i.e. 1 capsule of Acitretin 25 mg or 3 capsules of Acitretin 10 mg) for 2 to 4 weeks is recommended. After this initial phase, it may be necessary in some cases to increase the dose up to a maximum of 75 mg acitretin per day (i.e. 3 capsules of Acitretin 25 mg). This maximum dose should not be exceeded.

In patients with Darier's disease a starting dose of 10mg may be appropriate. The dose should be increased cautiously as isomorphic reactions may occur.

The maintenance dose must be adjusted to the therapeutic response and the tolerability. In general, a daily dose of 30 mg acitretin for a further 6 to 8 weeks allows an optimum therapeutic effect to be achieved in psoriasis. In keratinisation disorders, the maintenance dose should be kept as low as possible (possibly less than 10 mg acitretin per day). It should not on any account exceed 30 mg acitretin per day.

Therapy can generally be discontinued in patients with psoriasis whose lesions have improved sufficiently. Long-term therapy is not recommended in psoriasis patients. Relapses are treated in the same way.

Patients with severe congenital ichthyosis and severe Darier's disease may require therapy beyond 3 months. The lowest effective dosage, not exceeding 50mg/day, should be given.

Elderly

Dosage recommendations are the same as for other adults.

Combination therapy:

If the administration of acitretin is combined with other forms of treatment, it may be possible to reduce the dose of acitretin according to the therapeutic result. Other dermatological therapy, particularly with keratolytics, should normally be stopped before administration of acitretin. However, the use of topical corticosteroids or bland emollient ointment may be continued if indicated.

Additional topical treatments, including purely skincare treatments, during the administration of acitretin must be discussed with the doctor.

Method of administration

Acitretin hard capsules are for oral administration.

The hard capsules are taken whole once daily with meals or with milk. It is absolutely essential to keep to the dose of acitretin calculated by the doctor.

4.3 Contraindications

PREGNANCY: Acitretin, the active substance of Acitretin, is highly teratogenic and must not be used during pregnancy. The same applies to all women of childbearing potential, unless strict contraception is practiced 4 weeks before, during and for 3 years after treatment (see sections 4.4 and 4.6).

LACTATION: Acitretin is contraindicated during the period of breast-feeding.

Acitretin is not indicated in hepatic and renal dysfunction (liver and kidney failure), severe hyperlipaemia, concurrent use of vitamin A or other retinoids and during co-medication with methotrexate. Since Acitretin and tetracyclines can cause an increase in intracranial pressure, they must not be given concurrently.

Acitretin must not be used concomitantly with low dose progesterone-only products (minipills) (see sections 4.5 and 4.6).

Acitretin must not be used in patients with hypersensitivity to the active substance "acitretin" or other retinoids or to any of the excipients.

4.4 Special warnings and precautions for use

Teratogenic effects

Acitretin is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

Acitretin 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.

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

- Acitretin is indicated for (see section 4.1 "Therapeutic indications"):
  - Extensive and severe refractory forms of psoriasis;
  - Pustulous psoriasis of the hands and feet;
  - Sever congenital ichtyosisand ichthyosiform dermatitis;
  - Lichten ruber planus of skin and mucous membranes;
  - Other severe and refractory forms of dermatitis characterised by dyskeratosis and/or hyperkeratosis.
- 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.
- 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 with a minimum sensitivity of 25mUI/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 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 this medicine 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 this medicine 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

The available data suggest that the level of maternal exposure from the semen of the patients receiving this medicine is not of a sufficient magnitude to be associated with the teratogenic effects of acitretin. 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.

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.

Psychiatric disorders

Depression, depression aggravated, anxiety mood alterations and psychotic disorder 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.

Other warnings

Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and alcohol. Etretinate is highly teratogenic and has a longer half-life (approximately 120 days) than acitretin. Women of childbearing age must therefore not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after cessation of acitretin therapy. Contraceptive measures and pregnancy tests must also be taken for 3 years after completion of acitretin treatment (see section 4.6 and 5.2).

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 3 years after completion of treatment with acitretin.

Due to the risk of foetal malformations, the medicine must not be passed on to other people. Unused or expired products should be returned to a pharmacy for disposal.

In view of possible effects on liver function, this must be monitored regularly during treatment. Hepatic function should be checked before starting treatment with Acitretin, every 1 - 2 weeks for the first 2 months after commencement and then every 3 months during treatment. If abnormal results are obtained, weekly checks should be instituted. If hepatic function fails to return to normal or deteriorates further, Acitretin must be withdrawn. In such cases it is advisable to continue monitoring hepatic function for at least 3 months.

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. Acitretin treatment should be discontinued in case of uncontrolled levels of hypertriglyceridemia or if symptoms of pancreatitis occur.

