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

The medicine is dispensed with a physician's prescription only

Toctino 10 mg

Soft Capsules

The active ingredient and its quantity:
Each capsule contains:
Alitretinoin 10 mg

Toctino 30 mg

Soft Capsules

The active ingredient and its quantity:
Each capsule contains:
Alitretinoin 30 mg

For the list of inactive and allergenic ingredients in the preparation, see section 2: "Important information about some of the ingredients of the medicine" and section 6: "Additional information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the physician or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

The medicine is not intended for children under 18 years of age.

In addition to the leaflet, Toctino has a Patient Pamphlet. This pamphlet contains important safety information that you must know and adhere to before and during the treatment with Toctino. Read the Patient Pamphlet and the patient leaflet before starting to use the preparation. Keep the pamphlet for further reading, if necessary.

Women of child-bearing potential must avoid becoming pregnant for one month before starting treatment, during the course of treatment and for one month after discontinuing treatment. Use effective contraceptives. During the course of treatment, monthly pregnancy tests should be performed. If you discover that you are pregnant during the course of treatment or one month after treatment, stop the treatment immediately and report to the attending physician. Use of this medicine during pregnancy causes risk of defects in the unborn baby and increases the risk of miscarriage. See additional information in section "Pregnancy prevention program" and section "Pregnancy and breastfeeding".

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

1. WHAT IS THE MEDICINE INTENDED FOR?

To treat severe chronic hand eczema that does not respond to topical treatments. During the course of treatment with Toctino, you must be under the supervision of a dermatologist.

Therapeutic group: Other dermatologicals.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient (alitretinoin), to other retinoids (e.g., isotretinoin), to peanuts, soya or any of the additional ingredients contained in the medicine (listed in section 6).
- you are pregnant or breastfeeding.
- there is a chance that you could become pregnant. You must follow the precautions listed under "**Pregnancy prevention program**" later in this section.
- you have **liver disease.**
- you have **severe kidney disease.**
- you have **a high blood fat level** (such as high level of cholesterol or triglycerides).
- you have **untreated thyroid disease.**
- you have **a very high level of vitamin A** in your body (hypervitaminosis A).
- you are being **treated with tetracyclines** (a type of antibiotic).

If any of these apply to you, **refer to a physician and do not take Toctino.**

Special warnings regarding use of the medicine
Before treatment with Toctino, inform the physician if:

- **you have or have had in the past, any kind of mental health problems,** including depression, aggressive tendencies, mood changes and thoughts of hurting yourself or committing suicide. This is because your mood may be affected while taking Toctino.
- **you have kidney disease.** Use of Toctino is not recommended for people with moderate kidney disease. If you have kidney disease, check with the physician if Toctino is suitable for you.
- **you have a high blood fat level.** You may need to perform blood tests more often. Toctino often increases the level of blood fats, such as cholesterol or triglycerides. If your blood fat level stays high, the physician may lower the dosage or stop the treatment.
- **you have a high blood sugar level (diabetes).** You may have to check blood sugar levels more often. In addition, the physician may start your treatment with a lower dosage of Toctino.
- **you suffered in the past from thyroid disease.** Toctino may lower thyroid hormone levels. If your thyroid hormone level is low, your physician may

prescribe supplements for you.

During the course of treatment with Toctino, pay attention:

- **If you experience vision problems, tell the physician immediately.** You may need to stop Toctino treatment and check your eyesight.
- **If you suffer from a persistent headache,** nausea or vomiting and blurred vision, these may be signs of benign intracranial hypertension. **Stop using the medicine immediately** and refer to a physician as soon as possible.
- **If you have bloody diarrhea, stop using the medicine immediately** and refer to a physician as soon as possible.
- **Minimize exposure to sunlight as much as possible** and avoid exposure to sun lamps. Your skin may become more sensitive to sunlight. Before you go out in the sun, use a protection product with a high protection factor (SPF 15 or higher).
  If **you get dry skin and lips** during treatment, use a moisturizing ointment or cream and a lip balm.
- **Cut down on intensive physical exercise,** the medicine may cause muscle and joint pain.
- **If you develop dry eyes,** lubricating eye ointment or tear replacement drops can help.
  If you wear contact lenses, you may need to wear glasses during treatment with the medicine. Dry eyes and vision problems normally return to normal once treatment is stopped.
- **Toctino may increase liver enzyme levels.** The physician will refer you for blood tests during the course of treatment to check these levels. If the levels remain high, the physician may lower the dosage or stop treatment with the medicine.

Mental health problems

- You may notice some changes in your mood and behavior and it is therefore 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 problem that you need to talk to the physician about.
- **If you develop any mental health problem,** including depression, aggressive tendencies, mood changes, thoughts about hurting yourself or committing suicide, **you must stop taking Toctino immediately** and refer to a physician as soon as possible.

Children and adolescents

The medicine is not intended for use in children and adolescents under 18 years of age. It is not known how the medicine works in this age group.

Tests and follow-up

See section 2 “Special warnings regarding use of the medicine” and “Pregnancy prevention program”.

