

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neotigason 10mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules with brown cap and white body with ROCHE printed in black on both cap and body, containing 10mg acitretin.

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe extensive psoriasis which is resistant to other forms of therapy.

Palmo-plantar pustular psoriasis.

Severe congenital ichthyosis.

Severe Darier's disease (keratosis follicularis).

4.2 Posology and method of administration

It is recommended that Neotigason be given only by, or under supervision of, a dermatological specialist.

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

Neotigason is highly teratogenic. Its use is contra-indicated in pregnant women and women who might become pregnant during or within 2 years of the cessation of treatment (see section 4.4 *Special warnings and special precautions for use*).

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

Neotigason is contra-indicated in patients with hepatic or renal impairment and in patients with chronic abnormally elevated blood lipid values.

Rare cases of benign intracranial hypertension have been reported after Neotigason and after tetracyclines. Supplementary treatment with antibiotics such as tetracyclines is therefore contra-indicated.

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.

Concomitant administration of Neotigason with other retinoids or preparations containing high doses of Vitamin A, (i.e. more than the recommended dietary allowance of 4,000 - 5,000 i.u. per day) 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.

In view of the importance of the above precautions, Neotigason Patient Information Leaflets are available to doctors and it is strongly recommended that these be given to all patients.

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

Patients should not donate blood either during or for at least one year following discontinuation of therapy with Neotigason. 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.

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.

In adults 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.

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 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*).

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*).

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 4.3 *Contraindications*).

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.

Interaction studies show acitretin does not interfere with the anti-ovulatory action of the combined oral contraceptives.

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

4.6 Pregnancy and lactation

Neotigason is contra-indicated during pregnancy as it is a known human teratogen.

The use of Neotigason is contra-indicated in women who are breast feeding. It is also contra-indicated in women of childbearing potential unless specific criteria are met, (see section 4.4 *Special warnings and special precautions for use*).

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

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.

Skin: Dryness of the skin may be associated with scaling, thinning, erythema (especially of the face) and pruritus. Palmar and plantar exfoliation may occur. Sticky skin and dermatitis occur frequently. Epidermal fragility, nail fragility and paronychia have been observed.

Occasionally bullous eruptions and abnormal hair texture have been reported. Hair thinning and frank alopecia may occur, 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.

Granulomatous lesions have occasionally been observed.

Sweating has been reported infrequently.

Rarely, patients may experience photosensitivity reactions.

Mucous membranes: Dryness of mucous membranes, sometimes with erosion, involving the lips, mouth, conjunctivae and nasal mucosa have been reported. Corneal ulcerations have been observed rarely.

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.

Cheilitis, rhagades of the corner of the mouth, dry mouth and thirst have occurred. Occasionally stomatitis, gingivitis and taste disturbance have been reported.

Rhinitis and epistaxis have been observed.

Central nervous system: Headache has occurred infrequently. Benign intracranial hypertension has been reported. Patients with severe headache, nausea, vomiting and visual disturbance should discontinue Neotigason immediately and be referred for neurological evaluation and care.

Neuro-sensory system: Blurred or decreased night vision has been reported occasionally.

Musculo-skeletal system: Myalgia and arthralgia may occur and be associated with reduced tolerance to exercise. Bone pain has also been reported.

Maintenance treatment may result in hyperostosis and extraskeletal calcification, as observed in long-term systemic treatment with other retinoids.

Gastrointestinal tract: Nausea has been reported infrequently. Vomiting, diarrhoea and abdominal pain have been observed rarely.

Liver and biliary system disorders: Transient, usually reversible elevation of serum levels of liver enzymes may occur. When significant, dosage reduction or discontinuation of therapy may be necessary. Jaundice and hepatitis have occurred rarely.

Metabolic: Elevation of serum triglycerides above the normal range has been observed, especially where predisposing factors such as a family history of lipid disorders, obesity, alcohol abuse, diabetes mellitus or smoking are present. The changes are dose-related and may be controlled by dietary means (including restriction of alcohol intake) and/or by reduction of dosage of Neotigason. Increases in serum cholesterol have occurred.

Cardiovascular system: Occasionally peripheral oedema and flushing have been reported.

Miscellaneous reactions: Increased incidence of vulvo-vaginitis due to *Candida albicans* has been noted during treatment with acitretin. Malaise and drowsiness have been infrequently reported.

4.9 Overdose

Manifestations of acute Vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with Neotigason would probably be similar. They would be expected to subside without need for treatment.

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 black (E172)
Iron oxide yellow (E172)
Iron oxide red (E172)
Titanium dioxide (E171)

Printing ink:

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

6.2 Incompatibilities

None.

6.3 Shelf life

Neotigason capsules have a shelf-life of 3 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container

All aluminium blisters containing 56 capsules.

PVC/PVDC (Duplex) or PVC/PE/PVDC (Triplex) blisters with aluminium cover foil containing 56 or 60 capsules.