In diabetic patients, retinoids can alter glucose tolerance. Blood sugar levels should therefore be checked more frequently than usual at the beginning of the treatment period.

Before and during long-term therapy, x-rays (e.g. of the vertebral column, long bones, including ankles and wrists) must be taken at regular intervals (every year) in view of possible ossification abnormalities (see section 4.8). In the event of hyperostosis, the discontinuation of therapy must be discussed with the patient. The risks must be carefully weighed against the therapeutic benefit to be expected.

Since there have been occasional reports of bone changes in children, including premature epiphyseal closure, fractures, skeletal hyperostosis and extraosseous calcification after long-term treatment with etretinate, these effects may be expected with its active metabolite acitretin. Acitretin therapy in children is not, therefore, recommended unless, in the opinion of the physician, the benefits significantly outweigh the risks and all other alternative treatments have failed. If, in exceptional circumstances, such therapy is undertaken the child should be regularly monitored for any abnormalities of musculo-skeletal development and growth. Any symptoms that suggest possible bone changes (restricted mobility, bone pain) should be carefully investigated. As soon as the medical condition allows, the use of acitretin should be interrupted.

The dosage should be based on bodyweight (b.w.). An initial daily dose of 0.5 mg acitretin per kg b.w. is recommended. Higher doses up to 1 mg acitretin per kg b.w. per day may be necessary for a limited period in some cases. The maximum dose of 35 mg acitretin per day should not be exceeded.

The fixed-dose capsule formulations of 10 and 25 mg may not provide sufficient flexibility to cover the proposed paediatric dosing schedule per kg b.w. In this case preparation of a suitable dosage form (e.g. powders or capsules) made of the capsule content of Acitretin by qualified pharmaceutical personnel in a public or hospital pharmacy is suggested.

The mean maintenance dose lies at 0.1 mg acitretin per kg b.w. per day. The maintenance dose should be kept as low as possible and should generally not exceed 0.2 mg acitretin per kg b.w. per day (dosing every other day may be considered).

The effects of UV light are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and the unsupervised use of sun lamps.

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 (see sections 4.7 and 4.8).

Wearing of contact lenses might become impossible due to dryness of the eyes. Patients who wear contact lenses should be excluded from treatment or wear glasses throughout the treatment period.

Very rare cases of Capillary Leak Syndrome / retinoic acid syndrome have been reported from world-wide post marketing experience.

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

This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Systemic treatment with retinoids may lead to an increase in intracranial pressure. Since tetracyclines can also cause such an increase in pressure, patients must not be treated concurrently with Acitretin and a tetracycline.

An increased risk of hepatitis has been reported during co-medication with etretinate and methotrexate. Consequently, the concomitant use of methotrexate and acitretin (metabolite of etretinate) should be avoided.

In concurrent treatment with phenytoin Acitretin, it must be remembered that Acitretin partially reduces the protein binding of phenytoin. In contrast, an influence of this kind on plasma binding with concurrent use of Acitretin and coumarin-type anticoagulants has not been observed.

The contraceptive effect of low-dose progesterone pills (“the mini-pill”) may be reduced by interaction with acitretin. These pills must therefore not be used for contraception during acitretin therapy. Interactions with combined oral oestrogen/progestogen oral contraceptives have not been observed (see section 4.6).

In a study with healthy volunteers, concurrent intake of a single dose of acitretin together with alcohol led to the formation of etretinate which is highly teratogenic. Women of childbearing age must therefore not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after cessation of acitretin

therapy (see section 4.4 and 5.2). The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible.

For interactions with alcohol in women of childbearing age and the effects on pregnancy: see section 4.6.

Patients are advised against taking vitamin A and other retinoids concurrently in view of the possible occurrence of hypervitaminosis A.

Interactions of Acitretin with other products (e.g. digoxin, cimetidine) have not been observed to date.

4.6 Fertility, pregnancy and lactation

Acitretin is highly teratogenic. Its use is contraindicated in women who might become pregnant during or within 3 years of the cessation of treatment. The risk of giving birth to a deformed child (craniofacial, central nervous system, cardiovascular, skeleton, thymus) is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage. Also after use of acitretin during pregnancy, a single case with similar deformations has been reported.

Acitretin in common with vitamin A and other retinoids may cause malformations in offspring of various animal species, even at the dose levels recommended for humans. As acitretin is teratogenic in animals at human dose levels, Acitretin is absolutely contraindicated during pregnancy and women of childbearing age must not be treated with Acitretin, if pregnancy cannot be excluded (see section 4.3).