Drug interactions

If you are taking, or if you have recently taken, other medicines, including non-prescription medicines and nutritional supplements, inform the physician or pharmacist.

- **Do not take other retinoid medicines** (e.g., isotretinoin), **vitamin A supplements or tetracyclines** (a type of antibiotic) while taking Toctino. This increases the risk of side effects.
- **amiodarone** (a medicine that helps to regulate 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 reduce the dosage of Toctino.
- **simvastatin** (a medicine used to lower cholesterol). Toctino may decrease the amount of this medicine in your body.
- **gemfibrozil** (another medicine used to lower cholesterol) or **oxandrolone** (an anabolic steroid). The physician may decide to reduce the dosage of Toctino.
- **paclitaxel** (used to treat cancer), **rosiglitazone** or **repaglinide** (used to treat diabetes). Toctino may increase the amount of these medicines in your body.

Use of the medicine and food

See section 3 “How should you use the medicine?”.

Pregnancy prevention program

Pregnant women must not take Toctino.

This medicine can seriously harm an unborn baby (the medicine is considered “teratogenic”). It can cause serious abnormalities of the unborn baby’s brain, face, ears, eyes, 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 breastfeeding. The medicine is likely to pass into the breast milk and may harm the baby.
- You must not take Toctino if you may become pregnant during treatment.
- You must not get pregnant for one month after stopping treatment because some medicine may still be left in your body.

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

The conditions are:

- The physician must explain to you the risk of harm to the unborn baby. You must understand why you must not get pregnant and what you need to do to prevent getting pregnant.
- You must talk about contraception (birth control) with the physician. The physician will give you information how to prevent pregnancy. The physician

may send you to a specialist for advice on contraception.
- The physician will ask you to take a pregnancy test before you start treatment. The test must show that you are not pregnant when starting treatment with Toctino.

Women must use effective contraception before, during and after taking 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 the physician which method is suitable for you.
- You must use contraception for one month before taking Toctino, during treatment and for one month after the treatment.
- You must use contraception even if you do not have periods or you are not sexually active (unless the physician decides this is not necessary).

Women must perform a pregnancy test before, during and after taking 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 and up to one month after stopping treatment, because some medicine may still be left in your body (unless the physician decides this is not necessary in your case).
- You must agree to extra pregnancy tests if the physician asks you.
- You must not get pregnant during treatment and for one month after treatment because some medicine may still be left in your body.
- The 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 the risks have been explained to you, 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. The physician may refer you to a specialist for advice.
In addition, if you become pregnant within the first month after you stop taking Toctino, refer to a physician. The physician may refer you to a specialist for advice.
The physician will provide you written information about pregnancy. If you have not received this information, ask the physician.

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 medicine with anyone.

Additional precautions

You should never give this medicine to another person. At the end of treatment, return all unused medicine to the pharmacist.

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

Pregnancy and breastfeeding

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 stopping treatment with Toctino.

Breastfeeding

Do not take Toctino if you are breastfeeding.

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

For more information on pregnancy and contraception, see section 2 “Pregnancy prevention program”.

Driving and using machinery

You may not see well at night during the course of treatment with the medicine. If this happens to you, you should not drive or operate machinery.

Important information about some of the ingredients of the medicine

Toctino contains soybean oil and sorbitol (the sorbitol content in 10 mg capsules is 20.08 mg and in 30 mg capsules is 25.66 mg). If you are allergic to peanuts or soya, do not use this medicine. If you have been told by the physician that you have an intolerance to certain sugars, consult with the physician before taking Toctino.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the physician’s instructions. Check with the physician or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

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

- 10 mg or 30 mg, once a day. If your body can not tolerate the recommended dose of 30 mg once a day, the physician may lower your dosage to 10 mg once a day.
- The treatment usually lasts for 12 to 24 weeks, depending on your response to treatment. If the first treatment was successful, the physician may prescribe for you another course of treatment if the symptoms recur.

Do not exceed the recommended dose.

Swallow the capsule whole with a main meal, preferably at the same time every day. Do not chew the capsule.

If you accidentally take a higher dosage
If you took too many capsules or if a child or someone else has accidentally swallowed the medicine, refer immediately to a physician or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take the medicine
If you forgot to take the medicine at the scheduled time, take the dose as soon as you remember. However, if it is almost time to take the next dose, skip the forgotten dose and take the next dose at its scheduled time. Do not take a double dose to compensate for a forgotten dose.

Adhere to the treatment regimen as recommended by the physician.
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the physician.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the physician or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Toctino may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Stop taking the medicine and refer to a physician immediately if:
- you are suffering from **sight problems**, including blurred vision, distorted vision, a cloudy surface on the eye (corneal opacity, cataract). These effects are uncommon.
- you are suffering from a **lasting headache** accompanied by nausea, vomiting and vision changes, including blurred vision. These signs may be indicative of benign intracranial hypertension (a rare side effect).
- you are suffering from a **severe allergic reaction** (unknown frequency), whose symptoms include:
  - raised and itchy rash (hives)
  - swelling, sometimes of the face or mouth (angioedema), which causes breathing difficulty
  - collapse
- you are suffering from **gut and stomach disorders** (unknown frequency): severe stomach (abdominal) pain, with or without bloody diarrhea, nausea and vomiting. These may be signs of severe gut conditions.

