PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) -1986

This medicine can be sold with a physician's prescription only

Toctino 10 mg

Soft Capsules

Active ingredient and its quantity:

Each capsule contains:

Alitretinoin 10 mg

Toctino 30 mg

Soft Capsules

Active ingredient and its quantity:

Each capsule contains:

Alitretinoin 30 mg

For list of inactive ingredients, please see section 2: "Important information about some of the ingredients of this medicine" and section 6: "Additional Information".

Read this entire leaflet carefully before you start using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask your physician or pharmacist.

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if you think that their illness is similar to yours.

This medicine is not intended for children under 18 years of age as it is unknown how the medicine works in this age group.

In addition to the leaflet, there is a patient safety information card for Toctino. This card contains important safety information that you need to know, before commencing treatment and during the course of the treatment with Toctino and adhere to. Read the patient safety information card and this patient leaflet before commencing use of this medicine. Keep the card for further review, if necessary

Women of childbearing age must avoid getting pregnant a month before commencing treatment, during treatment and one month after ceasing treatment. Use effective contraceptives. During treatment monthly pregnancy tests should be performed. If you found out that you are pregnant during treatment or in the month after treatment, stop the treatment immediately and inform the attending physician. Use of this medicine during pregnancy causes risk of fetal defects and increases the risk of miscarriage. See more information in section "Pregnancy Prevention Program" and section "Pregnancy and breast-feeding".

Do not use the medicine if you are pregnant or you think you may be pregnant.

1. What is the medicine used for?

For the treatment of severe chronic hand eczema, that is unresponsive to topical treatment.

During treatment with Toctino you must be under surveillance of a dermatologist.

Therapeutic group: Retinoids

2. Before using the medicine

Do not use the medicine if:

- You are hypersensitive (allergic) to the active ingredient (alitretinoin), other retinoids (such as: isotretinoin), peanuts or soya or to any of the other ingredients of this medicine (see section 6).
- You are pregnant or breast-feeding.
- There is any chance you could become pregnant. You must follow the precautions listed in **"Pregnancy Prevention Program"** section, under **"Special warning regarding the use of this medicine"** section.
- You suffer from liver disease.
- You suffer from severe kidney disease.
- You suffer from high levels of blood lipids (such as: high cholesterol or high triglycerides).
- You suffer from untreated thyroid disease.
- You suffer from very high levels of vitamin A in your body (hypervitaminosis A).
- You are being treated with tetracyclines (a type of antibiotic).

Special warnings regarding the use of this medicine:

Before taking Toctino, tell the physician if:

- You suffer or have suffered in the past from any kind of mental health problems including depression, aggressive tendencies, mood changes and thoughts of self-harm or ending your life. This is because your mood may be affected while taking Toctino.
- You suffer from kidney disease. The use of Toctino is not recommended for patients with moderate kidney disease. If you suffer from kidney disease, check with your physician whether Toctino is suitable for you.
- You suffer from high levels of blood lipids. You will need to perform blood tests more often. Toctino usually increases the levels of blood lipids, such as cholesterol or triglycerides. If your blood lipid levels remain high, your physician may lower the dosage or even stop treatment.
- You suffer from high blood sugar levels (diabetes). You will need to perform blood sugar tests more often. Additionally, the physician may start the treatment with lower dosage of Toctino.
- You have suffered in the past from thyroid disease. Toctino may lower the level of the thyroid hormone. If your thyroid hormone level is low, the physician may prescribe you supplements.

During treatment with Toctino, you need to take care:

- If you suffer from vision problems, tell your physician immediately. You may have to stop treatment with Toctino and check your vision.
- If you feel persistent headache, nausea or vomiting and blurred vision, these may

be signs of benign intracranial hypertension. Stop treatment with the medicine immediately and refer to a physician as soon as possible.

- If you suffer from bloody diarrhea, you must stop treatment with the medicine immediately and refer to a physician as soon as possible.
- Minimize your exposure to sunlight and avoid sun lamps. Your skin may become more sensitive to sunlight. Before going out into the sun, use a sun protection product with a high protection factor (SPF 15 or higher).

  If during treatment you feel dryness in your skin and lips, use a moisturising ointment or cream and a lip balm.
- Minimize intensive physical exercise; the medicine may cause pain in muscles and joints.
- During treatment with Toctino you may feel dryness in your eyes. Eye ointment or drops intended to treat dryness can help.

