1. **What Levothyroxine tablets are and what they are used for**
Levothyroxine belongs to a group of medicines called thyroid hormones, which are used to treat hypothyroidism (underactive thyroid gland).

2. **Before you take**

*Do not take* Levothyroxine tablets and tell your doctor if you:

- are **allergic** (hypersensitive) to anhydrous levothyroxine sodium or any other ingredients in Levothyroxine tablets (see section 6).
- are suffering from a condition that produces excessive quantities of thyroid hormone (**thyrotoxicosis**).
- are suffering from **untreated adrenal** problems.

**Check with your doctor or pharmacist before taking Levothyroxine tablets** if you:

- have any heart problems or have had a heart attack
- suffer from high blood pressure
- are elderly or have severe long term hypothyroidism (underactive thyroid gland)
- are suffering from a condition caused by an underactive adrenal gland such as panhypopituitarism
- have diabetes.

**Taking other medicines**
Please **tell your doctor or pharmacist** if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:

- medicines to treat diabetes (eg insulin, metformin)
- medicines to control your heart rate such as digoxin
- tricyclic antidepressants (eg amitriptyline, dosulepin)
- medicines that stimulate the sympathetic nervous system such as adrenaline (epinephrine)
- anticoagulants (used to thin the blood) such as warfarin, dicoumarol, acenocoumarol, phenindione
- sodium polystyrene sulphonate (used to treat kidney disease)
- colesytramine (used to treat diarrhoea)

3. **How to take**
Always take Levothyroxine tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

**Swallow the tablets with water, before food.**

**Doses:**

**Adults:**
Initially 50-100 micrograms a day increased by 50 micrograms every 3-4 weeks up to a maximum of 150-300 micrograms a day, until normal metabolism is maintained.
Patients over 50 years:
Initially no more than 50 micrograms a day should be taken.

Patients over 50 years with heart disease:
25 micrograms a day or 50 micrograms every other day should be taken, this may be increased by 25 micrograms a day every 4 weeks.

Congenital hypothyroidism in infants:
Initially 25 micrograms a day, increased by 25 micrograms every 2-4 weeks until mild toxic symptoms appear, the dose will then be reduced slightly.

Juvenile myxoedema:
Initially 25 micrograms a day, increased by 25 micrograms every 2-4 weeks until mild toxic symptoms appear, the dose will then be reduced slightly.

In children over 1 year, initially 2.5-5 micrograms per kg of bodyweight a day should be taken.

If you take more than you should
If you (or someone else) swallow a lot of the tablets at the same time, or you think a child may have swallowed any, contact your nearest hospital casualty department or tell your doctor immediately. Symptoms of an overdose include:

- **Mild to moderate overdose:** fever, angina, a racing heart, irregular heart beats, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea.
- **Severe overdose:** thyroid crisis including irregular heart beats, heart failure, collapse, coma, death.

Signs and symptoms of increased thyroid hormone levels may not be seen for up to 5 days.

If you forget to take the tablets
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose take it as soon as you remember it and then take the next dose at the right time.

If you stop taking the tablets
Talk to your doctor before you stop taking the tablets and follow their advice.

### 4. Possible side effects

Like all medicines, Levothyroxine tablets can cause side effects, although not everybody gets them. Please tell your doctor or pharmacist if you notice any of the following effects or any effects not listed.

**Tell your doctor** if you notice any of the following side effects:

- **Allergic reactions:** including a rash which may be itchy or swelling.

The following side effects may be due to high doses and usually disappear after reducing the dose or stopping the tablets. **Tell your doctor** if you notice:

- **Heart:** a racing heart, irregular heart beats, palpitations, anginal pain.
- **Central nervous system:** headache, restlessness, excitability, difficulty in sleeping, flushing, sweating, fever, involuntary shakiness, heat intolerance.
- **Stomach and intestines:** diarrhoea, being sick, excessive weight loss.
- **Muscle and bone:** muscle cramps, muscular weakness.
- **Other:** partial hair loss during first few months of therapy.

