Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product name: NEOTIGASON 10 mg and 25 mg**
Date of Registration: 5/10/1995	**Dosage form & strength: 10 mg and 25 mg acitretin capsules**

PROFESSIONAL INFORMATION

Applicant: Teva Pharmaceuticals (Pty) Ltd	Product name: NEOTIGASON 10 mg and 25 mg
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SCHEDULING STATUS:

S5

1. NAME OF MEDICINE:

NEOTIGASON® 10 mg (capsules)

NEOTIGASON® 25 mg (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule contains 10 mg or 25 mg acitretin.

Contains sugar (glucose 410 mg).

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

3. PHARMACEUTICAL FORM:

Capsules.

NEOTIGASON 10 mg: capsules with a white, opaque body and brown, opaque cap, imprinted ‘10’ in black.

NEOTIGASON 25 mg: capsules with a yellow, opaque body and brown, opaque cap, imprinted ‘25’ in black.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Severe extensive forms of psoriasis, resistant to all other therapies including:

- local or generalised pustular psoriasis
- erythrodermic psoriasis

Severe disorders of keratinization resistant to all other therapies, including:

- congenital ichthyosis
- pityriasis rubra pilaris
- Darier's disease
- Other disorders of keratinization.

4.2 Posology and method of administration:

Posology:

The quantity of a prescription should only cover treatment for one month to ensure regular monitoring.

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

Adults:

The initial daily dosage:

25 mg (1 capsule; 25 mg) or 30 mg (3 capsules; 10 mg) for about two to four weeks may give satisfactory therapeutic results.

The maintenance dose:

Must be based on clinical efficacy and tolerability. In general, a daily dosage of 25 to 50 mg taken for a further six to eight weeks, achieves optimal therapeutic results. It may be necessary in some cases to increase the dose up to a maximum of 75 mg per day (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:

A continuous maintenance is mostly needed with the dose at the lowest possible level. This may be less than 20 mg/day and should not exceed 50 mg daily.

Combined 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 except keratolytics which should be stopped, can generally be continued and do not interfere with NEOTIGASON.

Method of administration:

NEOTIGASON capsules are for oral administration.

4.3 Contraindications:

Hypersensitivity to acitretin, to other retinoids or to any of the excipients (see **section 6.1**).

NEOTIGASON is highly teratogenic and must not be used by woman who are pregnant. The same applies to women of childbearing potential unless strict contraception is practised 4 weeks before, during and for 3 years after treatment. (See boxed warning under section 4.6).

NEOTIGASON is contraindicated in woman who are breastfeeding.

NEOTIGASON is also contraindicated in patients with severely impaired liver and kidney functions 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. Supplementary treatment with antibiotics such as tetracyclines is therefore contraindicated (see **section 4.5**).

An increased risk of hepatitis has reportedly resulted from the combined use of methotrexate and

etretinate. Consequently the combination of methotrexate with NEOTIGASON is contraindicated (see **section 4.5**).

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

The effect of microdosed progesterone preparations or 'minipills' may be diminished by interaction with acitretin and should not be used (see **section 4.5**).

Children less than 18 years of age or until bone development is complete.

Treatment for longer than 12 months, as limited safety and efficacy data are available.

NEOTIGASON contains glucose therefore 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:

NEOTIGASON is TERATOGENIC.

NEOTIGASON is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She has severe forms of psoriasis (erythrodermic psoriasis, local or generalised 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 4.1**).
- 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 amenorrhoea 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 to 3 monthly intervals for a period of 3 years after stopping NEOTIGASON treatment (see **section 4.6**).
- 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 NEOTIGASON treatment and is continuing to use effective contraception throughout the treatment period and for at least 3 years after cessation of NEOTIGASON treatment.
- Negative pregnancy test results have been obtained before, during and periodically with 1 to 3 monthly intervals for a period of 3 years after stopping NEOTIGASON 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 NEOTIGASON treatment there remains a risk of severe and serious malformation of the foetus. This risk persists until NEOTIGASON 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 provider.

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 NEOTIGASON treatment, throughout treatment and continue for at least 3 years after stopping NEOTIGASON treatment, even in patients with amenorrhoea.

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 25 mUI/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 NEOTIGASON 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 tests periodically with 1 to 3 monthly intervals for a period of 3 years after stopping NEOTIGASON 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 NEOTIGASON.

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 NEOTIGASON to another person and to return any unused capsules to their pharmacist at the end of NEOTIGASON treatment.

Patients should not donate blood during NEOTIGASON therapy and for 3 years following discontinuation of NEOTIGASON because of the potential risk to the foetus of a pregnant transfusion recipient.

Psychiatric disorders: depression, depression aggravated, anxiety, mood alterations and psychotic disorder have been reported in patients treated with systemic retinoids, including NEOTIGASON. 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 as found in NEOTIGASON.

