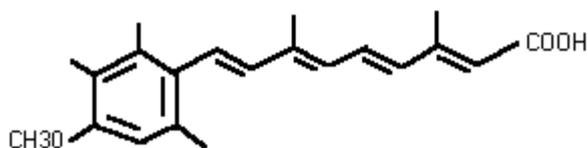


NAME OF THE MEDICINE

NEOTIGASON®

acitretin

CAS Registry Number: 55079-83-9



DESCRIPTION

NEOTIGASON (acitretin) is a retinoid for the oral treatment of severe cases of psoriasis and disorders of keratinisation. It is available in 10 and 25 mg capsules.

The chemical name of acitretin is all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. Its empirical formula is $C_{21}H_{26}O_3$ with a molecular weight of 326.44. Acitretin is a metabolite of etretinate and is related to both retinoic acid and retinol (Vitamin A).

Acitretin is a green-yellow crystalline powder. It is virtually insoluble in water (< 0.1 mg/100 mL). The pKa is approximately 5. It is present in the capsules as a spray-dried powder.

PHARMACOLOGY

Pharmacodynamics

NEOTIGASON reverses the epidermal proliferation and increased keratinisation seen both in chemically induced epithelial tumours in animals and in hyperkeratotic disorders in man.

Vitamin A (retinol and its esters) can beneficially influence hyperkeratotic changes in the skin or metaplasias of the mucous membranes.

Pharmacokinetics

Absorption and Bioavailability

Acitretin reaches peak plasma concentration 1 - 5 hours after ingestion of the medicine. Bioavailability of orally administered acitretin is best when the medicine is taken together with food. Bioavailability of a single dose is approximately 60%, but this may vary considerably from one patient to another (36 - 95%).

After administration of a single 50 mg oral dose of acitretin to 18 healthy subjects, maximum plasma concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in 2 to 5 hours (mean 3.5 hours). The oral absorption of acitretin is linear and proportional with increasing doses from 25 to 100 mg. Following multiple doses, acitretin plasma concentrations reached steady-state conditions within two weeks and accumulation was 0.5 to 2.6-fold higher than after a single dose. In patients with psoriasis, mean steady-state trough concentrations of acitretin increased in a proportional manner and ranged between 6 and 7 ng/mL, 11 and 14 ng/mL, and 19 and 25 ng/mL over an eight week period at daily oral doses of 10 mg, 25 mg and 50 mg, respectively. In this same

study, acitretin plasma concentrations were non-measurable (< 4 - 6 ng/mL) in all patients where blood samples were drawn three weeks after cessation of therapy.

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. Both acitretin and its 13-*cis* isomer are eliminated from the body primarily by metabolism to chain-shortened breakdown products and conjugates that are ultimately excreted in the faeces (35 - 45%) and urine (48 - 61%). The formation of the 13-*cis* isomer relative to parent compound is not altered by dose or fed/fasted conditions of oral administration of acitretin. The elimination of the 13-*cis* isomer is essentially parallel to that of acitretin after multiple doses.

There was no detectable formation of etretinate when a single 100 mg oral dose of acitretin was administered without concurrent ethanol ingestion. Although the formation of etretinate without concurrent ethanol ingestion cannot be excluded, only 7.5% of 240 evaluated psoriatic patients on acitretin therapy (5 - 60 mg/day) in controlled and uncontrolled clinical trials were found to have measurable etretinate concentrations (5 ng/mL). Of these patients, the last measurable etretinate concentration was observed at two months after cessation of acitretin therapy.

Animal studies confirm the possibility that, in the rat at least, metabolism of acitretin to etretinate in the absence of alcohol can occur.

Elimination

Multiple-dose studies in patients aged 21-70 years showed an elimination half-life of approximately 50 hours for acitretin and 60 hours for its main metabolite in plasma, *cis* acitretin, which is also a teratogen. From the longest elimination half-life observed in these patients for acitretin (96 hours) and *cis* acitretin (123 hours), and assuming linear kinetics, it can be predicted that more than 99% of the drug is eliminated within 36 days after cessation of long-term therapy. Furthermore, plasma concentrations of acitretin and *cis* acitretin dropped below the sensitivity limit of the assay (< 6 ng/mL) within 36 days following cessation of treatment. Acitretin is excreted entirely in the form of its metabolites, in approximately equal parts via the kidneys and the bile.

