

Patient Leaflet According to the Pharmacists'
Regulations (Preparations) – 1986

The medicine is dispensed with a physician's prescription only

Tramal Retard 100

Tramal Retard 50

The active ingredient and its quantity:

Tramadol hydrochloride 100 or 50 mg

Inactive ingredients and allergens: See under 'Important information about some of this medicine's ingredients, and section 6 'Additional information'.

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the physician or the 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 it seems to you that their medical condition is similar.

This medicine is not intended for children under the age of 14 years.

Opioid medicines can cause addiction (mainly with prolonged use), and potential abuse and overdose are possible. The reaction to overdose can be slow breathing and even death.

Make sure that you know the name of the medicine, the dosage you are taking, how often you take it, the duration of treatment, its side effects and potential risks.

Additional information about the risk of dependence and addiction can be found at:

https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

1. What is the medicine intended for?

Tramadol - the active ingredient in Tramal Retard - is a painkiller belonging to the class of opioids that acts on the central nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

Tramal Retard is intended for the treatment of moderate to severe pain.

Therapeutic group: opioids.

2. Before using the medicine

Do not take the medicine:

- if you are sensitive (allergic) to the active ingredient or any of the other ingredients of this medicine (listed in section 6).
- in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood and emotions).
- if you are taking MAO inhibitors (certain medicines to treat depression) or have taken them in the last 14 days before treatment with Tramal Retard (see section "Other medicines and Tramal Retard").
- if you are an epileptic and your fits are not adequately controlled by your treatment.
- as a substitute in drug withdrawal.

Special warnings about using this medicine Talk to your physician before taking Tramal Retard if:

- you think that you are or have ever been dependent on other pain relievers (opioids), alcohol, prescription medicines, or any illegal drugs.
- you have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking, or sweating when you have stopped taking alcohol or drugs.
- you feel you need to take more Tramal Retard to get the same level of pain relief, this may mean you are starting to become tolerant to the effects of this medicine and are becoming addicted to it. Contact your physician who will discuss your treatment and may change your dose or switch you to another pain reliever.
- you suffer from consciousness disorders (if you feel that you are going to faint).
- you are in a state of shock (cold sweat may be a sign of this).
- you suffer from increased pressure on the brain (this may happen after a head injury or brain disease).
- you have difficulty in breathing.
- you have epilepsy or a tendency to have convulsions, because the risk of convulsions may increase.
- suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see “Other medicines and Tramal Retard”);
- you suffer from a liver or kidney disease.

Sleep-related breathing problems

Tramal Retard contains an active ingredient that belongs to a group of medicines called opioids. Opioids can cause sleep-related breathing problems, for example pauses in breathing during sleep (shallow breathing /sleep apnea and sleep-related hypoxemia (low level of oxygen in the blood)).

The risk of experiencing pauses in breathing during sleep is dependent on the dose of opioid. Your physician may consider decreasing your total opioid dose if you experience pauses in breathing during sleep.

There is a small risk that you may experience a so-called serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you have any of the symptoms related to this serious syndrome (see section 4 “Side effects”).

Epileptic fits have been reported in patients taking tramadol at the recommended dose level. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg).

Taking this medicine regularly, particularly for a long time, can lead to addiction. Your physician should have explained how long you will be taking it for and when it is appropriate to stop, how to do this safely.

Rarely, increasing the dose of this medicine can make you more sensitive to pain. If this happens, you need to speak to your physician about your treatment.

Addiction can cause withdrawal symptoms when you stop taking this medicine. Withdrawal symptoms can include restlessness, difficulty sleeping, irritability, agitation, anxiety, palpitations, increased blood pressure, nausea or vomiting, diarrhea, loss of appetite, shaking, sweating. Your physician will discuss with you how to gradually reduce your dose before stopping the medicine. It is important that you do not stop taking the medicine suddenly as you will be more likely to experience withdrawal symptoms.

Opioids should only be used by those they are prescribed for. Do not give your medicine to anyone else. Taking higher doses or more frequent doses of opioids, may increase the risk of addiction. Overuse and misuse can lead to overdose and/or death.

Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme and this can affect people in different ways. In some people, they may not get enough pain relief but other people are more likely to get serious side effects. If you notice any of the following side effects, you must stop taking this medicine and contact your physician immediately: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

Children and adolescents

Use of Tramal Retard in children with breathing problems:

Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Other medicines and Tramal Retard

If you are taking or have recently taken other medicines including nonprescription medicines and dietary supplements, tell your physician or pharmacist.

Tramal Retard should not be taken together with MAO inhibitors (certain medicines for the treatment of depression), or if you have taken them during the 14 days before the treatment with Tramal Retard.

The pain-relieving effect of Tramal Retard may be reduced and the length of time it acts may be shortened, if you take it together with medicines which contain:

- carbamazepine (for epileptic fits);
- ondansetron (prevents nausea).

Your physician will tell you whether you should take Tramal Retard, and which dose.