Women of childbearing age must not consume alcohol (in drinks, food or medicines) during treatment with NEOTIGASON and for 2 months after cessation of NEOTIGASON therapy.

The following musculoskeletal changes have been reported after long-term systemic retinoid treatment: hyperostosis, including vertebral hyperostosis and bridging of vertebral bodies; exostoses; extraskeletal calcifications, including soft tissue calcifications; calcification of the anterior spinal ligament and calcification of tendons and ligaments especially ankles, knees and pelvis; periosteal thickening; disk narrowing; cortical bone resorption; osteoporosis; thinning of bones; fractures; premature epiphyseal closure and painless muscle stiffness.

Rarely, severe skin reactions, including erythema multiforme and toxic epidermal necrolysis may occur. Rarely, patients may experience photosensitivity reactions.

Transient and usually reversible elevation of transaminases and alkaline phosphatases have been observed. Elevation of serum triglycerides and serum cholesterol has occurred, especially in high-risk patients (disturbances of lipid metabolism, diabetes, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these disturbances persist.

Hepatic function should be monitored before and every one to two weeks for the first two months after starting treatment with NEOTIGASON and then every three months during treatment. If pathological values for hepatic function are found, monitoring should be repeated at weekly intervals. If they fail to return to normal or if they deteriorate, NEOTIGASON must be withdrawn. It is then advisable to continue monitoring hepatic function for at least three months.

Serum cholesterol and serum triglycerides (fasting values) must be monitored in high-risk patients (disturbances of lipid metabolism, diabetes, obesity, alcoholism) and in long-term treatment, one month after the commencement of NEOTIGASON and then every 3 months during NEOTIGASON treatment. NEOTIGASON treatment should be discontinued in case of uncontrolled levels of hypertriglyceridemia or if symptoms of pancreatitis occur.

High risk patients:
In patients with diabetes, alcoholism, obesity, cardiovascular risk factors or a lipid metabolism disorder

undergoing treatment with NEOTIGASON, 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 should be checked more frequently than usual in the early stages of NEOTIGASON treatment.

For all high risk patients where cardiovascular risk indicators fail to return to normal or deteriorate further, dose reduction or withdrawal of NEOTIGASON should be considered.

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**).

Benign intracranial hypertension has been reported with NEOTIGASON. Patients with severe headache, nausea, vomiting, and visual disturbances should discontinue NEOTIGASON immediately and be referred for neurologic evaluation and care (see **section 4.8**). Since tetracyclines can also cause an increase in intracranial pressure, their combination with NEOTIGASON should be avoided (see **section 4.3**).

In adults, especially elderly, receiving long-term treatment, appropriate examinations should periodically be performed in view of possible ossification abnormalities. In the event of ossification disorders, NEOTIGASON should be discontinued. Any patient complaining of atypical musculoskeletal symptoms during treatment with NEOTIGASON should be promptly and fully investigated to exclude acitretin induced bone changes or extra-skeletal calcification.

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 in children is not, therefore, recommended (see **section 4.3**). If, in exceptional

circumstances, such therapy is undertaken the child should be carefully monitored for any abnormalities of musculoskeletal 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 NEOTIGASON are known.

The effects of UV light are enhanced by retinoid therapy, therefore excessive exposure to sunlight and the unsupervised use of sunlamps should be avoided. 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.

Very rare cases of Capillary Leak Syndrome/retinoic acid syndrome have been reported from worldwide post marketing experience.

Very rare cases of exfoliative dermatitis have been reported from worldwide 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 NEOTIGASON 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.

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 NEOTIGASON therapy.

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

Patients should not donate blood either during or for at least three years following discontinuation of NEOTIGASON.

4.5 Interaction with other medicines and other forms of interaction:

Alcohol (in drinks, food or medicines) must not be ingested during treatment with NEOTIGASON by women of childbearing age as etretinate, which is highly teratogenic, can be formed with concurrent ingestion of NEOTIGASON and ethanol. Etretinate formation from acitretin is enhanced by the ingestion of alcohol. Alcohol should also be avoided during NEOTIGASON treatment and for 2 months after cessation of NEOTIGASON therapy.

Concomitant administration of vitamin A and other retinoids must be avoided because hypervitaminosis A could arise.

In investigations on the effect of NEOTIGASON on the protein binding of anticoagulants of the coumarin type (warfarin), no interaction was detected.

In concurrent treatment with phenytoin, it must be remembered that NEOTIGASON partially reduces the protein binding of phenytoin.

Further interactions between NEOTIGASON and other substances e.g. digoxin, cimetidine, combined

estrogen/progesterone oral contraceptives, have not been observed so far.

The effect of microdosed progesterone preparations or “minipills” may be diminished by interaction with NEOTIGASON and should not be used. Interactions with combined estrogen/progestogen oral contraceptives have not been observed.

