

# Data Sheet

## Neotigason<sup>®</sup>

Acitretin 10mg and 25mg capsules

**Retinoid for oral treatment of severe cases of psoriasis and of disorders of keratinization**

### Composition

#### **Active ingredient**

acitretin

Capsules: 10 mg, 25 mg.

#### **Excipient**

The excipients are microcrystalline cellulose, nonatetraenoic acid, gelatin, glucose liquid spray-dried, sodium ascorbate and the colourants iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172) and titanium dioxide (E171).

#### **Appearance**

Neotigason 10mg capsules are oval in shape and have an opaque white body and an opaque brown cap with 'Actavis' printed on the cap and '10' printed on the capsule body. The capsules are No. 4 in size and measure 14mm by 4mm.

Neotigason 25mg capsules are oval in shape and have an opaque yellow body and an opaque brown cap with 'Actavis' printed on the cap and '25' printed on the capsule body. The capsules are No. 1 in size and measure 18mm by 6mm.

### Properties and effects

Acitretin, the active ingredient of Neotigason, is a synthetic aromatic analogue of retinoic acid. In preclinical investigations of the tolerability of acitretin, no relevant mutagenic or carcinogenic effects were found, nor was there any evidence of direct liver toxicity. Acitretin was found to be highly teratogenic in animals.

Clinical trials confirmed that, in psoriasis and disorders of keratinization, acitretin brought about normalization of epidermal cell proliferation, differentiation and cornification, while the side effects were, in general, tolerable. The effect of Neotigason is purely symptomatic; the mechanism of action is as yet largely unknown.

## Pharmacokinetics

### **Absorption**

Acitretin reaches peak plasma concentration 1-4 hours after ingestion of the medicine. Bioavailability of orally administered acitretin is best when the medicine is taken together with food. Bioavailability of a single dose is approximately 60%, but this may vary considerably from one patient to another (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 metabolized by isomerization 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 medicine 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 (<6 ng/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.

## Indications

- Severe psoriasis
- Disorders of keratinization, such as ichthyotic disorders, palmoplantar keratoderma, Darier's disease and lichen planus.
- Other dermatoses responsive to etretinate.

## Dosage and administration

Because there are differences in the absorption and rate of metabolism of acitretin, the dosage must be individually adjusted. The capsules should preferably be taken once daily with a meal, or with milk. The following will serve as guidelines.

## **Adults**

The *initial daily dosage*, 25 mg (i.e. 1 capsule 25 mg) or 30 mg (i.e. 3 capsules 10 mg) for about 2-4 weeks may give satisfactory therapeutic results.

The *maintenance dose* must be based on clinical efficacy and tolerability. In general, a daily dosage of 25-50 mg taken for a further 6-8 weeks achieves optimal therapeutic results.

It may be necessary in some cases to increase the dose up to a maximum of 75 mg/day (i.e. 3 capsules 25 mg).

Therapy can be terminated in patients with *psoriasis* whose lesions have resolved sufficiently. Relapses should be treated as described above.

In *disorders of keratinization*, maintenance therapy is usually needed, though the lowest possible dosage should be given. This may be less than 20 mg/day and should not exceed 50 mg/day.

## **Children**

In view of possible severe side effects associated with long-term treatment, the risk should be carefully weighed against the therapeutic benefit. Acitretin should be used only when all alternative therapies have proved inadequate.

The dosage should be established according to bodyweight. The *daily dosage* is about 0.5 mg/kg. Higher doses (up to 1 mg/kg daily) may be necessary in some cases for limited periods, but only up to a maximum of 35 mg/day. The *maintenance dose* should be kept as low as possible in view of possible long-term side effects.

## **Combination treatment**

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

Standard topical treatments can generally be continued and do not interfere with Neotigason.

## **Contraindications**

Neotigason 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 practised 4 weeks before, during and for 2 years after treatment (see below).

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Women of childbearing potential must not receive blood from patients being treated with Neotigason. Donation of blood by a patient being treated with Neotigason is prohibited during and for two years after completion of treatment with Neotigason.

Neotigason is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values.

Since both Neotigason and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated.

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with Neotigason is also contraindicated.

Concomitant administration of Neotigason and vitamin A or other retinoids is contraindicated due to the risk of hypervitaminosis A.

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

## Precautions

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.

Alcohol (in drinks, food or medicines) must not be ingested during treatment with Neotigason by women of childbearing age, as clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and alcohol. The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible. Etretinate is highly teratogenic and has a longer half life than acitretin. Ethanol should be avoided for 2 months after cessation of acitretin therapy.

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.

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Serum cholesterol and serum triglycerides (fasting values) must be monitored, especially in high-risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism) and during long-term treatment.

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.

In adults receiving long-term treatment with Neotigason, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see Undesirable effects). If such disorders arise, the continuation of therapy should be discussed with the patient on the basis of a careful risk/benefit analysis.

In children, growth parameters and bone development must be closely monitored.

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 Undesirable effects).

Low dosed progesterone preparations (minipills) may be an inadequate method of contraception during Neotigason therapy.

