Neotigason®

Acitretin

28068535

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

Product name

Neotigason capsules 10mg
Neotigason capsules 25mg

Composition

Active ingredient: acitretin.
Capsules 10 mg and 25 mg.
Excipient: antioxidant, sodium ascorbate.
The 10mg capsules have a brown cap and a white body with "10", printed in black. Capsule content: powder, eventually with lumps, yellowish to yellow.
The 25mg capsules have a brown cap and a yellow body with "25", printed in black. Capsule content: powder, eventually with lumps, yellowish to yellow.

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 drug. Bioavailability of orally administered acitretin is best when the drug 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 fetal 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 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 (<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 forms of psoriasis including
- erythrodermic psoriasis
- local or generalized pustular psoriasis

Severe disorders of keratinization, such as
- congenital ichthyosis;
- pityriasis rubra pilaris;
- Darier's disease;
- other disorders of keratinization, which may be resistant to other therapies.

Dosage and administration

Acitretin hard capsules are for oral 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 all of the conditions of the Pregnancy Prevention Programme are met (see Warnings and Precautions).
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 3 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.

Warnings and Precautions

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

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.
Ethanol 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 ethanol. The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible. 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.
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).
Microdosed 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.

Psychiatric disorders
Depression, depression aggravated, anxiety, and mood alterations 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.

Pregnancy Prevention Programme
Neotigason is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:
- Severe forms of psoriasis including erythrodermic psoriasis; local or generalized pustular psoriasis, and/or Severe disorders of keratinization, such as congenital ichthyosis; pityriasis rubra pilaris; Darier's disease; other disorders of keratinization which may be resistant to other therapies. (see Indications)
- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk.
- She understands the need for frequent follow-up (e.g. 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 Neotigason.

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 Neotigason, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.
If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within 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 Neotigason, 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
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 Neotigason.
Follow-up visits
Follow-up visits should be arranged at regular intervals, ideally monthly. 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 Neotigason 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 Neotigason 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 Neotigason is not of a sufficient magnitude to be associated with the teratogenic effects of Neotigason. 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 Neotigason because of the potential risk to the foetus of a pregnant transfusion recipient.
Educational material
In order to assist healthcare professionals and patients in avoiding fetal exposure to Neotigason the Product Registration Holder will provide educational material to reinforce the warnings about the teratogenicity of Neotigason, 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.

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 3 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. Fetal exposure to Neotigason always involves a risk of congenital malformation. Neotigason is contraindicated in every woman of childbearing potential. (see Pregnancy Prevention Programme in Warnings and Precautions).

Nursing mothers
Neotigason must not be given to nursing mothers.

Undesirable effects
Undesirable effects are seen in most patients receiving Neotigason. However, they usually disappear when the dosage is reduced or the drug 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 Warnings and 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 extraskeletal calcification, as has been observed in long-term systemic treatment with retinoids. Occasionally, peripheral edema 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.

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 phenytoin's protein binding.
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 behavior 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 3 years after completion of Neotigason treatment (see Pregnancy).

Overdosage
In the event of acute overdosage, 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.

Stability
This medicine should not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.

Storage condition
Do not store above 25°C, store in the original package.

Packs

Capsules 10 mg	30, 100
Capsules 25 mg	30, 100

Medicine: keep out of reach of children.

Date of revision: October 2023

Made under licence from
Actavis Group PTC ehf.
Dalshraun 1, 220 Hafnarfjordur, Iceland.
By Cenexi, 17 rue de Pontoise, 95520, Osny, France.

Actavis
129830_s2
28068535