The risk of side effects increases if you are taking:

- Other pain relievers such as morphine and codeine (also for cough relief), and alcohol while you are taking Tramal Retard. You may feel drowsier or feel that you might faint. If this happens tell your physician.
- Concomitant use of Tramal Retard and tranquillizers or sleeping pills (e.g. benzodiazepines), increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However, if your physician prescribes Tramal Retard together with sedating medicines the dose and the duration of concomitant treatment should be limited by your physician. Please tell your physician about all sedating medicines you are taking, and follow your physician's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your physician if you experience such symptoms.
- Medicines which may cause convulsions (epileptic fits), such as certain antidepressants or antipsychotics. The risk of having a fit may increase if you take Tramal Retard at the same time. Your physician will tell you whether Tramal Retard is suitable for you.
- Certain antidepressants. Tramal Retard may interact with them and you may experience serotonin syndrome (see section 4 "Side effects").
- Coumarin anticoagulants (medicines for blood thinning), e.g. warfarin. The effect of these medicines on blood clotting may be affected and bleeding may occur.

Tramal Retard with food and alcohol

Do not drink alcoholic beverages during treatment with Tramal Retard as its effect may be intensified.

Food does not influence the effect of Tramal Retard.

Pregnancy, breastfeeding and fertility

Do not take Tramal Retard if you are pregnant or think you might be pregnant, unless you have discussed this with your physician and the benefits of treatment outweigh the risk of harm to the baby. If you take Tramal Retard during pregnancy, your baby may become dependent and experience withdrawal symptoms after the birth which may need to be treated.

Do not take Tramal Retard while you are breastfeeding because it passes into breast milk and may affect your baby.

Based on human experience, tramadol does not influence female or male fertility.

Driving and using machines

Tramal Retard may cause drowsiness, dizziness and blurred vision and therefore may impair your reactions. If you feel that your reactions are affected, do not drive a car or other vehicles, do not use electric tools or operate machinery.

The medicine can affect your ability to drive as it may make you sleepy or dizzy.

Do not drive while taking this medicine until you know how it affects you.

Talk to your physician or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

Important information about some of this medicine's ingredients

Tramal Retard contains lactose

If you have been told by your physician that you have an intolerance to some sugars, consult your physician about this medicinal product. This is because this medicinal product contains lactose.

3. How to use this medicine?

Always use according to the physician's instructions.

You should check with your physician or pharmacist if you are not sure about your dose or about how to take this medicine.

Only your physician will determine your dose and how you should take this medicine. The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be taken. Do not take more than 400 mg tramadol hydrochloride daily, unless your physician has instructed you to do so.

Unless otherwise prescribed by your physician, the usual dose is:

Adults and adolescents from the age of 14 years

One Tramal Retard tablet twice daily (equivalent to 100 - 200 mg tramadol hydrochloride per day), preferably in the morning and evening. Your physician may prescribe a different dosage that is more appropriate for you, if necessary.

If necessary, the dose may be increased up to 150 mg or 200 mg twice daily (equivalent to 300 mg – 400 mg tramadol hydrochloride per day).

Children

Tramal Retard is not suitable for children below the age of 14 years.

The elderly

In the elderly (above 75 years) the excretion of tramadol from the body, may be delayed. If this applies to you, your physician may recommend prolonging the dosage interval.

Severe liver or kidney disease (insufficiency)/dialysis patients

Patients with severe liver and/or kidney insufficiency should not take Tramal Retard. If in your case the insufficiency is mild or moderate, your physician may recommend prolonging the dosage interval.

Do not exceed the recommended dose

How and when should you take Tramal Retard?

Tramal Retard is for oral use.

Always swallow the Tramal Retard tablet whole, never split or chew the tablets, take with sufficient amount of water, preferably in the morning and evening. You may take the tablet on an empty stomach or after meals.

How long should you take Tramal Retard?

Your physician should have discussed with you how long the course of treatment will last and arranged a plan for stopping treatment. This plan outlines how to gradually reduce the dose until you stop taking the medicine.

If you have accidentally taken a higher dose than required

If you have taken an additional dose by mistake, this will generally have no negative effects. You should take your next dose as prescribed.

If you (or someone else) take a lot of Tramal Retard at once you should go to a hospital or to a physician straight away. Signs of an overdose include very small pupils, being sick, fall in blood pressure, fast heartbeat, collapse, unconsciousness, fits and breathing difficulties or shallow breathing.

If you forget to take the medicine

If you forget to take Tramal Retard, pain is likely to return. Do not take a double dose to make up for forgotten individual doses, simply continue taking the medicine as before.

If you stop taking the medicine

Do not suddenly stop taking this medicine. If you want to stop taking your medicine, consult your physician first. Your physician will explain to you how to do this, usually by reducing the dose gradually so that any unpleasant withdrawal effects are kept to a minimum.

Withdrawal symptoms such as restlessness, difficulty sleeping, irritability, agitation, anxiety, palpitations, increased blood pressure, nausea or vomiting, diarrhea, shaking, or sweating may occur if you suddenly stop taking this medicine.