Special Populations

Plasma concentrations of acitretin were significantly lower in end stage renal failure subjects ($n = 6$) when compared to age-matched controls following single 50 mg oral doses. However, acitretin was not removed by haemodialysis in these subjects.

In a multiple-dose study in healthy young ($n = 6$) and elderly ($n = 8$) subjects, increased acitretin plasma concentrations were seen in elderly subjects although the elimination half-life did not change.

CLINICAL TRIALS

Use of NEOTIGASON in psoriatic patients results in improvement manifested by a decrease in scale, erythema and thickness of lesions, and decreased inflammation in the epidermis.

INDICATIONS

Acitretin may be used for the treatment of:

- Severe intractable psoriasis in all its forms
- Severe forms of disorders of keratinisation such as
 - hyperkeratosis palmaris et plantaris
 - pustulosis palmaris et plantaris
 - ichthyosis
 - keratosis follicularis (Darier's disease)
 - lichen planus affecting the skin or the mucosae
 - pityriasis rubra pilaris

CONTRAINDICATIONS

NEOTIGASON is teratogenic and must not be used by patients who are pregnant or who intend to become pregnant during therapy or for 2 years after cessation of therapy.

NEOTIGASON is also contraindicated in people who are hypersensitive to acitretin or other ingredients in NEOTIGASON capsules or to other retinoids.

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

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

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

An increased risk of hepatitis has been reported to result from combined use of methotrexate and Tigason[®] (active ingredient: etretinate). Consequently, the combination of methotrexate with NEOTIGASON is also contraindicated.

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

PRECAUTIONS

Use in Pregnancy: Category X

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 must not be used by females who are pregnant or who may become pregnant while undergoing treatment. There have been no reports of births where there had been foetal exposure to NEOTIGASON. However, acitretin is a metabolite of etretinate and major human foetal abnormalities have been reported with the administration of etretinate and could be expected with NEOTIGASON. Potentially any exposed foetus can be affected. Acitretin has been shown to be embryotoxic and/or teratogenic in mice, rats and rabbits at doses approximately 3, 15 and 0.5 times the maximum recommended therapeutic dose, respectively.

NEOTIGASON is contraindicated in women of childbearing potential unless the patient meets all of the following conditions:

- has severe psoriasis or disorder of keratinisation
- is unresponsive to or intolerant of standard non-teratogenic therapies
- is reliable in understanding and carrying out instructions
- is capable of complying with the mandatory contraceptive measures
- has received both oral and written warnings of the hazards of foetal exposure to NEOTIGASON and the risk of possible contraception failure and has acknowledged her understanding of these warnings
- has had a negative serum or urine pregnancy test within two weeks prior to beginning therapy
- will begin therapy only on the second or third day of the next normal menstrual period.

It is recommended that a prescription should not be issued until a report of a negative pregnancy test has been obtained and the patient has begun her menstrual period. It is also recommended that pregnancy testing and contraception counselling be repeated on a regular basis.

Acitretin is a metabolite of etretinate. Major human foetal abnormalities related to etretinate administration have been reported, including meningocele, meningoencephalocele, multiple synostoses, facial dysmorphism, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray. Fatalities related to some of these malformations have been reported.

Effective contraception must be used for at least one month before beginning NEOTIGASON therapy and throughout therapy.

The formation of etretinate has been observed in certain patients treated with NEOTIGASON. Until this phenomenon has been fully explained, the pharmacokinetic behaviour of etretinate must be taken into account. Since the elimination half-life of etretinate is approximately 120 days, contraceptive measures must be taken for two years following discontinuation of therapy even where there has been a history of infertility, unless due to hysterectomy.

Women who have taken Tigason[®] (etretinate) must continue to follow the contraceptive recommendations for Tigason[®].

If pregnancy does occur, the physician and patient should discuss the desirability of continuing the pregnancy.

Use in Lactation

NEOTIGASON must not be given to nursing mothers.

Hepatic Toxicity

Elevated transaminase and alkaline phosphatase levels have been noted in a number of patients receiving acitretin. Several cases of hepatitis have been noted in association with etretinate.

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 hepatotoxicity is suspected during NEOTIGASON treatment the drug must be discontinued and the aetiology further investigated.

