Neotigason 10mg and 25mg Capsules

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1 NAME OF THE MEDICINAL PRODUCT

Neotigason 10mg, 25mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard contains Acitretin 10mg, 25mg Capsules

Excipients include glucose and sodium (see section *4.3 Contraindications*).

For a full list of excipients, see section *6.1*.

3 PHARMACEUTICAL FORM

Capsules for oral administration

10 mg Capsules:

Capsules with brown cap and white body with actavis printed in black on the cap and "10" printed in black on the body, containing 10mg acitretin.

25mg Capsules:

Capsules with brown cap and yellow body with actavis printed in black on the cap and "25" printed in black on the body, containing 25mg acitretin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe disorders of keratinization such as erythrodermic psoriasis local or generalized or pustular psoriasis congenital ichthyosis pityriasis rubra pilaris darier's disease.

4.2 Posology and method of administration

Acitretin should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy (see Section 4.6).

Neotigason capsules are for oral administration.

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 Neotigason. 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 contra-indicated 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.

Children
In view of possible severe side-effects associated with long-term treatment, Neotigason is contra-indicated 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 Neotigason. However, the use of topical corticosteroids or bland emollient ointment may be continued if indicated.

When Neotigason 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 Neotigason.

4.3 Contraindications

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 2 years after treatment (see section 4.6).

The use of Neotigason is contra-indicated in women who are breast feeding.

Neotigason is contra-indicated 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 contra-indicated (see section 4.5).

An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate. Consequently, the concomitant use of methotrexate and Neotigason should be avoided (see section 4.5).

Concomitant administration of Neotigason with other retinoids or Vitamin A is contra-indicated due to the risk of hypervitaminosis A.

Neotigason is contra-indicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

Owing to the presence of glucose, patients with rare glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Neotigason 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.

Neotigason is highly teratogenic. The risk of giving birth to a deformed child is exceptionally high if Neotigason is taken before or during pregnancy, no matter for how long or at what dosage. Foetal exposure to Neotigason always involves a risk of congenital malformation.

Neotigason is contra-indicated in women of childbearing potential unless the following criteria are met:

1. Pregnancy has been excluded before instituting therapy with Neotigason (negative pregnancy test within 2 weeks prior to therapy). Whenever practicable a monthly repetition of the pregnancy test is recommended during therapy.

2. She starts Neotigason therapy only on the second or third day of the next menstrual cycle.

3. Having excluded pregnancy, any woman of childbearing potential who is receiving Neotigason must practice effective contraception for at least one month before treatment, during the treatment period and for at least 2 years following its cessation.

   Even female patients who normally do not practice contraception because of a history of infertility should be advised to do so, while taking Neotigason.

4. The same effective and uninterrupted contraceptive measures must also be taken every time therapy is repeated, however long the intervening period may have been, and must be continued for 2 years afterwards.

5. Any pregnancy occurring during treatment with Neotigason, or in the 2 years following its cessation, carries a high risk of severe foetal malformation. Therefore, before instituting Neotigason the treating physician must explain clearly and in detail what precautions must be taken. This should include the risks involved and the possible consequences of pregnancy occurring during Neotigason treatment or in the 2 years following its cessation.

6. She is reliable and capable of understanding the risk and complying with effective contraception, and confirms that she has understood the warnings.

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.

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.
If oral contraception is chosen as the most appropriate contraceptive method for women undergoing retinoid treatment, then a combined oestrogen-progestogen formulation is recommended.

Women of childbearing potential must not receive blood from patients being treated with acitretin. Theoretically there would be a small risk to a woman in the first trimester of pregnancy who received blood donated by a patient on Neotigason therapy. Therefore donation of blood by a patient being treated with acitretin is prohibited during and for two years after completion of treatment with acitretin.

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 2 years after completion of acitretin treatment (see section 4.6 and 5.2).

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.

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. Neotigason 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.

In adults, especially elderly, receiving long-term treatment with Neotigason, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see section *4.8 Undesirable effects*). Any patients complaining of atypical musculo-skeletal symptoms on treatment with Neotigason should be promptly and fully investigated to exclude possible acitretin-induced bone changes. If clinically significant bone or joint changes are found, Neotigason therapy should be discontinued.

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.

Hepatic function should be checked before starting treatment with Neotigason, 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, Neotigason must be withdrawn. In such cases it is advisable to continue monitoring hepatic function for at least 3 months (see section 4.8).

Serum cholesterol and serum triglycerides (fasting values) must be monitored, before starting treatment, one month after the commencement and then every 3 months during treatment especially in high-risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism) and during long-term treatment.

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.

Patients should be warned of the possibility of alopecia occurring (see section *4.8 Undesirable effects*).

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 section 4.8).

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 (see section 4.8).

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

Treatment with high dose retinoids can cause mood changes including irritability, aggression and depression.

High risk patients:
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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Existing data suggests that concurrent intake of acitretin with ethanol led to the formation of etretinate. However, etretinate formation without concurrent alcohol intake cannot be excluded. Therefore, since the elimination half-life of etretinate is 120 days the post-therapy contraception period in women of childbearing potential must be 2 years (see section *4.4 Special warnings and precautions for use).*

Concomitant administration of methotrexate, tetracyclines or vitamin A and other retinoids with acitretin is contraindicated, see section 4.3. An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate.

In concurrent treatment with phenytoin, it must be remembered that Neotigason partially reduces the protein binding of phenytoin. The clinical significance of this is as yet unknown.