Amber glass bottles with metal screw caps containing 30 or 100 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

MA628/04101.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neotigason 25mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules with brown cap and yellow body with ROCHE printed in black on both cap and body, containing 25mg acitretin.

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe extensive psoriasis which is resistant to other forms of therapy.

Palmo-plantar pustular psoriasis.

Severe congenital ichthyosis.

Severe Darier's disease (keratosis follicularis).

4.2 Posology and method of administration

It is recommended that Neotigason be given only by, or under supervision of, a dermatological specialist.

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

Neotigason is highly teratogenic. Its use is contra-indicated in pregnant women and women who might become pregnant during or within 2 years of the cessation of treatment (see section 4.4 *Special warnings and special precautions for use*).

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

Neotigason is contra-indicated in patients with hepatic or renal impairment and in patients with chronic abnormally elevated blood lipid values.

Rare cases of benign intracranial hypertension have been reported after Neotigason and after tetracyclines. Supplementary treatment with antibiotics such as tetracyclines is therefore contra-indicated.

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.

Concomitant administration of Neotigason with other retinoids or preparations containing high doses of Vitamin A, (i.e. more than the recommended dietary allowance of 4,000 - 5,000 i.u. per day) 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.

In view of the importance of the above precautions, Neotigason Patient Information Leaflets are available to doctors and it is strongly recommended that these be given to all patients.

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

Patients should not donate blood either during or for at least one year following discontinuation of therapy with Neotigason. 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.

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.

In adults 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.

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 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*).

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*).

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 4.3 *Contraindications*).

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.

Interaction studies show acitretin does not interfere with the anti-ovulatory action of the combined oral contraceptives.

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

4.6 Pregnancy and lactation

Neotigason is contra-indicated during pregnancy as it is a known human teratogen.

The use of Neotigason is contra-indicated in women who are breast feeding. It is also contra-indicated in women of childbearing potential unless specific criteria are met, (see section 4.4 *Special warnings and special precautions for use*).

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

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.

Skin: Dryness of the skin may be associated with scaling, thinning, erythema (especially of the face) and pruritus. Palmar and plantar exfoliation may occur. Sticky skin and dermatitis occur frequently. Epidermal fragility, nail fragility and paronychia have been observed.

Occasionally bullous eruptions and abnormal hair texture have been reported. Hair thinning and frank alopecia may occur, 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.

Granulomatous lesions have occasionally been observed.

Sweating has been reported infrequently.

Rarely, patients may experience photosensitivity reactions.

Mucous membranes: Dryness of mucous membranes, sometimes with erosion, involving the lips, mouth, conjunctivae and nasal mucosa have been reported. Corneal ulcerations have been observed rarely.

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.

Cheilitis, rhagades of the corner of the mouth, dry mouth and thirst have occurred. Occasionally stomatitis, gingivitis and taste disturbance have been reported.

Rhinitis and epistaxis have been observed.

Central nervous system: Headache has occurred infrequently. Benign intracranial hypertension has been reported. Patients with severe headache, nausea, vomiting and visual disturbance should discontinue Neotigason immediately and be referred for neurological evaluation and care.

Neuro-sensory system: Blurred or decreased night vision has been reported occasionally.

Musculo-skeletal system: Myalgia and arthralgia may occur and be associated with reduced tolerance to exercise. Bone pain has also been reported.

Maintenance treatment may result in hyperostosis and extraskeletal calcification, as observed in long-term systemic treatment with other retinoids.

Gastrointestinal tract: Nausea has been reported infrequently. Vomiting, diarrhoea and abdominal pain have been observed rarely.

Liver and biliary system disorders: Transient, usually reversible elevation of serum levels of liver enzymes may occur. When significant, dosage reduction or discontinuation of therapy may be necessary. Jaundice and hepatitis have occurred rarely.

Metabolic: Elevation of serum triglycerides above the normal range has been observed, especially where predisposing factors such as a family history of lipid disorders, obesity, alcohol abuse, diabetes mellitus or smoking are present. The changes are dose-related and may be controlled by dietary means (including restriction of alcohol intake) and/or by reduction of dosage of Neotigason. Increases in serum cholesterol have occurred.

Cardiovascular system: Occasionally peripheral oedema and flushing have been reported.

Miscellaneous reactions: Increased incidence of vulvo-vaginitis due to *Candida albicans* has been noted during treatment with acitretin. Malaise and drowsiness have been infrequently reported.

4.9 Overdose

Manifestations of acute Vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of

accidental or deliberate overdosage with Neotigason would probably be similar. They would be expected to subside without need for treatment.

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 black (E172)
Iron oxide yellow (E172)
Iron oxide red (E172)
Titanium dioxide (E171)

Printing ink:

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

6.2 Incompatibilities

None.

6.3 Shelf life

Neotigason capsules have a shelf-life of 3 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container

All aluminium blisters containing 56 capsules.

PVC/PVDC (Duplex) or PVC/PE/PVDC (Triplex) blisters with aluminium cover foil containing 56 or 60 capsules.

Amber glass bottles with metal screw caps containing 30 or 100 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

MA628/04102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)