  If you wear contact lenses, you may need to wear glasses during treatment with the medicine. Usually, eye dryness and sight problems, if appear, pass once treatment has ended.
- Toctino may increase liver enzyme levels. Your physician will perform blood tests during treatment to check these levels. If the levels remain high, the physician may lower the dosage or discontinue treatment with the medicine. See further on section "Tests and follow up".

Mental health problems

- You may notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your physician about.
- If you develop any mental health problems including depression, aggressive tendencies, mood changes, thoughts about hurting yourself or ending your life, you must stop using Toctino immediately and contact your physician as soon as possible

Children and Adolescents:

The medicine is not intended for children under 18 years of age, since it is unknown how well the medicine works in this age group.

Tests and follow up:

- Your physician will perform blood tests during the treatment to check liver enzymes level as Toctino may increase liver enzymes level. If the level stays high, your physician may lower the dose of Toctino or discontinue the treatment. See "Special warnings regarding the use of this medicine" section.
- Blood fats and/or blood sugar levels should be checked more often in diabetic patients, obese patients, patients with cardiovascular diseases risk factors or patients with fats metabolism disorders who are treated with Toctino. In these patients, it is recommended to start treatment with a lower dose.

Drug Interactions:

Tell your physician or pharmacist if you are taking or have recently taken any other medicines, including non-prescription drugs and food supplements.

Especially if you are taking:

- Do not take other medicines containing retinoids (such as: isotretinoin), vitamin A supplements or tetracyclines (a type of antibiotic) due to the increased risk of side effects.
- Amiodarone (a medicine which helps regulating the heart rate). Amiodarone is not recommended to be taken together with Toctino.
- Ketoconazole, fluconazole, miconazole (medicines used to treat fungal infections). The physician may decide to lower your dose of Toctino.
- Simvastatin (a medicine used to lower cholesterol). Toctino may lower the amount of this medicine in your body.
- Gemfibrozil (another medicine used to lower cholesterol) or oxandrolone (an anabolic steroid). Your physician may decide to lower your dosage of Toctino.
- Paclitaxel (for cancer treatment), rosiglitazone or repaglinide (used to treat diabetes). Toctino may increase the amount of these medicines in your body.

Use of this medicine and food:

Swallow the capsule whole with a main meal.

Pregnancy Prevention Program

Women who are pregnant must not take Toctino.

This medicine can seriously harm an unborn baby (the medicine is said to be "teratogenic"). It can cause serious abnormalities of the unborn baby's brain, face, ear, eye, heart and certain glands (thymus gland and parathyroid gland). It also makes a miscarriage more likely. This may happen even if Toctino is taken only for a short time during pregnancy.

- You must not take Toctino if you are pregnant or if you think you might be pregnant.
- You must not take Toctino if you are breast-feeding. The medicine is likely to pass into your milk and may harm your baby.
- You must not take Toctino if you could get pregnant during treatment.
- You must not get pregnant for one month after stopping this treatment because some medicine may still be left in your body.

Women who could get pregnant are prescribed Toctino under strict rules. This is because of the risk of serious harm to the unborn baby.

These are the rules:

- Your physician must have explained to you the risk of harm to the unborn baby, and make sure you understand why you must not get pregnant, and what you must do to prevent getting pregnant.

- You must have talked about contraception with your physician. Your physician will give you information how not to get pregnant. The physician may refer you to a specialist for contraception advice.
- Before you start treatment, your physician will ask you to take a pregnancy test. The test must show that you are not pregnant when starting treatment with Toctino.

Women must use effective contraception before, during and after using Toctino

- You must use at least one very reliable method of contraception (for example an intrauterine device or contraceptive implant) or two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your physician which method would be suitable for you.
- You must use contraception for a month before using Toctino, during treatment and for a month afterwards.
- You must use contraception even if you do not have periods or you are not sexually active (unless your physician decides that this is not necessary).

Women must perform pregnancy testing before, during and after using Toctino

- You must agree to regular follow-up visits, ideally every month.
- You must agree to have regular pregnancy tests ideally every month during treatment, because some medicine may still be left in your body, one month after stopping treatment with Toctino (unless your physician decided this is not necessary in your case).
- You must agree to additional pregnancy tests if your physician asks you.
- You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body.
- Your physician will discuss all these points with you, using a checklist and will ask you (or a parent/guardian) to sign it. This form confirms that you have been told about the risks, and that you will follow the rules above.