### 5. How to store

- Keep out of the reach and sight of children.
- Do not store above 25ºC. Store in the original package. Keep container in the outer carton.
- Do not use Levothyroxine tablets after the expiry date stated on the label/carton/bottle. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

### 6. Further information

**What Levothyroxine tablets contain**

- The active substance (the ingredient that makes the tablets work) is anhydrous levothyroxine sodium. Each tablet contains either 50 micrograms or 100 micrograms of the active substance.
- The other ingredients are lactose, magnesium stearate, maize starch, stearic acid and pregelatinised maize starch.

**What Levothyroxine tablets look like and contents of the pack**

50 microgram tablets are white, circular, biconvex, uncoated tablets.
100 microgram tablets are white, circular, shallow convex, uncoated tablets. Pack size is 28 and 1000 tablets.

**Marketing Authorisation Holder and Manufacturer**

Actavis, Barnstaple, EX32 8NS, UK.

This leaflet was last revised in August 2007.

In addition to advice from your doctor or pharmacist, you can also contact the association listed below for more information on thyroid disease:
The British Thyroid Foundation, PO Box 97, Clifford, Wetherby, West Yorkshire, LS23 6XD, Tel/Fax: 01423 709707

**Lactation**

Neotigason must not be given to nursing mothers. Progestogen-only agents (minipills) should not be used for contraception during retinoid therapy as their efficacy may be reduced. It is not known whether acitretin in the seminal fluid of male patients treated with the drug poses teratogenic risk to a fetus.

**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 disorders should be carefully monitored (see Undesirable effects).

**Undesirable Effects**

Most side effects of Neotigason are dose-related. In general, they are reversible after discontinuing Neotigason treatment. An initial worsening of psoriasis symptoms has been observed at the beginning of the treatment period. Frequently, symptoms are analogous to hypervitaminosis A, i.e. dryness of the skin and mucous membranes and dry lips.

**Metabolic and nutritional disorders**

During high-dose treatment with Neotigason, reversible elevation of serum triglyceride and cholesterol levels has occurred, especially in high-risk patients (disturbed lipid metabolism, diabetes mellitus, obesity, alcoholism). An associated risk of atherogenesis cannot be ruled out if these conditions persist.

**Nervous system**

Occasional: headache. Rare: pseudomotor cerebri. Patients with strong headaches, nausea, vomiting and visual disorders should discontinue Neotigason therapy immediately and be referred for neurologic evaluation and care.

**Eyes**

Occasional: Xerophthalmia; conjunctivitis, which may lead to intolerance of contact lenses; blurred vision; decreased night vision. Rare: corneal ulcer (rare).

**Vascular disorders**

Occasional: peripheral edema; flushing.

**Gastrointestinal tract**

Rare: gastrointestinal disorders; pancreatitis.

**Liver and/or bile**

Transient, usually reversible elevation of transaminases and alkaline phosphatases. Rare: hepatitis and icterus.

**Skin and subcutaneous Tissue**

Cheilitis, rhagades of the corner of the mouth; dry mouth and thirst may occur, besides thinning of the skin and scaling may occur all over the body, particularly on the palms and soles. Increased incidence of vulvovaginitis due to Candida albicans has been noted during treatment. Frequent: sticky skin, dermatitis, erythema, pruritus, increased hair-loss, nail fragility, paronychia. Occasional: stomatitis, gingivitis, taste disturbances; epidermal necrolysis, epistaxis, rhinitis, pharyngitis (hoarseness), bullous eruptions, and change of the tegmental structure. Rare: increased sensitivity to light, photosensitivity reactions.

**Skeletal Muscles, Connective tissue, Bones**

Occasional: myalgia, arthralgia, bone pain. Maintenance therapy can lead to progression of a pre-existing spinal hyperostosis, to the occurrence of new hyperostotic lesions, to extraskeletal sclerosis and premature epiphyseal closing, as has been observed in patients after systemic long-term treatment with high doses of retinoids.

**Overdosage**

Overdosage symptoms correspond to an acute hypervitaminosis A, i.e., headache and nausea.
occur. In the event of acute overdosage, Neotigason must be withdrawn at once. Further special measures are unnecessary because of the low acute toxicity of the preparation.

