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

The medicine is dispensed with a doctor's prescription only

Topitrim 25 mg, 50 mg, 100 mg, 200 mg tablets

Each tablet contains: topiramate 25 mg, 50 mg, 100 mg, 200 mg

For inactive ingredients and allergens: see section 2 under "Important information about some of this medicine's ingredients" and section 6 "Additional information".

Read this 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 doctor or pharmacist.

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

This medicine is not intended for infants and for children under 2 years of age and as a monotherapy in children under 7 years of age.

1. WHAT IS THE MEDICINE INTENDED FOR?

This medicine is intended for:

- Treatment of seizures as combination therapy with other medicines in adults and children aged two years and above, or as monotherapy in adult patients and children aged 7 years and above.
- Prevention of migraine in adults. The medicine is not intended for pain relief during a migraine attack.

Therapeutic group: Antiepileptics.

2. BEFORE USING THE MEDICINE

Do not use the medicine:

- If you are sensitive (allergic) to the active ingredient or any of the additional ingredients contained in the medicine, listed in section 6.

Preventing migraine

- Do not use Topitrim if you are pregnant.
- If you are a woman of childbearing age, do not use Topitrim unless you use highly effective contraception during your Topitrim treatment (further information under "Pregnancy and breastfeeding – Important advice for women of childbearing age")

Treating epilepsy

- Do not use Topitrim if you are pregnant, unless no other treatment gives you sufficient seizure control.
- If you are a woman of childbearing age, do not take Topitrim unless you use highly effective contraception during your Topitrim treatment. The only exception is when Topitrim is the only treatment that gives sufficient seizure control and you are planning a pregnancy. Talk to your doctor to make sure you receive information about the risks of taking Topitrim during pregnancy and the risks of seizures during pregnancy (further information under "Pregnancy and breast-feeding – Important advice for women of childbearing age").

Special warnings regarding use of the medicine:

Do not use the medicine without consulting the doctor before commencing treatment if you have:

- Kidney problems, especially kidney stones or if you are a patient undergoing dialysis.
- A history of problems related to blood and body fluids (metabolic acidosis).
- Liver problems.
- Eye problems (especially if you have glaucoma).
- Growth problems.
- If you are on a ketogenic diet (a low carbohydrate and high-fat diet).
- You are a woman of childbearing age. Topitrim can harm an unborn child when taken during pregnancy. Use highly effective contraception during your Topitrim treatment and for at least 4 weeks after your Topitrim treatment ends (see the section "Pregnancy and breastfeeding" for further information).
- You are pregnant. Topitrim can harm an unborn child when taken during pregnancy.

If any of the conditions above apply to you, speak with the doctor before using the medicine.

- If you have epilepsy, it is important that you do not stop taking the medicine without first consulting the doctor.
- Do not take any other medicine containing topiramate, given to you as a substitute for this medicine, without first consulting the doctor.
- You may lose weight while taking Topitrim. Weigh yourself regularly during the course of treatment with Topitrim. If you lose a lot of weight or if a child taking Topitrim does not gain enough weight, consult the doctor.
- In a small number of patients treated with antiepileptics, such as Topitrim, suicidal thoughts or suicidal behavior have been reported. In case suicidal thoughts occur, refer to the doctor immediately!
- Topitrim can cause serious skin reactions. Tell your doctor immediately if you develop a skin rash and/or blisters.
- Topitrim may in rare cases cause high levels of ammonia in the blood (seen in blood tests) which may lead to a change in brain function, especially upon combined administration with valproic acid or sodium valproate. Since this may be a severe condition, contact your doctor if the following symptoms occur:
  - difficulty thinking, remembering information, or solving problems
  - feeling less alert/aware
  - feeling of sleepiness and lack of energy

At higher doses of Topitrim, the risk of developing these symptoms may increase.

Children and adolescents:

The side effects in children are generally similar to those seen in adults. However, the side effects indicated in section "Side effects in children" may be more common in children than in adults.

Tests and follow up:

A pregnancy test should be performed before starting treatment with Topitrim.

Drug interactions:

If you are taking, or have recently taken, other medicines, including nonprescription medicines or nutritional supplements, tell the doctor or pharmacist. Topitrim and other medicines can affect each other. The doctor will consider whether the dose of Topitrim or your other medicines needs to be adjusted.