If you get pregnant while taking Toctino, **stop taking the medicine immediately,** and refer to the attending physician. Your physician may refer you to a specialist for advice.

Also, if you become pregnant within one month after you stop taking Toctino, you should refer to your physician. Your physician may refer you to a specialist for advice.

Your physician will provide you written information on pregnancy. If you have not seen this information already, ask your physician for it.

Advice for men

The levels of oral retinoid in the semen of men taking Toctino are too low to harm their partners' unborn baby. However, you must never share your medication with anyone.

Additional precautions

You should never give this medicine to another person. Return any unused medicine to your pharmacist at the end of the treatment.

You should not donate blood during treatment with this medicine and for one month after stopping the treatment because an unborn baby could be harmed if a pregnant patient receives your blood.

Pregnancy and breast-feeding

Pregnancy

Do not take Toctino if you are pregnant.

Toctino is likely to cause severe birth defects. It also increases the risk of miscarriage.

- You must not take Toctino when you are pregnant.
- **You must not get pregnant during treatment with Toctino**, or during the month after treatment with Toctino.

Breast-feeding

Do not take Toctino if you are breast-feeding.

- The medicine is likely to pass into your breast milk and may harm your baby.

Driving and use of machinery:

During treatment with the medicine, you may not see as well at night. If this happens to you, you should not drive or operate machinery

Important information about some of the ingredients of this medicine:

Toctino contains soya bean oil and sorbitol (sorbitol liquid content in 10 mg capsules is 20.08 mg and in 30 mg capsules it is 25.66 mg). If you are allergic to peanuts or soya, do not use this medicine.

If you suffer from intolerance to certain sugars, consult the physician before using Toctino

3. How to use this medicine

Always use the medicine according to the physician's instructions. Check with your physician or pharmacist if you are not sure about the dosage and the treatment regimen with the medicine.

The dosage and treatment regimen will be determined by the physician only. Usual recommended dosage:

- 10 mg or 30 mg once daily. If your body does not respond well to the recommended dose of 30 mg once daily, the physician may lower your dosage to 10 mg once daily.
- Treatment usually lasts for 12 to 24 weeks according to your response to treatment. If your first treatment was successful, the physician may prescribe you another course of treatment if the symptoms return.

Do not exceed the recommended dose.

The capsule should be swallowed whole with a main meal, preferably at the same time every day.

Do not chew the capsule.

If you have taken an overdose or if a child or someone else has accidentally swallowed the medicine, proceed immediately to a physician or a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the set time, take the dose as soon as you remember. However, if the time to take the next dose is soon, skip the forgotten dose and take the next dose at its specified time. Do not take a double dose to compensate for a missed one!

Continue with the treatment as recommended by your physician.

Even if there is an improvement in your health, do not stop the treatment of this medicine without consulting the physician.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult a physician or pharmacist.

4. <u>Side effects</u>

Like all medicines, Toctino can cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.

Stop use of this medicine and refer to your physician immediately if:

- You suffer from visual disorders including blurred vision, distorted vision, cloudy surface on the eye (corneal opacity, cataract). These side effects are uncommon.
- You suffer from **persistent headache**, accompanied by nausea, vomiting and changes in vision including blurred vision. These signs may indicate benign intracranial hypertension (a rare side effect).
- You suffer from a **severe allergic reaction** (unknown frequency) manifested by:
  - itchy rash with raised skin (hives)
  - swelling, sometimes of the face or mouth (angioedema), causing breathing difficulty
  - collapse
- You suffer from **intestinal and gastric disorders** (unknown frequency): severe abdominal pain, with or without bloody diarrhea, nausea and vomiting. These may be signs of serious intestinal conditions.

Refer to your physician immediately if you get signs of any of the following **mental problems**. Your physician may instruct you to stop treatment, but that may not be enough to stop the effect. You may need further help and your physician can arrange this.