Refer to your physician immediately if you suffer from the following signs of mental health problems. Your physician may instruct you to stop the

treatment, yet this may not be enough to stop the effect. You may need additional help and your physician can take care of that.

Rare side effects

These may affect **up to 1 in 1,000** people:

- Depression or depression-related disturbances. Signs of these effects include sadness or altered mood, anxiety, feelings of emotional discomfort
- Existing depression getting worse
- Becoming violent or aggressive.

Very rare side effects

These may affect **up to 1 in 10,000** people:

- Some users have had thoughts or feelings about harming themselves or committing suicide (suicidal thoughts), have attempted suicide or have committed suicide. These people may not appear to be depressed.
- Unusual behavior
- 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

These may affect **more than 1 in 10** people:

- **Headache**
- **Raised blood fat levels:** higher levels of fats (triglycerides) and cholesterol in the blood.

Common side effects

These may affect **up to 1 in 10** people:

- **Blood cell disorders:** increase in the number of blood platelets (cells that help blood to clot), decrease in the number of red and white blood cells seen in blood tests
- **Thyroid problems:** decreased levels of thyroid hormones
- **Eye problems:** inflammation of the eye (conjunctivitis) and eyelid area, eyes feel dry and irritated
  Ask a pharmacist for suitable eye drops. If you wear contact lenses and suffer from dry eyes, you may need to wear glasses instead.
- **Ear problems:** persistent noise in the ears (tinnitus)
- **Dizziness**
- **Blood and circulation:** flushing, high blood pressure
- **Gut and stomach problems:** nausea, vomiting, dry mouth
- **Muscle and joint pains:** muscle pain, joint pain, lack of energy (fatigue). Intense physical activity may cause high levels of muscle breakdown products in the blood
- **Skin and hair problems:** dry skin, especially of the face, dry and inflamed lips, redness of the skin, itchy skin rash, inflamed skin, hair loss
- **Liver problems:** raised liver enzymes seen in blood tests.

Uncommon side effects
These may affect **up to 1 in 100** people:
- **Skin problems:** itchy skin, skin peeling, rash, dry skin eczema
- **Ear, nose and throat problems:** nosebleed
- **Gut and stomach problems:** indigestion (dyspepsia)
- **Bone disorders:** extra growth of bone, including the spine disorder ankylosing spondylitis.

Rare side effects
These may affect **up to 1 in 1,000** people**:**
- **Blood and circulation:** inflammation of blood vessels
- **Skin, hair and nail problems:** nail problems, increased sensitivity of the skin to sunlight, hair texture changes.

Side effects of unknown frequency (side effects whose frequency was not yet determined):
- **Problems seeing at night**: sight problems normally return to normal once treatment is stopped
- **Blood and circulation:** swelling of the hands, lower legs and feet (peripheral edema).

The following effects have been observed when other retinoids were used.
To date, these effects have not been observed with use of Toctino, but they cannot be ruled out.

Very rare side effects
These may affect **up to 1 in 10,000** people:
- **Diabetes:** excessive thirst, frequent need to urinate, increase in blood sugar levels. These can all be signs of diabetes.
- **Bone disorders:** arthritis, bone disorders (delayed growth, change to bone density), growing bones may stop growing
- **Eye and visual disorders:** colour blindness and colour vision gets worse; intolerance to contact lenses.

If a side effect occurs, if one of the side effects worsens, or if you are suffering from a side effect not mentioned in the leaflet, consult the 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" found on the Ministry of Health homepage (www.health.gov.il), which directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed 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 a physician.
- Do not use the medicine after the expiry date (exp. date) that appears on the package and blister (tray). The expiry date refers to the last day of that month.
- **Storage conditions:**
  Toctino 10 mg: Store below 30°C, store in the original carton package to protect from light.
  Toctino 30 mg: Store below 25°C, store in the original carton package to protect from light.
- Do not throw away medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines that are not in use. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

- **In addition to the active ingredient, the medicine also contains:**
  Soybean oil, gelatin, partially hydrogenated soybean oil, sorbitol liquid (non-crystalizing), medium chain triglycerides, purified water, glycerol, yellow wax, red and black iron oxide (E172) (10 mg capsules), red and yellow iron oxide (E172) (30 mg capsules), DL-α-tocopherol**.**
- **What the medicine looks like and contents of the pack:**
  Toctino 10 mg: soft, oval, opaque brown capsules, marked with “A1”.
  Toctino 30 mg: soft, oval, reddish-brown capsules, marked with “A3”.
  The capsules are packaged in blisters (trays), each package contains 30 capsules.

Manufacturer: GlaxoSmithKline Trading Services Ltd., Dublin, Ireland.

License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Toctino 10 mg: 145-92-33163
Toctino 30 mg: 146-64-33164

Revised in September 2023 according to MOH guidelines.

Toc PT v1.1C