In particular, inform the doctor or pharmacist if you are taking:

- Other medicines that affect or decrease your level of thinking, concentration or muscle coordination (e.g., central nervous system depressants such as muscle relaxants and sedatives and hypnotics).
- Hormonal contraceptives. Topitrim may make your hormonal contraceptive less effective. Use a barrier method of contraception in addition, such as a condom, pessary (cervical cap), or diaphragm. Talk to your doctor about the method of contraception which is most suitable for use during treatment with Topitrim. Tell the doctor if you experience changes in your menstrual cycle while using hormonal contraception and Topitrim. Irregular bleeding may occur. If this happens, continue taking the hormonal contraceptive and inform your doctor.

Keep a list of all the medicines you take and show this list to your doctor or pharmacist before you start taking a new medicine.

You should also discuss taking the following medicines with your doctor or pharmacist:

- Other antiepileptics.
- Risperidone (for treatment of schizophrenia).
- Lithium (for treatment of manic depression).
- Hydrochlorothiazide, propranolol, diltiazem (for treatment of heart problems and to lower blood pressure).
- Metformin, pioglitazone, glyburide, glibenclamide (for treatment of diabetes).
- Amitriptyline, venlafaxine (for treatment of depression).
- Flunarizine (to prevent migraines and to treat vertigo).
- Hypericum perforatum (St. John's wort, a herbal medicine to treat depression).
- Warfarin (for blood thinning).

Use of the medicine and food:

Topitrim can be taken with or without food.

Be sure to drink plenty of fluids during the course of treatment (to reduce the risk of formation of kidney stones).

Use of the medicine and alcohol consumption:

Abstain from drinking alcohol during the course of treatment with the medicine.

Pregnancy and breastfeeding:

Important advice for women of childbearing age

Topitrim can harm an unborn child. If you are a woman of childbearing age, talk to your doctor about other treatments options. Make sure to visit your doctor at least once a year for follow-up and to discuss your treatment and its risks.

Migraine prevention

Do not use Topitrim to treat migraine if you are pregnant.

You must not use Topitrim for migraine prevention if you are a woman of childbearing potential unless you are using highly effective contraception. Women of childbearing age should have a pregnancy test before starting treatment with Topitrim.

Treatment of epilepsy

Do not use Topitrim to treat epilepsy if you are pregnant, unless no other treatment gives you sufficient seizure control.

Do not use Topitrim to treat epilepsy if you are a woman of childbearing age unless you are using highly effective contraception. The only exception is when Topitrim is the only treatment that gives you sufficient seizure control and you are planning a pregnancy. Talk to your doctor and make sure you have information about the risks of taking Topitrim during pregnancy and of seizures during pregnancy, which may put your unborn child at risk.

Women of childbearing age should have a pregnancy test before starting treatment with Topitrim.

The risks of topiramate when taken during pregnancy (irrespective of the indication for which it is used)

There is a risk of harm to the unborn child if Topitrim is used during pregnancy.

If you take Topitrim during pregnancy, your child has a higher risk for birth defects. In women who take topiramate, 4–9 children in every 100 will have birth defects compared to 1–3 children in every 100 born to women who do not have epilepsy and do not take antiepileptic medicines. Cleft lip (split in the top lip) and cleft palate (split in the roof of the mouth) were mainly observed. Newborn boys may also have a malformation of the penis (hypospadia). These defects may develop early in pregnancy, sometimes before pregnancy is detected.

If you take topiramate during pregnancy, your child may have a 2- to 3-fold higher risk for autism spectrum disorders, intellectual disabilities, or attention deficit hyperactivity disorder (ADHD) compared with children born to women with epilepsy not taking antiepileptic medication.

- If you take Topitrim during pregnancy, your baby may be smaller and weigh less than expected at birth. In one study, around 18% of the children of mothers taking topiramate during pregnancy were smaller and weighed less than expected at birth, while around 5% of the children born to women without epilepsy and not taking antiepileptic medication were smaller and weighed less than expected at birth.
- Talk to your doctor if you have questions about this risk during pregnancy.
- There may be other medicines to treat your condition that have a lower risk of birth defects.

Need for contraception in women of childbearing age

If you are a woman of childbearing age, talk to your doctor about other possible treatments instead of Topitrim. If the decision is made to use Topitrim, you must use highly effective contraception during your treatment and for 4 weeks after your treatment ends.