Rare Side effects (appear in 1-10 users out of 10,000):

- Depression or related disorders. Signs of these effects include sadness or altered mood, anxiety, feeling of emotional discomfort
- Worsening of existing depression
- Becoming violent or aggressive

Very rare side effects (appear in less than 1 user out of 10,000):

- Some people have had thoughts or feelings about harming themselves or ending their own lives (suicidal thoughts), have attempted suicide or have suicided. These people may not appear to be depressed.
- Unusual behaviour
- Signs of psychosis: a loss of contact with reality, such as hearing voices or seeing things that are not there

Additional side effects:

Very common side effects (appear in more than 1 user out of 10):

- Headache
- Increase in blood lipid levels: increased blood levels of triglycerides and cholesterol.

Common side effects (appear in 1-10 users out of 100):

- An increase in the number of blood platelets (cells that help blood to clot), a decrease in the number of red and white blood cells seen in blood tests
- Decreased level of the thyroid hormone
- Inflammation of the eye (conjunctivitis) and eyelid area, dry and irritated eyes - ask the pharmacist for suitable eye drops. If you wear contact lenses and suffer from dry eyes, you may need to wear glasses instead.
- Persistent noise in your ears (tinnitus)
- Dizziness
- Flushing, high blood pressure
- Nausea, vomiting, dry mouth
- Muscle pain, joint pain, lack of energy (fatigue). Intensive physical activity can cause high levels of muscle breakdown products in blood
- Dryness of the skin, especially of the face, dry and inflamed lips, skin redness, itchy skin rash, inflammation of the skin, hair loss
- Increased liver enzymes levels in blood tests

Uncommon side effects (appear in 1-10 users out of 1,000):

- Skin itching, skin peeling, rash, eczema as a result of dry skin
- Nose bleeding
- Indigestion (dyspepsia)
- Extra growth of the bones including spine disturbances and ankylosing spondylitis

Rare side effects (appear in 1-10 users out of 10,000):

- Vascular inflammation

- Nail problems, hypersensitivity of the skin to sunlight, hair texture changes

Side effects with an unknown frequency (their frequency has not yet been determined):

- Night vision disorders - vision disorders usually disappear after ceasing treatment
- Swelling of the hands, shins and feet (peripheral edema)

The following side effects have been observed when using other medicines of the retinoid family, therefore it can't be ruled out that they may occur when taking Toctino:

Very rare side effects (appear in less than 1 user out of 10,000):

- Signs of diabetes: excessive thirst, frequent need to urinate, elevated blood sugar levels
- Bone disorders: arthritis, bone disorders (delayed growth, change in bone density), growing bones may stop growing
- Color blindness, worsening of color blindness, intolerance to contact lenses

If a side effect appears, if any of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult your physician.

Reporting Side Effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report

Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by the following link:

https://sideeffects.health.gov.il/

In addition, side effects can be reported by sending an email to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

5. How to store the medicine

- Avoid poisoningl This medicine, and all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.
- Do not use the medicine after the expiry date (exp. date) stated on the package and blister.

  The expiry date refers to the last day of that month.
- **Storage conditions:**

  Toctino 10 mg: store below 30°C, keep in the original carton package in order to protect from light.

  Toctino 30 mg: store below 25°C, keep in the original carton package in order to protect from light.
- Do not dispose of medicines via wastewater or household waste. Ask your

pharmacist how to dispose of medicines no longer in use. These measures will help to protect the environment

6. Additional information

- **In addition to the active ingredient, the medicine also contains:**

Soya Bean Oil (refined), Gelatin, Partially Hydrogenated Soya Bean Oil, Sorbitol Liquid (non-crystallising), Medium Chain Triglycerides, Purified Water, Glycerol, Yellow Beeswax, Red and Black Iron Oxide (E172) (10 mg capsules), Red and Yellow Iron Oxide (E172) (30 mg capsules), All-rac-α-tocopherol.

- **What does the medicine look like and what does the package contain?**

Toctino 10 mg: elliptic brown opaque soft capsules marked "A1"

Toctino 30 mg: elliptic reddish-brown soft capsules marked "A3"

The capsules are packed in blisters, each pack contains 30 capsules.

Manufacturer and his address: Swiss Caps GMBH, Grassingstrasse 9,83043 Bad Aibling, Germany.

Registration holder and his address: Neopharm Scientific Ltd., Hashiloach 6, P.O. Box 7063, Petach Tiqva 49170.

Drug registration numbers at the national medicines registry of the Ministry of Health:

Toctino 10 mg: 145-92-33163

Toctino 30 mg: 146-64-33164

Revised in June 2022 according to MOHs guidelines.