Lipids

Blood lipid determinations should be performed before NEOTIGASON is administered and again at intervals of one to two weeks until the lipid response to the drug is established, which is usually within four to eight weeks. Approximately 65% of patients receiving NEOTIGASON during clinical trials experienced an elevation in triglycerides. Approximately 30% developed a decrease in high density lipoproteins (HDL). The mean cholesterol level of the study population rose slightly with time but never exceeded the normal range, although some individual patients did exceed the normal range. These effects of NEOTIGASON were reversible upon cessation of therapy.

Patients with an increased tendency to develop hypertriglyceridaemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions.

Hypertriglyceridaemia and lowered HDL may increase a patient's cardiovascular risk status. Therefore, every attempt should be made to control significant elevations of triglycerides or HDL decreases by reduction of weight or restriction of dietary fat and alcohol intake while continuing NEOTIGASON therapy.

Use in Diabetes

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.

Paediatric Use

Skeletal changes in premature epiphysial ossification are seen in young animals treated with etretinate. These effects have not been observed in man but only a limited number of children have been studied. Because of the uncertain effects of acitretin on growth and skeletal development, the drug should only be used in those under 18 in the following situations: life-threatening circumstances where other therapy cannot be used or is not effective; and in severe forms of the

disorder for which there is no alternative therapy. Growth parameters and bone development must be closely monitored in all patients on long-term therapy, by regular measurement and X-ray.

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

Pseudotumour Cerebri

NEOTIGASON and other retinoids administered orally have been associated with cases of pseudotumour cerebri (benign intracranial hypertension). Early signs and symptoms include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these signs and symptoms should be examined for papilloedema and, if present, should discontinue NEOTIGASON immediately and be referred for neurologic evaluation and care.

Hyperostosis

In clinical trials with NEOTIGASON, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column. Of 262 patients treated with NEOTIGASON, 7% had pre-existing abnormalities of the spine, which showed new changes or progression of pre-existing findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, and narrowing and destruction of a cervical disc space. These existing abnormalities may be in some part attributable to the underlying psoriasis and/or the patient's age. No bone changes were seen in patients who had normal pre-treatment X-rays. A substantially higher incidence of hyperostosis has been observed with oral administration of other retinoids also involving patients without pre-existing abnormalities of the spine.

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

Patients should be advised that a transient increase in psoriasis is sometimes seen during the initial treatment period.

Patients should be advised that they may experience decreased tolerance to contact lenses during the initial treatment period.

It is recommended that patients do not donate blood during and for two years following therapy.

Carcinogenicity

Carcinogenicity studies carried out with acitretin showed an increase in the frequency of blood vessel tumours (haemangiomas and haemangiosarcomas) in male mice.

Interactions with Other Medicines

Preliminary studies indicated that acitretin does not interfere with the actions of oestrogen-progesterone oral contraceptives. In a study of ten healthy male volunteers, acitretin did not interfere with the hypoprothrombinemic effect of the coumarin-type anticoagulant, phenprocoumon. Progestogen-only oral contraceptives ("Minipills") should be avoided as a contraceptive measure because their efficacy may be reduced by retinoid treatment.

In a study of twelve healthy male subjects, the concomitant administration of digoxin and acitretin did not alter the pharmacokinetics of either drug. In a study of ten healthy men, the concomitant administration of cimetidine and acitretin did not alter the pharmacokinetics of either drug.

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

Concomitant administration of alcohol may cause increased levels of etretinate, which is much slower than acitretin to be eliminated from the body. Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol. In a 2-way crossover study, all 10 subjects formed etretinate with concurrent ingestion of a single 100 mg oral dose of acitretin during a 3 hour period of ethanol ingestion (total ethanol ~1.4 g/kg body weight). A mean peak etretinate concentration of 59 ng/mL (range: 22 - 105 ng/mL) was observed and extrapolation of AUC values indicated that the formation of etretinate in this study was comparable to a single 5 mg oral dose of etretinate. Ethanol must not be ingested during treatment with NEOTIGASON by women of childbearing age, as clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol. The mechanism of this metabolic process has not been defined, so it is not clear whether other interacting agents are also possible. Ethanol should be avoided for two months after cessation of acitretin therapy.

There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, phenprocoumon, oral contraceptives or glyburide.

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.

ADVERSE EFFECTS

Adverse effects are seen in most patients receiving NEOTIGASON. However, they usually disappear when the dosage is reduced or the drug withdrawn. An initial worsening of the disease symptoms is sometimes seen.