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

For male patients treated with Neotigason, 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, nursing mothers**

### ***Pregnancy***

Neotigason is highly teratogenic. Its use is contraindicated not only in pregnant women and women who might become pregnant during or within 2 years of the cessation of treatment, but in all women of childbearing potential. 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 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 keratinization 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 Neotigason uses an effective contraceptive (preferably 2 complementary methods) without interruption for four weeks before, during and for 2 years after the discontinuation of treatment with Neotigason. Primary contraceptive method is a combination hormonal contraceptive product or an intrauterine device and it is recommended that a condom or a diaphragm (cap) is also used. Low dose progesterone-only products (minipills) are not recommended due to indications of possible interference with their contraceptive effect.
5. Therapy should not begin until the second or third day of the next normal menstrual period.
6. A negative pregnancy test result must be obtained as minimum, one week before commencement of treatment. (It is advisable to perform additional pregnancy tests at monthly intervals during therapy and at 1-3 monthly intervals after stopping therapy.)
7. Before therapy with Neotigason is instituted, the physician must give patients of childbearing potential detailed verbal and written 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 Neotigason 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, during treatment with Neotigason or up to 2 years after its discontinuation there is a high risk of severe malformation of the fetus (e.g. exencephaly).
10. She must avoid alcohol consumption during treatment and for 2 months after stopping treatment.

### ***Nursing mothers***

Neotigason must not be given to nursing mothers.

### **Undesirable effects**

Side effects are seen in most patients receiving Neotigason. However, they usually disappear when the dosage is reduced or the medicine is withdrawn. An initial worsening of psoriasis symptoms is sometimes seen at the beginning of the treatment period.

The most frequent side effects observed are symptoms of hypervitaminosis A, e.g. dryness of the lips, which can be alleviated by application of a fatty ointment.

Mucous membranes and transitional epithelia become dried out or exhibit inflammatory lesions. This has occasionally led to nosebleeds and rhinitis, to ocular disturbances (xerophthalmia, conjunctivitis) and may lead to intolerance of contact lenses. Corneal ulcerations have been observed rarely.

Cheilitis, rhagades of the corner of the mouth, dry mouth and thirst may also occur. Occasionally, stomatitis, gingivitis and taste disturbances have been reported.

Increased incidence of vulvo-vaginitis due to *Candida albicans* has been noted during treatment with Neotigason.

Thinning of the skin and scaling may occur all over the body, particularly on the palms and soles. Sticky skin, dermatitis, erythema and pruritus have been frequently reported.

Increased hair loss, nail fragility and paronychia are frequently observed. Occasionally, bullous eruption and abnormal hair texture have been reported. Rarely, patients may experience photosensitivity reactions.

These side effects are in general reversible after discontinuation of Neotigason treatment.

Headache is occasionally reported although intracranial hypertension (*Pseudotumor cerebri*) is rare. Patients with severe headache, nausea, vomiting, and visual disturbances should discontinue Neotigason immediately and be referred for neurologic evaluation and care. Occasionally, blurred vision and impaired night vision have been noted (see Precautions).

Muscle, joint and bone pain have also been occasionally reported. Maintenance treatment may result in progression of existing spinal hyperostosis, in appearance of new hyperostotic lesions and in extraskkeletal calcification, as has been observed in long-term systemic treatment with retinoids.

Occasionally, peripheral oedema and flushing have been reported. Gastro-intestinal disorders, hepatitis and icterus have been observed rarely.

Transient, usually reversible elevation of transaminases and alkaline phosphatases has been observed.

During treatment with high doses of Neotigason, reversible elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these conditions persist.

Peripheral neuropathy may occur rarely under Neotigason treatment.

## Interactions

Concomitant administration of vitamin A and other retinoids must be avoided because of the risk of hypervitaminosis A.

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

If Neotigason is given concurrently with phenytoin, it must be remembered that Neotigason partially reduces the latter's protein binding.

Low dose progesterone-only products (minipills) may be an inadequate method of contraception during Neotigason therapy.

Methotrexate, tetracyclines: see Contraindications

Further interactions between Neotigason and other substances (e.g. digoxin, cimetidine, combined estrogen/progestogen oral contraceptives) have not been observed so far.

In a study with healthy volunteers concurrent intake of a single dose of acitretin together with ethanol led to the formation of etretinate. This was already observed in vitro. In recent investigations, the formation of etretinate has also been observed in certain patients treated with Neotigason. Until this phenomenon has been fully explained, the pharmacokinetic behaviour of etretinate must be taken into account. Therefore, since the elimination half-life of etretinate is approximately 120 days, contraceptive measures must be taken for 2 years after completion of Neotigason treatment (see Pregnancy).

## Overdosage

In the event of acute overdose, Neotigason must be withdrawn at once. Further special measures are unnecessary because of the low acute toxicity of the preparation. Symptoms of overdose are identical to an acute hypervitaminosis A, i.e. headache and vertigo.

## Special remarks

### **Stability**

The product is sensitive to moisture. Therefore store in the original package.

Store below 25°C.

This medicine should not be used after the expiry date shown on the pack.

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## Medicine Classification

Prescription Medicine.

## Packs

Capsules 10 mg 100's

Capsules 25 mg 100's

## Name and Address

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## Date of Preparation

4 February 2010

**Reference: International Core Data Sheet Version 2, 24-04-2009**