Use one highly effective contraceptive (such as an intrauterine device) or two complementary contraceptives such as birth control pills together with a barrier method of birth control (such as a condom, pessary (cervical cap), or diaphragm). Talk to your doctor about what contraception is most appropriate for you.

If you are taking a hormonal contraceptive, it may be less effective when taken together with Topitrim, so use a barrier contraceptive method in addition (such as a condom, pessary (cervical cap), or diaphragm).

Tell your doctor if you experience irregular menstrual bleeding.

Use of Topitrim in girls

If you are a parent or a caregiver of a girl treated with Topitrim, you must contact her doctor immediately once she experiences her first period. The doctor will inform you about the risks to an unborn child due to Topitrim exposure during pregnancy, and the need for using highly effective contraception.

If you wish to become pregnant while taking Topitrim

- Schedule an appointment with your doctor.
- Do not stop using your contraception until you have discussed this with your doctor.
- If you take Topitrim for epilepsy, do not stop taking it until you have discussed this with your doctor, because your condition could get worse.
- Your doctor will reassess your treatment and evaluate other treatment options. Your doctor will counsel you about the risk of taking Topitrim during pregnancy and may refer you to another specialist.

If you have become pregnant or think you may be pregnant while taking Topitrim

- Schedule an urgent appointment with your doctor.
- If you are taking Topitrim to prevent migraine, stop taking the medicine straight away, and contact your doctor who will consider whether you need a different treatment.
- If you are taking Topitrim for epilepsy, do not stop taking this medicine until you have talked to your doctor, because your illness could get worse. If your epilepsy gets worse, this may put you or your unborn child at risk.
- Your doctor will reassess your treatment and evaluate other treatment options. Your doctor will counsel you about the risk of taking Topitrim during pregnancy and may refer you to another specialist.

If Topitrim is taken during pregnancy, you must have frequent check-ups to see how your unborn child is developing.

Breastfeeding

The active substance in Topitrim (topiramate) passes into breast milk. Effects have been observed in breastfed babies of mothers treated with topiramate, including diarrhea, sleepiness, irritability, and poor weight gain.

Therefore, your doctor will discuss with you whether you should abstain from breastfeeding or abstain from treatment with Topitrim. The doctor will consider the importance of the medicine to the mother against the risk for the baby.

Mothers who breastfeed while taking Topitrim must tell the doctor immediately if the baby experiences any unusual effect.

Driving and operating machinery:

Use of the medicine may cause dizziness, tiredness and vision problems. Do not drive or operate dangerous machines before first talking with the doctor.

Important information about some of the ingredients in the medicine:

Topitrim tablets contain lactose. If you suffer from an intolerance to certain sugars, consult the doctor before using the medicine.

Topitrim tablets contain less than 1 millimole sodium (23 mg) per tablet, which is actually considered as "sodium free".

3. HOW SHOULD THE MEDICINE BE USED?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about your dose or about how to use this medicine. The dosage and treatment regimen will be determined by the doctor only.

The doctor will usually start with a low dosage of Topitrim and will gradually increase the dosage until the dosage suitable for you is found.

Do not exceed the recommended dose.

Swallow Topitrim tablets whole.

In the absence of a score line, do not halve the tablet. There is no information regarding crushing/chewing the tablet. Crushed or chewed tablet may leave a bitter taste.

Topitrim can be taken before, with or after food.

Be sure to drink a lot during the course of treatment to prevent formation of kidney stones during the treatment.

Girls and women of childbearing age

Start treatment with Topitrim and remain under the supervision of an epilepsy or migraine specialist.

Consider other treatment options in girls and women of childbearing age. Visit your doctor to evaluate your treatment at least once a year.

If you accidentally took a higher dosage

If you took an overdose, or if a child has accidentally swallowed the medicine, refer immediately to a hospital emergency room and bring the package of the medicine with you. Do not induce vomiting unless explicitly instructed to do so by a doctor!

If you took an overdose, you may feel sleepy, tired or less alert, experience lack of coordination, difficulty speaking or difficulty concentrating, double vision or blurred vision, feel depressed or nervous, dizziness due to low blood pressure, abdominal pain, seizures.

Overdose can occur when you take other medicines together with Topitrim.

If you forgot to take this medicine

Take a dose as soon as you remember, but if you remember close to the time for taking the next dose, skip the forgotten dose and continue as usual. Never take two doses together!