**Properties/Effects**

ATC code: 0058802 Acitretin, the active ingredient of Neotigason, is a synthetic aromatic analogue of retinoic acid. Clinical trials confirmed that, in psoriasis and disorders of keratinization, acitretin brought about normalization of epidermal cell proliferation, differentiation and cornification, while the side effects were, in general, tolerable. The effect of Neotigason is purely symptomatic; the mechanism of action is as yet largely unknown.

**Pharmacokinetics**

**Absorption**

Acitretin reaches peak plasma concentration 1-4 hours after ingestion of the drug. Bioavailability of orally administered acitretin is best when the drug is taken together with food. Bioavailability of a single dose is about 60%, but this may vary considerably from one patient to another (between 36% and 95%).

**Distribution**

Acitretin is highly lipophilic and diffuses readily into body tissues. Protein binding of acitretin exceeds 99%. In animal studies, acitretin passed the placental barrier in quantities sufficient to produce fetal malformations. Due to its lipophilic nature, it can be assumed that acitretin passes into breast milk.

**Metabolism**

Acitretin is metabolized by isomerization into its 13-cis isomer (cis acitretin), by glucuronidation and cleavage of the side chain.

**Elimination**

Multiple dose studies in patients aged 21-70 years showed an elimination half-life of approximately 50 hours for acitretin and 60 hours for its main metabolite in plasma, cis acitretin, which is also a teratogen. From the longest elimination half-life observed in these patients for acitretin (96 hours) and cis acitretin (123 hours), and assuming linear kinetics, it can be predicted that more than 99% of the drug is eliminated within 36 days after cessation of long-term therapy. Furthermore, plasma concentrations of acitretin and cis acitretin dropped below the limit of detection (<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.

**Preclinical Data**

Mutagenicity and carcinogenicity in-vitro and in-vivo mutagenicity tests have shown that neither acitretin nor its 13-cis metabolite causes chromosomal anomalies. In rats treated orally with up to 3 mg/kg/day for 2 years, no carcinogenic effect was demonstrated. On the contrary, in the highest-dose group the incidence of multiple tumours and mammary tumours in female animals was less than in the control group.

**Embryotoxicity and teratogenicity**

In rats given acitretin at a dose of 7.5 mg/kg/day from day 7 to day 16 of pregnancy, no effect on the embryo or fetus was detected; at a dose of 15 mg/kg/day a slight teratogenic effect on the skeletal system was noted; at a dose of 30 mg/kg/day there was a pronounced teratogenic effect manifest as cleft palate and malformations of the humerus, ulna and radius. In mice, teratogenic effects occurred after doses of 3 and 10 mg/kg/day and involved the skeletal system (skull, hard palate, long bones) and various organs (brain, kidney, eyes). In rabbits, administration of 0.6 mg/kg/day caused a slight increase in the incidence of malformations of the brain and of cleft palate. A dose of 2 mg/kg/day was embryotoxic. Perinatal mortality rose to 80% and there were various malformations of the palate and limbs and disturbances of ossification.

**Cytogenetic studies**

The studies performed to date in men have revealed no evidence of any disturbance of spermiogenesis due to Neotigason in therapeutic doses.

**Special remarks**

**Stability**

This medicine should not be used after the expiry date (EXP) shown on the pack.
Special instructions for storage
Store in the original pack to protect the contents from light and moisture.

Packs
Capsules 10 mg: 30, 100
Capsules 25 mg: 30, 100

Council of Arab Health Ministers Union of Arab Pharmacists
• A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
• Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.
• The doctor and the pharmacist are experts in medicine, its benefits and risks.
• Do not by yourself interrupt the period of treatment prescribed for you.
• Do not repeat the same prescription without consulting your doctor.

Medicine: Keep out of the reach of children

Marketing Authorization Holder.
Actavis hf, Reykjavikurvegur 76-78, 220 Hafnarfjördur, Iceland

Manufactured by:
Patheon Inc., Mississauga, Canada

Packaged and Released by:
CENEXI, 94120 Fontenay-sous-bois, France.

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