At treatment of female patients of childbearing age with a very severe or disabling clinical picture, the treating physician may consider prescribing Acitretin, in case no alternative therapy, is available. Acitretin should only be prescribed by doctors, who have experience in treatment with systemic retinoids, preferably dermatologists, and who are aware of the teratogenic risk associated with acitretin if used during pregnancy.

Transformation of acitretin into etretinate is enhanced by alcohol. The formation, in vivo, of etretinate from acitretin with concomitant intake of alcohol, cannot be excluded. Etretinate is also teratogenic. As etretinate may be stored in fatty tissue and has a longer elimination half-time (approximately 120 days) than acitretin, women of childbearing age must not consume alcohol (in drinks, food or medicines) during treatment with acitretin and for 2 months after cessation of acitretin therapy (see section 4.4, 4.5 and 5.2). Also women of childbearing age should keep on practicing contraception for 3 years after stopping treatment.

Before Acitretin treatment is instituted, the potential risks must be weighed against the expected therapeutic effect. Furthermore, a number of precautionary measures must be STRICTLY followed:

Acitretin is contraindicated in every woman of childbearing potential unless each of the following conditions is met:

1) The patient is suffering from a severe disorder of keratinisation which is resistant to standard therapies.

2) She can be relied on to understand and follow the physician's instructions.

3) She is capable of taking the stipulated contraceptive measures reliably and without fail.

4) 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. The patient should be instructed to immediately contact a doctor in case of suspected pregnancy.

5) Therapy should not begin until the second or third day of the next normal menstrual period.

6) At the start of therapy, a negative pregnancy test result (minimum sensitivity of 25mIU/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.

7) Before therapy with acitretin is instituted, the physician must give patients of childbearing potential detailed information about the precautions to be taken, the risk of very severe foetal malformation, and the possible consequences if pregnancy occurs during the course of treatment with acitretin or within 3 years of discontinuing therapy.

8) 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.

9) 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. This 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.

10) She must avoid alcohol consumption (in drinks, food or medicines) during treatment and for 2 months after stopping treatment (see section 4.4, 4.5 and 5.2).

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.

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.

Pregnancy

Acitretin is contraindicated in pregnant women (see section 4.3).

Lactation

Acitretin is lipophilic and passes into the breast milk. Patients must not breast-feed during treatment with Acitretin (see section 4.3)

4.7 Effects on ability to drive and use machines

Acitretin has moderate influence on the ability to drive and use machines.

Decreased night vision has been reported with Acitretin therapy. In rare cases, this has continued after the treatment has stopped. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night or in a tunnel. Visual problems should be carefully monitored (see section 4.8).

4.8 Undesirable effects

Possible side effects of Acitretin occur in varying degrees from patient to patient. Most of the side effects are dose-related and usually reversible with reduction of dosage or discontinuation of therapy.

At the start of treatment with Acitretin there may be a transient worsening of the psoriasis symptoms.

The skin and mucous membranes are most commonly affected, and it is recommended that patients should be so advised before treatment is commenced.

The reported adverse reactions are listed below by system organ class and by frequency.

Frequencies 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)

Not known (frequency cannot be estimated from the available data)

<u>Skin and subcutaneous tissue disorders:</u>

Very common: over 80% of patients experienced: hypervitaminosis A as e.g. dry lips and possibly inflamed lips (using moisturisers or ‘emollients’ from the start of treatment can help to relieve dry skin problems.)

40 – 80% of patients experienced: dry mucous membranes of mouth and nose, peeling of skin, especially the palms of the hands and soles of the feet, rhinitis.

10 – 40% of patients experienced: nose bleed, scaling and thinning of healthy skin with increased sensitivity, erythema, pruritus, sensation

of “burning skin”, sensation of “sticky skin”, dermatitis, hair loss, inflammation of the nail wall, nail fragility.

Common: up to 10% of patients experienced: development of rhagades, inflammation of oral mucosa and gingiva associated with taste disturbances, blistering of the skin, change in pigmentation of the skin and hair, change in growth rate of hair, change in hair structure.

Marked dose dependence has been observed especially with regard to

– dry skin and mucous membranes, especially of the lips and nose,

– increased sensitivity of the skin and mucous membranes and

– hair loss.

Side effects of the skin and mucous membranes occur rather soon (a few days) after start of treatment, hair loss cannot be expected until several weeks into the treatment.

These side effects are reversible after altering the dose or discontinuation of treatment. However, new growth of hair will take some months, due to the hair growth cycle.

Rare: Increased sensitivity of the skin to light, as a result of which a sunburn can occur after only brief exposure to the sun. In these cases, care must be taken to wear adequate sun protection.

Not known: Madarosis and exfoliative dermatitis.

