SUMMARY OF PRODUCT CHARACTERISTICS

Neotigason 10mg

Neotigason 25mg

Capsules

1. NAME OF THE MEDICINAL PRODUCT

Neotigason 10mg
Neotigason 25mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Neotigason 10 mg:
Each capsule contains Acitretin 10 mg

Neotigason 25 mg:
Each capsule contains Acitretin 25 mg

Excipients with known affect: Glucose (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules for oral administration

Neotigason 10 mg:
Hard gelatin capsules with white body and brown cap with “10” printed in black on the body, containing 10 mg acitretin.

Neotigason 25mg:
Hard gelatin capsules with yellow body and brown cap with “25” printed in black on the body, containing 25 mg acitretin.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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 (see Section 4.6).

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. The maintenance dose must be based on clinical efficacy and tolerability. 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, Neotigason is contra-indicated in children unless, in the opinion of the physician, the benefits significantly outweigh the risks.

Neotigason should be used only when all alternative therapies have proved inadequate. The dosage should be established according to bodyweight. The daily dosage is about 0.5mg/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.

Method of administration
Neotigason capsules are for oral administration.

4.3 Contraindications

Hypersensitivity to the active substance, to other retinoids or to any of the excipients listed in section 6.1.

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 practiced 4 weeks before, during and for **3 years** after treatment (see section 4.6).

The use of Neotigason is contraindicated in women who are breastfeeding.

Neotigason 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 (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 is contraindicated (see section 4.5).

Concomitant administration of Neotigason 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.

4.4 Special warnings and precautions for use

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.

Pregnancy Prevention Programme

This medicinal product is **TERATOGENIC**.

Neotigason is contra-indicated in women of childbearing potential unless the following conditions of the Pregnancy Prevention Programme are met:

- She has severe forms of psoriasis (erythrodermic psoriasis, local or generalized pustular psoriasis) or severe keratinization disorders (congenital ichthyosis, pityriasis rubra pilaris, Darier's disease, other disorders of keratinization which may be resistant to other therapies) (see section "Indications").

- 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 (see section "Fertility, pregnancy and lactation" *and 5.2 in the SPC*).

- 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 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 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
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 Neotigason.

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 Neotigason 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 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 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.

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.

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

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).

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*). 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.

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. 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.

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.

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.

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

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.
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 Neotigason 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 (see section 4.8 *Undesirable effects*).

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

Excipients
Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.
Glucose
This medicine contains glucose. For details please see section 4.3.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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.

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. 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).

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.

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

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

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Neotigason 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 is exceptionally high if acitretin is taken before or during pregnancy, no matter for how long or at what dosage.

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

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). 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 3 years following its cessation.

10) 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).

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

Breastfeeding
Neotigason 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 (see section 4.8 "Undesirable effects"). 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).

4.8 Undesirable effects

Summary of the safety profile

Undesirable effects are seen in most patients receiving acitretin. 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. The frequencies of adverse events are ranked according to the following:
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
Psychiatric disorders	
Not known	Altered mood, psychotic disorder
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)
Frequency not known	Dysphonia
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, madarosis, dryness of the skin may be associated with scaling, thinning, erythema (especially of the face), hair thinning and frank alopecia**, granulomatous lesions, sweating, rhagades of the corner of the mouth, angioedema, urticaria, 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 long-term 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.

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.

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics, retinoids for treatment of psoriasis
ATC code: D05BB02

Mechanism of action
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.

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 (see section 4.4, 4.5 and 4.6).

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

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

Printing ink:
Shellac
Isopropyl alcohol
Iron oxide black (E172)
N-Butyl alcohol
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

None.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from light and moisture. 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 marketed.

6.6 Special precautions for disposal

None.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel.

8. REGISTRATION NUMBERS

Neotigason 10mg: 100.62.28448
Neotigason 25mg: 100.61.28449

The leaflet was revised in November 2024.