If you forgot two or more doses, contact the doctor.

Adhere to the treatment regimen recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment without consulting the doctor, as symptoms may return. If the doctor decides to discontinue treatment, the dosage will be gradually lowered over several days.

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 doctor or pharmacist.

4. SIDE EFFECTS

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

Refer to the doctor immediately if you notice any of the following effects:

Very common side effects - effects that occur in more than one in ten users:

depression (new onset or worsening).

Common side effects - effects that occur in 1-10 in 100 users:

- Seizures
- Anxiety, nervousness, mood changes, confusion, disorientation
- Concentration disturbances, slowed thinking, loss of memory, memory problems (new onset, sudden change or deterioration)
- Kidney stones, frequent or painful urination.

Uncommon side effects - effects that occur in 1-10 in 1,000 users:

- Increased acid level in the blood (may cause breathing problems including shortness of breath, loss of appetite, nausea, vomiting, excessive tiredness and fast or uneven heartbeats)
- decreased or termination of sweating (especially in young children exposed to high temperatures)
- thoughts and attempts of serious self-harm
- loss of part of the field of vision

Rare side effects - effects that occur in 1-10 in 10,000 users:

- Glaucoma (blockage of fluid in the eye, causing intraocular pressure, pain or decreased vision)
- Difficulty thinking, remembering information, or solving problems, lack of alertness or awareness, feeling very sleepy with lack of energy – these symptoms may be a sign of a high level of ammonia in the blood (hyperammonemia), which may lead to a change in brain function (hyperammonemic encephalopathy)
- Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis - these may appear as a rash with or without blisters, skin irritation, sores and swelling in the area of the mouth, throat, nose, eyes and in the area of the genitals. The skin rash may develop into serious widespread skin damage (peeling of the outer layer of the skin and superficial mucous membranes) with life-threatening consequences.

Other side effects whose frequency is not known (not established yet):

- Inflammation of the eye uvea (uveitis) with symptoms such as eye redness, pain, sensitivity to light, runny eyes, seeing small dots or getting blurred vision.

Other side effects, of which the doctor should be informed if they get worse:

Very common side effects – effects which occur in more than one in ten users:

- Nasal congestion, runny nose, sore throat • Tingling, pain and/or numbness of various body parts • Tiredness or sleepiness • Dizziness • Diarrhea • Nausea • Weight loss

Common side effects - effects that occur in 1-10 in 100 users:

- Anemia (low blood count) • Allergic reaction (such as skin rash, redness, itching, facial swelling, hives) • Decreased appetite or loss of appetite • Aggression, anxiety, anger, abnormal behavior • Difficulty falling or staying asleep • Problems with speech, speech disorder, slurred speech • Clumsiness or lack of coordination, feeling of unsteadiness when walking • Decreased ability to complete routine tasks • Decrease/loss/absence of sense of taste • Involuntary trembling • Rapid, uncontrollable movements of the eyes • Vision disturbances, such as double vision, blurred vision, decreased vision, difficulty focusing • Sensation of spinning (vertigo), ringing in the ears, ear pain • Shortness of breath • Cough • Nose bleed • Fever • Weakness • General unwell feeling • Vomiting • Constipation • Abdominal pain or discomfort in the stomach • Indigestion • Stomach or intestinal infection • Dry mouth • Hair loss • Itching • Joint pain or swelling • Muscle cramps or muscle spasms, muscle aches or weakness • Chest pain • Weight gain

Uncommon side effects - effects that occur in 1-10 in 1,000 users:

- Abnormal blood count, including decrease in number of white blood cells (that assist in protection from infections) or platelets (blood cells that assist in stopping bleeding) or an increase in the number of eosinophils (a type of white blood cells)
- Low potassium levels in the blood
- Increase in liver enzyme levels
- Swollen glands in the neck, armpit or groin
- Increased appetite
- Elevated mood
- Hearing, seeing or feeling things that are not there, severe mental disorder (psychosis)
- Feeling or exhibiting apathy, unusual suspiciousness, panic attacks
- Problems with reading, speech disorders, problems with handwriting
- Restlessness or hyperactivity
- Slowed thinking, decreased wakefulness or alertness
- Slow body movements or reduced mobility
- Abnormal and involuntary or repetitive muscle movements
- Fainting
- Impaired or abnormal sense of touch
- Impaired or distorted or absence of sense of smell
- Unusual feeling or sensation that can precede a migraine or a certain type of seizure
- Eye problems including dry eyes, sensitivity of the eyes to light, involuntary eyelid twitching, watery eyes
- Decreased or loss of hearing, loss of hearing in one ear
- Irregular or slow heartbeat, palpitations
- Low blood pressure or drop in blood pressure upon standing (therefore, some people taking Topitrim may feel faint, dizzy or may pass out when they stand or sit up suddenly)
- Flushing, feeling warm
- Pancreatitis
- Flatulence, heartburn, feeling of bloating or abdominal fullness
- Bleeding gums, increased production of saliva, drooling, bad breath
- Thirst and drinking large amounts of fluids
- Skin discoloration
- Muscle stiffness, side pain
- Blood in urine, urinary incontinence, a sense of urgency in urination, pain in the kidney area
- Sexual dysfunction, difficulty getting or keeping an erection
- Flu-like illness
- Cold sensation in the fingers and toes
- Feeling drunk
- Learning disabilities

Rare side effects - effects that occur in 1-10 in 10,000 users:

- Abnormally elevated mood
- Loss of consciousness
- Blindness in one eye, temporary blindness, night blindness
- Lazy eye
- Swelling in and around the eye
- numbness, tingling, color change (white, blue, red) in the fingers and toes when exposed to the cold
- Inflammation of the liver, liver failure
- Bad skin odor
- Discomfort in the arms or legs
- Kidney problems

Side effects of unknown frequency (has not yet been established):

- Maculopathy - a disease of the macula area of the eye. This is the small spot in the retina where vision is keenest. If you notice a change or decrease in vision - refer to the doctor.

Side effects in children

The side effects in children are generally similar to those seen in adults. However, the following side effects may be more common in children than in adults:

- Concentration problems • Increased acid level in the blood • Thoughts of serious self-harm • Tiredness • Decreased or increased appetite • Aggression, abnormal behavior • Difficulty falling or staying asleep • Feeling of unsteadiness when walking • Not feeling well • Decrease in potassium levels in the blood • Displaying lack of emotion or not feeling emotions • Watery eyes • Slow or irregular heartbeat

Other side effects that may occur in children are:

Common side effects - occur in 1-10 in 100 users:

- Sensation of spinning (vertigo) • Vomiting • Fever

Uncommon side effects - occur in 1-10 in 1,000 users:

- Increased level of eosinophils (a type of white blood cell) in the blood • Hyperactivity • Feeling warm • Learning disabilities

If a side effect occurs, if one of the side effects worsens or if you suffer from side effects not mentioned in the leaflet, consult the doctor.

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), that directs you to the online form for reporting side effects, or by using the following link: https://sideeffects.health.gov.il.

In addition, you can also report to the following email: safety@trima.co.il

5. HOW SHOULD THE MEDICINE BE STORED?

- Prevent poisoning! This medicine, and any other medicine, should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package/blister. The expiry date refers to the last day of that month.

Storage conditions

- Store in a dry place below 25°C.

6. FURTHER INFORMATION

- **In addition to the active ingredients, the medicine also contains the following inactive ingredients:**
  Lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycollate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol.
  Topitrim 25 mg contains 17 mg lactose and 0.1 mg sodium.
  Topitrim 50 mg contains 34 mg lactose and 0.2 mg sodium.
  Topitrim 100 mg contains 68 mg lactose and 0.4 mg sodium.
  Topitrim 200 mg contains 136 mg lactose and 0.8 mg sodium.
- **What does the medicine look like and what are the contents of the package?**
  Topitrim 25 mg, Topitrim 50 mg, Topitrim 100 mg: circulair, white to off-white film coated tablet.
  Topitrim 200 mg: oblong, white to off-white film coated tablet.
  The tablets are packed in blisters. Each pack contains 60 tablets.
- **Manufacturer and registration holder:** Trima Israel Pharmaceutical Products Maabarot Ltd., Maabarot 4023000, Israel.
- Revised in February 2025.
- Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
  Topitrim 25 mg 136.63.31514.00
  Topitrim 50 mg 136.64.31515.00
  Topitrim 100 mg 136.65.31516.00
  Topitrim 200 mg 136.66.31517.00

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