Eye disorders

Common: Conjunctivitis (10 to 40%), visual disturbances, e.g. xerophthalmia, blurred vision, impaired night vision (see also sections 4.4 and 4.7).

Wearing of contact lenses might become impossible. For this reason, patients should wear glasses during treatment with Acitretin.

Rare: Inflammation or ulcers of the cornea.

Respiratory, thoracic and mediastinal disorders

Not known: Dysphonia

Musculoskeletal and connective tissue disorders

Uncommon: Myalgia, arthralgia and bone pain.

After long-term treatment (see section 4.2) with acitretin, bone changes may occur (hyperostosis, thinning of bone, osteoporosis, premature epiphyseal closure) and soft-tissue calcification (extraosseous calcification).See section 4.4.

Gastrointestinal tract disorders

Rare: Gastrointestinal symptoms (e.g. nausea, vomiting, abdominal pain, diarrhoea, dyspepsia).

Hepatobiliary disorders

Rare: Hepatitis and jaundice.

Reproductive system and breast disorders

During treatment with Acitretin an increase in vulvovaginitis caused by Candida albicans has been observed.

General disorders

Common: Thirst and feeling of cold (10 to 40%).

Uncommon: Peripheral oedema, sensation of heat, dysgeusia, headache.

Investigations

In addition to a possible increase in liver function values, an elevation of blood lipids has also been observed during treatment with Acitretin.

The following changes in laboratory values occurred in patients during clinical trials:

– Elevation of triglycerides, total cholesterol, SGPT, creatine phosphokinase, SGOT, γ-GT, alkaline phosphatase, direct bilirubin, lactate dehydrogenase and uric acid

– Lowering of HDL cholesterol.

Occasionally an increase in creatinine, BUN and total bilirubin was observed.

Nervous system disorders

Rare: An increase of intracranial pressure (pseudotumor cerebri) may occur, which may be accompanied by severe headache, lightheadedness, nausea, vomiting, dizziness or visual disturbances, but subsides after discontinuation of treatment. If these symptoms occur the treating physician should be consulted immediately.

Immune system disorders

Not known: Type 1 hypersensitivity.

Vascular disorders

Not known: Capillary Leak Syndrome / retinoic acid syndrome.

Not all the consequences of long-term therapy with Acitretin can be estimated as yet.

Psychiatric disorders

Not known: Altered mood; psychotic disorder

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. Health professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdose of Acitretin leads to the signs and symptoms of acute hypervitaminosis A, with headache, nausea and/or vomiting, drowsiness, irritability and pruritus.

In the event of acute overdose, the use of Acitretin must be stopped. No further specific measures are necessary because of the low acute toxicity of the product.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics, retinoids for treatment of psoriasis

ATC code: D05BB02

Retinol (Vitamin A) is known to be essential for normal epithelial growth and differentiation, though the mode of this effect is not yet established. Both retinol and retinoic acid are capable of reversing hyperkeratotic and metaplastic skin changes. However, these effects are generally only obtained at dosages associated with considerable local or systemic toxicity.

Acitretin, the active ingredient of Acitretin, is a synthetic aromatic analogue of retinoic acid and the main metabolite of etretinate, which has been used with success for a number of years in the treatment of psoriasis and other disorders of keratinisation.

Clinical studies have confirmed that, in psoriasis and dyskeratosis, acitretin brings about a normalisation of epidermal cell proliferation, differentiation and keratinisation in doses at which the side effects are generally tolerable. The effect of Acitretin is purely symptomatic: the mechanism of action is still largely unknown.

In the case of keratinisation disorders, experience for up to 2 years is available.

5.2 Pharmacokinetic properties

Absorption

Acitretin reaches peak plasma concentration 1 - 4 hours after ingestion of the drug. Bioavailability of orally administered acitretin is enhanced by food. Bioavailability of a single dose is approximately 60%, but inter-patient variability is considerable (36 95%).

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.

Elimination

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 (< 6ng/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.

Clinical evidence has shown that etretinate can be formed with concurrant ingestion of acitretin and alcohol. Etretinate is highly teratogenic and has a longer half-life (approximately 120 days) than acitretin (see section 4.4, 4.5 and 4.6).

5.3 Preclinical safety data

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

For teratogenic effects see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:

Maltodextrin

Sodium ascorbate

Microcrystalline cellulose

Capsule shell:

Gelatin

Propylene glycol (E1520)

Sodium laurilsulfate

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide black (E172)

Iron oxide red (E172)

Purified water

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 years

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original package, in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC aluminium blister packs

Pack sizes:

30 and 60 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals
Linthwaite
Huddersfield
HD7 5QH
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0252

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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