Persist with the treatment as recommended by the physician.

Even if there is an improvement in your health, do not stop the 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 a medicine. Wear glasses if you need them.

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

4. Side effects

As with any medicine, use of Tramal Retard may cause side effects in some of the users. Do not be alarmed by this list of side effects. You may not experience any of them.

You should see a physician immediately if you experience symptoms of an allergic reaction such as swollen face, tongue and/or throat, and/or difficulty swallowing or hives together with difficulties in breathing.

The most common side effects during treatment with Tramal Retard are nausea and dizziness, which occur in more than 1 in 10 people.

Very common side effects - may affect more than 1 in 10 people

- dizziness
- nausea

Common side effects - may affect up to 1 in 10 people

- headaches, drowsiness
- fatigue
- constipation, dry mouth, vomiting
- sweating

Uncommon side effects - may affect up to 1 in 100 people:

- effects on the heart and blood circulation (heart rate, fast heartbeat, feeling faint or collapse). These adverse effects may particularly occur in patients in an upright position or under physical strain.
- urge to vomit (retching), stomach trouble (e.g. feeling of pressure in the stomach, bloating), diarrhea
- skin reactions (e.g. tingling, rash)

Rare side effects - may affect up to 1 in 1,000 people:

- allergic reactions (e.g. difficulty in breathing, wheezing, swelling of skin) and shock (sudden failure of blood circulation)
- slow heartbeat
- increase in blood pressure
- abnormal sensations (e.g. itching, tingling, numbness), trembling, epileptic fits, muscle twitches, uncoordinated movement, transient loss of consciousness (syncope), speech disorders
- epileptic fits have occurred mainly at high doses of tramadol or when tramadol was taken at the same time as other medicines which may induce fits.
- changes in appetite
- hallucination, confusion, sleep disorders, anxiety and nightmares
- psychological complaints may appear after treatment with Tramal Retard. Their intensity and nature may vary (according to the patient's personality and length of therapy). These may appear as a change in mood (mostly high spirits, occasionally irritated mood), changes in activity (usually suppression, occasionally increase) and decreased cognitive and sensory perception (being less aware and less able to make decisions, which may lead to errors in judgement).
- visual disturbances, excessive dilation of the pupils, constriction of the pupil
- slow breathing, shortness of breath
- worsening of asthma has been reported, however it has not been established whether it was caused by tramadol. If the recommended doses are exceeded, or if other medicines that depress brain function are taken at the same time, breathing may slow down.
- muscle weakness
- passing urine with difficulty or pain, passing less urine than normal

Very rare side effects - may affect up to 1 in 10,000 people:

- hepatic enzyme increased

Side effects with unknown frequency (frequency cannot be estimated from the available data)

- blood sugar level is too low
- Serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 2 'Before using the medicine').
- dependence and addiction (see below 'How do I know if I am addicted')

Drug withdrawal

When you stop taking Tramal Retard, you may experience withdrawal symptoms, which include restlessness, difficulty sleeping, irritability, anxiety, palpitations, increased blood pressure, nausea, diarrhea, shaking, sweating.

How do I know if I am addicted?

If you notice any of the following signs while you are taking Tramal Retard, this could be a sign of addiction:

- You feel you need to take the medicine for longer than advised
- You feel you need to use more than the recommended dose
- You are using the medicine for reasons other than prescribed
- When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again

If you notice any of these signs, it is important that you talk to your physician.

If a side effect has appeared, if any of the side effects get worse or when you suffer from a side effect that has not been mentioned in the leaflet, you should consult the physician.

Reporting of side effects

Side effects may 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 refers 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 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 without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.

Storage conditions

- Store at a temperature below 30°C.

6. Additional information

In addition to the active ingredient the medicine also contains:

microcrystalline cellulose, hypromellose (methyl-hydroxypropyl-cellulose), magnesium stearate, colloidal anhydrous silica, lactose monohydrate, talc, macrogol 6000, titanium dioxide (E171), propylene glycol.

Tramal Retard 50 only - yellow iron oxide (E172)

What does the medicine look like and what is the content of the package:

Tramal Retard 100 tablets are white and round and have T1 and $\frac{\infty}{\infty}$ marked on them.

Tramal Retard 50 tablets are pale yellow, round, and bevel-edged and have T0 and $\frac{\infty}{\infty}$ marked on them.

Tramal Retard 100 tablets are packed in blisters strips and are supplied in boxes of 10, 30, 50 and 150 tablets.

Tramal Retard 50 tablets are supplied in boxes of 10 and 30 tablets.

Not all pack sizes may be marketed.

License Holder: Tec-O-Pharm-Libra LTD, POB 45054, Jerusalem.

Manufacturer: Grünenthal GmbH, Zieglerstrasse 6 52078, Germany

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

TRAMAL RETARD 100 126-46-30529

TRAMAL RETARD 50 140-71-31758

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