Trustretin-10
Acitretin 10 mg Capsules BP

Trustretin-25
Acitretin 25 mg Capsules BP

Composition
Each Capsule contains
Acitretin Ph.Eur. 10mg / 25mg

Pharmaceutical Form
Capsules for oral administration.
CLINICAL PARTICULARS

Therapeutic indications
Severe extensive psoriasis which is resistant to other forms of therapy.
Palmo-plantar pustular psoriasis.
Severe congenital ichthyosis.
Severe Darier's disease (keratosis follicularis).

Posology and method of administration
Posology
Acitretin should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.
The capsules should be taken once daily with meals or with milk.There is a wide variation in the absorption and rate of metabolism of Acitretin. This necessitates individual adjustment of dosage. For this reason the following dosage recommendations can serve only as a guide.
Adults
Initial daily dose should be 25mg or 30mg for 2 to 4 weeks. After this initial treatment period the involved areas of the skin should show a marked response and/or side-effects should be apparent. Following assessment of the initial treatment period, titration of the dose upwards or downwards may be necessary to achieve the desired therapeutic response with the minimum of side-effects. In general, a daily dosage of 25 - 50mg taken for a further 6 to 8 weeks achieves optimal therapeutic results. However, it may be necessary in some cases to increase the dose up to a maximum of 75mg/day.
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.
Therapy can be discontinued in patients with psoriasis whose lesions have improved sufficiently. Relapses should be treated as described above.
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.
Continuous use beyond 6 months is contraindicated as only limited clinical data are available on patients treated beyond this length of time.
Elderly
Dosage recommendations are the same as for other adults.
Paediatric population
In view of possible severe side-effects associated with long-term treatment, Acitretin is contraindicated in children unless, in the opinion of the physician, the benefits significantly outweigh the risks.
The dosage should be established according to bodyweight. The daily dosage is about 0.5mg/kg. Higher doses (up to 1mg/kg daily) may be necessary in some cases for limited periods, but only up to a maximum of 35mg/day. The maintenance dose should be kept as low as possible in view of possible long-term side-effects.

Combination therapy
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.
When Acitretin is used in combination with other types of therapy, it may be possible, depending on the individual patient's response, to reduce the dosage of Acitretin.

Method of administration
Acitretin capsules are for oral administration.

CONTRAINDICATIONS
Hypersensitivity to the active substance, to other retinoids or to any of the excipients.

Acitretin is highly teratogenic and must not be used by women who are pregnant. The same applies to women of childbearing potential unless strict contraception is practiced 4 weeks before, during and for 3 years after treatment.

The use of Acitretin is contraindicated in women who are breastfeeding.
Acitretin is contraindicated in patients with severe hepatic or renal impairment and in patients with chronic abnormally elevated blood lipid values.
Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated. Supplementary treatment with antibiotics such as tetracyclines is therefore contraindicated .
An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate. Consequently, the concomitant use of methotrexate and Acitretin is contraindicated .
Concomitant administration of Acitretin with other retinoids or Vitamin A is contraindicated due to the risk of hypervitaminosis A.
Owing to the presence of glucose, patients with rare glucose-galactose malabsorption should not take this medicine.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Full patient information about the teratogenic risk and the strict pregnancy prevention measures should be given by the physician to all patients, both male and female.
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 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 .
Women of childbearing potential must not receive blood from patients being treated with acitretin. Therefore donation of blood by a patient being treated with acitretin is prohibited during and for three 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.
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.
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 .
There have been rare reports of benign intracranial hypertension. Patients with severe headache, nausea, vomiting, and visual disturbances should discontinue acitretin immediately and be referred for neurologic evaluation and care.
In adults, especially elderly, receiving long-term treatment with Acitretin, appropriate examinations should be periodically performed in view of possible ossification abnormalities. Any patients complaining of atypical musculo-skeletal symptoms on treatment with Acitretin should be promptly and fully investigated to exclude possible acitretin-induced bone changes. If clinically significant bone or joint changes are found, Acitretin therapy should be discontinued.
Paediatric population
Since there have been occasional reports of bone changes in children, including premature epiphyseal closure, skeletal hyperostosis and extraosseous calcification after long-term treatment with etretinate, these effects may be expected with acitretin. Acitretin therapy in children is not, therefore, recommended. If, in exceptional circumstances, such therapy is undertaken the child should be carefully monitored for any abnormalities of musculo-skeletal development and growth parameters and bone development must be closely monitored.
It should be emphasized that, at the present time, not all the consequences of life-long administration of acitretin are known.
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. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.
High risk patient:
In patients with diabetes, alcoholism, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with acitretin, more frequent checks are necessary of serum values for lipids,and/or glycaemia and other cardiovascular risk indicators, e.g. blood pressure. In diabetics, retinoids can either improve or worsen glucose tolerance. Blood-sugar levels must therefore be checked more frequently than usual in the early stages of treatment.
For all high risk patients where cardiovascular risk indicators fail to return to normal or deteriorate further, dose reduction or withdrawal of acitretin should be considered.
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.
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.
Acitretin should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.
Acitretin is highly teratogenic. The risk of giving birth to a deformed child is exceptionally high if Acitretin is taken before or during pregnancy, no matter for how long or at what dosage. Foetal exposure to Acitretin always involves a risk of congenital malformation.
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.
Acitretin has been shown to affect diaphyseal and spongy bone adversely in animals at high doses in excess of those recommended for use in man.

Since skeletal hyperostosis and extraosseous calcification have been reported following long-term treatment with etretinate in man, this effect should be expected with acitretin therapy.
Patients should be warned of the possibility of alopecia occurring.
Treatment with high dose retinoids can cause mood changes including irritability, aggression and depression.