Low dose progesterone-only products (minipills) may be an inadequate method of contraception during acitretin therapy, see section 4.6. Interactions with combined estrogen/progestogen oral contraceptives have not been observed.

Interactions between Neotigason and other substances (e.g. digoxin, cimetidine) have not been observed to date.

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. The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible. This should be taken into account when treating women of childbearing age (see section 4.4 and 5.2).

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

4.6 Pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Acitretin is highly teratogenic. Its use is contraindicated in women who might become pregnant during or within 2 years of the cessation of treatment. The risk of giving birth to a deformed child is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage.

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 2 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 2 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 2 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 2 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 2 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 during treatment and for 2 months after stopping treatment (see section 4.4. and 4.5).

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).

Breastfeeding
Acitretin must not be given to nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

Decreased night vision has been reported with Neotigason 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 section *4.8 Undesirable effects*).

4.8 Undesirable effects

Undesirable effects are seen in most patients receiving acitretin. Most of the clinical side-effects of Neotigason are dose-related and are usually well-tolerated at the recommended dosages. However, the toxic dose of Neotigason 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.

Undesirable effects reported for acitretin in clinical trials or as post-marketing events are listed below by System Organ Class and 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 (cannot be estimated from the available data)

Infections and infestations	
Frequency not known	Vulvo-vaginitis due to *Candida albicans*
Immune system disorders	

Frequency not known	Type I hypersensitivity
Nervous system disorders	
Common	Headache
Uncommon	Dizziness
Rare	Neuropathy peripheral
Very rare	Benign intracranial hypertension (see section 4.4)
Eye disorders	
Very common	Drying of and inflammation of mucous membranes (e.g. conjunctivitis, xerophthalmia)*
Uncommon	Vision blurred
Very rare	Night blindness (see section 4.4), ulcerative keratitis
Ear and labyrinth disorders	
Frequency not known	Hearing impaired, tinnitus
Vascular disorders	
Frequency not known	Flushing, Capillary Leak Syndrome/ retinoic acid syndrome
Respiratory, thoracic and mediastinal disorders	
Very common	Drying of and inflammation of mucous membranes (e.g.epistaxis and rhinitis)
Gastrointestinal disorders	
Very common	Dry mouth, thirst
Common	Stomatitis, gastro-intestinal disorders (e.g. abdominal pain, diarrhoea, nausea, vomiting)
Uncommon	Gingivitis
Frequency not known	Dysgeusia, rectal haemorrhage
Hepatobiliary disorders	
Uncommon	Hepatitis
Very rare	Jaundice
Skin and subcutaneous tissue disorders	
Very common	Cheilitis, pruritus, alopecia, skin exfoliation (all over the body, particularly on the palms and soles)
Common	Skin fragility, sticky skin, dermatitis, hair texture abnormal,

	brittle nails, paronychia, erythema
Uncommon	Rhagades, dermatitis bullous, photosensitivity reaction
Frequency not known	Pyogenic granuloma, angioedema,dryness of the skin may be associated with scaling, thinning, erythema (especially of the face), urticaria, hair thinning and frank alopecia**, granulomatous lesions, sweating, rhagades of the corner of the mouth, exfoliative dermatitis
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia
Very rare	Bone pain, exostosis (maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic lesions and in extraskeletal calcification, as has been observed in longterm systemic treatment with retinoids) (see section 4.4).
General disorders and administration site conditions	
Common	Peripheral oedema
Frequency not known	malaise, drowsiness
Investigations	
Very common	Liver function test abnormal (transient, usually reversible elevation of transaminases and alkaline phosphatises) (see section 4.4) Lipids abnormal (during treatment with high doses of acitretin, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients and during long-term treatment (see section 4.4). An associated risk of atherogenesis cannot be ruled out if these conditions persist)

* Dryness of the conjunctivae may lead to mild-to-moderate conjunctivitis or xerophthalmia and result in intolerance of contact lenses; it may be alleviated by lubrication with artificial tears or topical antibiotics.

** Usually noted 4 to 8 weeks after starting therapy, and are reversible following discontinuation of Neotigason. Full recovery usually occurs within 6 months of stopping treatment in the majority of patients.

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

Diabetics
Retinoids can either improve or worsen glucose tolerance (see section 4.4).

4.9 Overdose

In the event of acute overdose, acitretin must be withdrawn at once.

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 Neotigason 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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.

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.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Glucose, liquid, spray-dried
Sodium ascorbate
Gelatin
Purified water
Microcrystalline cellulose

Capsule shell:
Gelatin
Iron oxide red (E172)
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide yellow (E172)

Printing ink:
Shellac
Isopropyl alcohol
N-Butyl alcohol
Black iron oxide
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

None.

6.3 Shelf life

Neotigason 10mg & 25 mg capsules have a shelf-life of 3 years (36 months).

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture. Do not store above 25°C, protect from heat.

6.5 Nature and contents of container

PVC/PVDC (Duplex) blisters with aluminium cover foil containing 30 or 100 capsules.
Not all pack sizes may be available.

6.6 Special precautions for disposal

None.

7 MANUFACTURER(S)

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjordur
Iceland.

8 MARKETING AUTHORISATION HOLDER

Abic Marketing Ltd.
POB 8077,
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Israel

9 MARKETING AUTHORISATION NUMBER(S)

Neotigason 10 mg: 100-62-28448-11

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