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

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential / Contraception in males and females:

NEOTIGASON is highly teratogenic.

NEOTIGASON 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 NEOTIGASON 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 keratinization which is resistant to standard therapies.
2. She can be relied on to understand and follow the physician's instructions.
3. She is capable of taking the stipulated contraceptive measures reliably and without fail.
4. It is absolutely essential that every woman of childbearing potential who is to undergo treatment with NEOTIGASON uses effective contraception (preferably 2 complementary methods) without interruption for four weeks before, during and for 3 years after the discontinuation of treatment with NEOTIGASON. 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. NEOTIGASON 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 NEOTIGASON 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 NEOTIGASON prescription is made at these visits. After stopping NEOTIGASON therapy, pregnancy tests should be performed at 1 to 3 monthly intervals for a period of 3 years after the last dose is given.
7. Before therapy with NEOTIGASON is instituted, patients of childbearing potential must be examined for pregnancy and told clearly and in detail by the physician about the precautions to be taken, the risk of severe foetal malformation, and the possible consequences should pregnancy occur during the course of treatment with NEOTIGASON or within three years of discontinuing therapy.
8. The same effective and uninterrupted contraceptive measures must be taken every time NEOTIGASON therapy is repeated, independently of the intervening period, and must be continued for three 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 NEOTIGASON and 2 months after treatment. For up to 3 years after NEOTIGASON 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.

Women of childbearing age must not consume alcohol (in drinks, food or medicines) during treatment with NEOTIGASON and for 2 months after cessation of NEOTIGASON therapy (see **sections 4.4** and **4.5**).

Women of childbearing potential must not receive blood from patients treated with NEOTIGASON.

NEOTIGASON must not be given to nursing mothers.

Primary contraceptive method can be 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 NEOTIGASON, available data, based on the level of maternal exposure from the semen and seminal fluid indicate a minimal, if any, risk of teratogenic effects.

Pregnancy:

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**). 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:

Patients must be informed about all the possible side effects before treatment is commenced, and

patients must confirm in writing that they have understood what has been explained to them.

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

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

Undesirable effects reported for NEOTIGASON 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:	
Frequency 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)* which may lead to intolerance of contact lenses
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, gastrointestinal 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, acne, 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, angioedema, urticaria, thinning of skin, exfoliative dermatitis, 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
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 phosphatases) (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 NEOTIGASON. 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose:

In the event of acute overdosage, NEOTIGASON must be withdrawn at once. Further treatment is supportive and symptomatic.

Manifestations of acute Vitamin A toxicity include severe headache, vertigo, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with NEOTIGASON would probably be similar. Specific treatment is unnecessary because of the low acute toxicity of the preparation.

Because of the variable absorption of NEOTIGASON, gastric lavage may be worthwhile within the first few hours after ingestion.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 13.4.2 Dermatological preparations - other.

Pharmacotherapeutic group: Antipsoriatics, retinoids for treatment of psoriasis

ATC code: D05BB02

Acitretin, the active ingredient of NEOTIGASON, is a synthetic aromatic analogue of retinoic acid. The mechanism of action is unknown.

5.2 Pharmacokinetic properties:

Absorption:

Acitretin reaches maximum plasma concentration one to four hours after ingestion. Bioavailability of orally administered acitretin is best when it is taken together with food. Bioavailability of a single dose is

approximately 60 %, but this may vary from one patient to another (36 to 95 %).

Distribution:

Acitretin is highly lipophilic and penetrates readily into the body tissues. It is highly bound to plasma proteins. In animal studies, acitretin passed the placental barrier in quantities sufficient to produce foetal malformations. Due to its lipophilic nature, acitretin passes into the breast milk.

Metabolism:

Acitretin is metabolised 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 to 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 for acitretin (96 hours) and *cis* acitretin (123 hours), it can be predicted that more than 99 % 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule contents: microcrystalline sodium, gelatin, glucose, sodium ascorbate.

Capsule shell: gelatin, iron oxide black (E172), iron oxide yellow (E172), iron oxide red (E172), titanium dioxide (E171), shellac, propylene glycol and ammonium hydroxide.

6.2 Incompatibilities:

None.

6.3 Shelf life:

3 years.

6.4 Special precautions for storage:

Store below 25˚C. Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container:

NEOTIGASON capsules 10 mg: Pack size 30.

NEOTIGASON capsules 25 mg: Pack size 30.

6.6 Special precautions for disposal:

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park,

Magwa Crescent West,

Waterfall City, Midrand,

Gauteng,

South Africa,

2090

8. REGISTRATION NUMBER:

NEOTIGASON 10 mg: W/13.4.2/73

NEOTIGASON 25 mg: W/13.4.2/74

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

5 October 1995

10. DATE OF REVISION OF THE TEXT:

13 February 2026