INTERACTION WITH OTHER MEDICAMENTS
As with other retinoids, acitretin therapy has been associated with hepatotoxicity, increased intracranial pressure, alterations in glucose tolerance, and photosensitivity. Concurrent use of retinoids with other therapies having similar side effects may increase the risk of these adverse events. Various drug interactions are observed in clinical experience wherein patients were administered other medications along with acitretin. Few examples are: Tetracycline (increased photosensitivity, pseudotumor cerebri), minocycline (pseudotumor cerebri), alcohol (increased conversion to etretinate, hepatotoxicity), and other retinoids or vitamin A supplements in excess of minimal daily requirements (hypervitaminosis). Other therapeutic agents that may interact with acitretin and should be monitored carefully include antidiabetic agents (alterations in blood glucose), corticosteroids (hyperlipidemia, pseudotumor cerebri), and methotrexate (increased methotrexate level, hepatotoxicity). In addition, acitretin has been shown to possibly interfere with the contraceptive effect of microdose progestin ("minipill") preparations and in 1 patient was associated with a significant increase in serum progesterone, necessitating withdrawal of acitretin therapy. However, in the same analysis acitretin was shown to not interfere with the antiovulatory effect of estrogen-progesterone combinations even after a prolonged period of intake. Unsupervised excessive exposure to sunlight or sun lamps should be avoided because of increased photosensitivity during retinoid therapy.
Serious Drug Interactions *(Soriatane® Actavis, Product Monograph, 2014, Ormerod AD et al, 2010)*
Vitamin A/retinoids: Concomitant administration of acitretin and vitamin A and other systemic retinoids must be avoided due to the risk of possible additive toxic effects and increased risk of hypervitaminosis A.
Methotrexate: The combined administration of acitretin and methotrexate is contraindicated because of an increased risk of hepatitis reported to result from the combination of methotrexate and etretinate.
Tetracycline: Combined use of acitretin and tetracyclines is contraindicated since both can cause increased intracranial pressure
Alcohol: Clinical evidence has shown that etretinate (prodrug of acitretin) can be formed with concurrent ingestion of acitretin and alcohol
In addition to the drug interactions indicated as serious above the following considerations for drug interactions may apply:
Oral Contraceptives: Low dose progesterone-only products (minipills) may be an inadequate method of contraception during acitretin treatment and are not recommended due to indications of possible interference with their contraceptive effect.
Phenytoin: If acitretin is given concurrently with phenytoin, it must be remembered that acitretin partially reduces phenytoin's protein binding. The clinical significance of this is unknown. Therefore, caution should be exercised when using these drugs together.
Sulfonylurea (glyburide): Limited data indicates that acitretin treatment either increased insulin sensitivity directly or interacted with glyburide to do so. Careful supervision of diabetic patients under treatment with acitretin is recommended
Warfarin: Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction
Phenprocoumon: Concomitant administration of phenprocoumon and acitretin does not alter the hypothrombinemic effect of phenprocoumon or the plasma disposition of Acitretin.
Digoxin: The pharmacokinetics of acitretin and digoxin are not altered by concomitant multiple dose regimens of these two drugs.
Cimetidine: Concomitant administration of cimetidine did not alter the oral bioavailability of acitretin or the isomerization to its 13-cis form. Single oral doses of acitretin did not affect the steady state plasma concentration or renal clearance of cimetidine.

PREGNANCY AND LACTATION
Pregnancy
Acitretin is contraindicated in pregnant women .

Breastfeeding
Acitretin must not be given to nursing mothers .

UNDESIRABLE EFFECTS
Undesirable effects are seen in most patients receiving acitretin. However, the toxic dose of Acitretin is close to the therapeutic dose and most patients experience some side-effects during the initial period whilst dosage is being adjusted. They are usually reversible with reduction of dosage or discontinuation of therapy.
The skin and mucous membranes are most commonly affected, and it is recommended that patients should be so advised before treatment is commenced. An initial worsening of psoriasis symptoms is sometimes seen at the beginning of the treatment period.
The most frequent undesirable effects observed are symptoms of hypervitaminosis A, e.g. dryness of the lips, which can be alleviated by application of a fatty ointment.

Paediatric population
There have been occasional reports of bone changes in children, including premature epiphyseal closure, skeletal hyperostosis and extraosseous calcification after long-term treatment with etretinate, these effects may be expected with acitretin. In children, growth parameters and bone development must be closely monitored.
Diabetics
Retinoids can either improve or worsen glucose tolerance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

OVERDOSE
Manifestations of acute Vitamin A toxicity include severe headache, vertigo, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with Acitretin would probably be similar. Specific treatment is unnecessary because of the low acute toxicity of the preparation.
Because of the variable absorption of the drug, gastric lavage may be worthwhile within the first few hours after ingestion.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties

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, a synthetic aromatic derivative of retinoic acid, has a favourable therapeutic ratio, with a greater and more specific inhibitory effect on psoriasis and disorders of epithelial keratinisation. The usual therapeutic response to acitretin consists of desquamation (with or without erythema) followed by more normal re-epithelialisation.
Acitretin is the main active metabolite of etretinate.

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.
Biotransformation
Acitretin is metabolised by isomerisation into its 13-cis isomer (*cis* acitretin), by glucuronidation and cleavage of the side chain.
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 .
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.

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

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

STORAGE
Store below 30°C.

SHELF LIFE: 36 Months

PRESENTATION
Acitretin Capsules packed in Alu-Alu blisters of 10's pack.

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