Most of the adverse effects occurring in association with systemic retinoids including NEOTIGASON resemble those of excessive vitamin A intake.

Skin and Appendages

Very Common: dry skin, pruritus, erythema, rash, scaling particularly on palms and soles, skin fragility, thinning of skin, sticky skin, alopecia, nail fragility, paronychia.

Common: bullous eruption, abnormal hair texture.

Uncommon: photosensitivity reactions.

Rare: retinoid dermatitis (occasionally provoking psoriatic lesions), urticaria.

Ocular

Very Common: dry eyes, eye irritation, intolerance of contact lenses, xerophthalmia, conjunctivitis.

Common: blurred vision, impaired night vision.

Rare: keratitis, corneal erosions, abrasion and irregularities leading to corneal opacities, papilloedema.

Special Senses Other

Common: tinnitus, taste perversion.

Uncommon: deafness.

Respiratory

Common: epistaxis, rhinitis.

Cardiovascular

Common: flushing.

Musculoskeletal

Common: arthralgia, arthritis, muscle, joint and bone pain. In chronic hypervitaminosis A syndrome, demineralisation and rarefaction of bone, cortical hyperostosis, periosteal calcification, premature epiphyseal closures (see Precautions, Paediatric Use). In long-term treatment, irreversible hyperostosis and extra-skeletal calcification e.g. spinal hyperostosis and calcification of spinal ligaments resulting in spinal cord compression (see Precautions, Hyperostosis).

Rare: elevated serum creatine kinase (CK); myalgia in the case of marked CK elevation.

Neurological and Psychiatric

Common: headache, fatigue, depression, somnolence.

Uncommon: lassitude, vertigo, disturbance of consciousness, abnormal thinking, emotional lability, aggressive feelings.

Rare: pseudotumour cerebri (see Precautions, Pseudotumour Cerebri).

Endocrine

Rare: gynaecomastia.

Metabolic and Nutritional

Very Common: elevated serum cholesterol and triglycerides (see Precautions, Hepatic Toxicity).

Rare: oedema, thirst.

Liver and Biliary System

Very Common: elevated serum transaminases and alkaline phosphatase (see Precautions, Lipids).

Uncommon: jaundice, hepatitis.

Gastrointestinal

Very Common: cheilitis, rhagades of corner of mouth, dry mouth.

Common: stomatitis, gingivitis.

Uncommon: gastritis, heartburn, inflammatory bowel disorders.

Rare: pancreatitis.

Genitourinary

Rare: metrorrhagia.

Immunological

Uncommon: vulvovaginitis due to *Candida albicans*.

DOSAGE AND ADMINISTRATION

Adults

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 meals, or with milk.

An initial dosage of 25 mg or 30 mg for about two to four weeks may give satisfactory therapeutic results.

The maintenance dose must be based on clinical efficacy and tolerance. In general, a daily dosage of 25 - 50 mg taken for a further six to eight weeks achieves optimal therapeutic results.

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

In disorders of keratinisation, a continuous maintenance is mostly needed with the dose at the lowest possible level. This may be less than 20 mg and should not exceed 50 mg daily.



Children

The dosage should be established on a weight basis. The daily dosage is about 0.5 mg/kg. Higher doses up to 1 mg/kg or 35 mg daily may be necessary in some cases for limited periods. Maintenance doses should be kept as low as possible in view of possible long term adverse effects.

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 (see **PRECAUTIONS Interactions with Other Medicines**). Standard topical treatments can generally be continued and do not interfere with NEOTIGASON.

OVERDOSAGE

In the event of acute overdosage, NEOTIGASON must be withdrawn at once. Symptoms of overdose are identical to an acute hypervitaminosis A, i.e. headache and vertigo. The acute oral toxicity (LD₅₀) of acitretin in both mice and rats was greater than 4000 mg/kg.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

NEOTIGASON 10 mg hard gelatine capsules have a white opaque body and a brown opaque cap with the word "ROCHE" printed in black ink on both body and cap.

NEOTIGASON 25 mg hard gelatine capsules have a yellow opaque body and a brown opaque cap with the word "ROCHE" printed in black ink on both body and cap.

Capsules 10 mg, cartons of 100

Capsules 25 mg, cartons of 100

Store below 25°C

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

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine



NAME AND ADDRESS OF THE SPONSOR

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