Patient package insert according to Pharmacists' Regulations (Preparations) – 1986

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

TRAMADEX® OD 100, 200, 300

Prolonged release tablets

Each prolonged release tablet contains: tramadol hydrochloride in dosages of 100, 200, or 300 mg, accordingly.

Inactive ingredients and allergens in the medicine – see section 6 "Additional information" and in section 2 "Important information about some of the ingredients of this medicine".

Read this entire leaflet carefully before using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if you think that their medical condition is the same as yours.

Prescription opioids carry serious risks of addiction especially with prolonged use and they have a potential for misuse and overdose. An opioid overdose, often marked by slowed breathing, can cause death.
Make sure you know the name of your medication, how much and how often to take it, the duration of treatment and its potential risks & side effects. Additional information about the risk of dependence and addiction can be found at the link:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

Taking this medicine with benzodiazepines, other central nervous system depressants (including street drugs) or alcohol can cause severe drowsiness, breathing problems (respiratory depression), coma and death.

1. What is the medicine intended for?

For the treatment of moderate to severe pain.
Therapeutic group: opioid analgesic.

2. Before using the medicine

Do not use the medicine:

- If you are hypersensitive (allergic) to the active ingredient (tramadol hydrochloride), or to any of the other ingredients this medicine contains (see section 6).
- in case of acute alcohol poisoning, sleeping pills, analgesics or other psychotropic medicines (medicines that affect mood and emotions).
- If you are taking or have taken during the last two weeks medicines from the Monoamine oxidase inhibitor group – MAOIs (used to treat depression).
- If you suffer from severe liver disease or severe kidney disease.
- If you suffer from epilepsy that is not adequately controlled by treatment.
- If you are breastfeeding, in the case of long-term treatment (see also section "Pregnancy, breastfeeding and fertility").

If you are not sure, it is important to consult the doctor or pharmacist.

Special warnings regarding the use of the medicine
Consult the doctor or pharmacist before the treatment with **Tramadex OD.**
Tell the doctor if you suffer from addiction to another medicine, are being treated for withdrawal from another medicine or have a dependency on another medicine. This medicine may cause a psychic or physical dependence (addiction) with long-term use. In patients with a tendency to become addicted to medicines, this medicine should only be used for very short periods and under strict medical supervision.
Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme which can affect them 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, stop using the medicine and seek immediate medical assistance: slow or shallow breathing, confusion, sleepiness, small pupils, nausea or vomiting, constipation, lack of appetite.

Sleep-related respiratory disorders
Tramadex OD can cause sleep-related respiratory disorders, such as sleep apnoea (breathing pauses during sleep) and sleep-related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dosage reduction may be considered by your doctor.

Tell the doctor or pharmacist if you experience any of the following symptoms while taking **Tramadex OD**: Extreme fatigue, loss of appetite, severe abdominal pain, nausea, vomiting or low blood pressure. This may indicate that you have adrenal insufficiency (low cortisol levels). If you experience these symptoms, contact your doctor, who will decide if you need to take a hormone supplement.

Tell the doctor before taking this medicine if you suffer from depression and you are taking antidepressants, as some of them may interact with tramadol (see "Drug interactions").

There is a small risk that you may experience serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you experience any symptoms associated with this severe syndrome (see section 4 "Side effects").
Use the medicine with caution in the following cases:
- reduced consciousness
- head trauma or any brain disorder such as infection or tumor
- state of shock (cold sweat may be a sign of it)
- breathing difficulties
- a history of epileptic seizures
- kidney or liver disorders
- an increase in brain pressure causing symptoms such as headache and vomiting (an increase in intracranial pressure)
- diabetes

Epileptic fits have been reported in patients who took tramadol at the recommended dosage. The risk may increase in dosages that exceed the recommended maximum daily dosage (400 mg).
If you are not sure, consult the doctor or pharmacist.

Children and adolescents
The use of this medicine is not recommended in children under 14 years of age.
Use in children with breathing problems: tramadol is not recommended for use in children with breathing problems since the symptoms of tramadol toxicity may be worse in these children.

Drug interactions
If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking the following medicines, because there may be drug interactions with **Tramadex OD**:
- carbamazepine (used for the treatment of epilepsy)
- buprenorphine, nalbuphine, pentazocine (other painkillers)
- alcohol
- naltrexone (used for alcohol or drug withdrawal treatment)

This medicine may cause seizures at therapeutic dosages and especially when taken at high dosages and in combination with other medicines including:
- bupropion (used to help stopping smoking)
- mefloquine (for the treatment of malaria)

The risk of side effects increases if:
- you are taking medicines that may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk of having a fit may increase if you are taking **Tramadex OD** at the same time. The doctor will tell you if **Tramadex OD** is suitable for you.
- you are taking certain antidepressants. **Tramadex OD** may interact with these medicines and you may experience serotonin syndrome (see section 4 "Side effects").

This medicine may also interact with the following medicines:
- morphine-like medicines such as: cough medicines or as a substitute in drug withdrawal such as methadone
- other pain relievers
- warfarin (for blood thinning)
- benzodiazepines and other medicines to treat anxiety
- certain medicines for the treatment of hypertension
- antihistamines (for the treatment of allergies) that cause sleepiness
- thalidomide (for the treatment of certain types of cancer and skin conditions)
- barbiturates (sleeping medicines)
- neuroleptics, phenothiazines, butyrophenone (to treat mental illness)
- baclophene (a muscle relaxant)

Use of this medicine and food
The medicine can be taken regardless of meals.

Use of this medicine and alcohol consumption
Alcohol consumption is not recommended during treatment.

Pregnancy, breastfeeding and fertility
Do not use the medicine if you are pregnant unless it is absolutely necessary.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, consult a doctor or pharmacist before using this medicine.
Tramadol is excreted into breast milk. For this reason, you should not take **Tramadex OD** more than once during breastfeeding. Or alternatively, if you take **Tramadex OD** more than once, you should stop breastfeeding.
Consult the doctor or pharmacist before using any medicine.

Driving and using machines
Tramadex OD may cause drowsiness. Do not drive or engage in activities requiring alertness (for example using tools or machines), until you know how the medicine affects you. Do not take with alcohol or medicines that cause sleepiness.
The medicine can affect your ability to drive because it may cause sleepiness or dizziness.
Consult the doctor or pharmacist if you are not convinced that it is safe for you to drive while taking this medicine.
As for children, they should be warned about riding a bicycle or playing near roads etc.

Important information about some of the ingredients of this medicine
This medicine contains less than 1 mmol sodium (23 mg) per tablet i.e. it is essentially "sodium-free".

3. How to use this medicine

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine.
The dosage will be adjusted to the intensity of your pain and your individual pain sensitivity. In general, take the lowest pain-relieving dose.
The dosage and manner of treatment will be determined by the doctor only. The usual recommended dosage is:
Adults and adolescents 14 years of age and older:
The starting dosage is 100 mg, once daily. Afterwards, continue with a dosage of 200 mg, once daily. If the pain relief is not enough, the maximum dosage is 300 or 400 mg once daily.
Elderly patients (up to 75 years of age) - there is no need to adjust the dosage.
Elderly patients (over 75 years of age) - in elderly patients (over the age of 75) the excretion of tramadol from the body may be delayed. If this applies to you, the doctor may recommend prolonging the dosage interval.
Serious liver or kidney disease (insufficiency)/dialysis patients - in cases of serious liver and/or kidney insufficiency do not take **Tramadex OD**. If your insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.
Do not exceed the recommended dose.

Method of administration:
Swallow the tablet whole with a glass of water, preferably in the evening.
Tramadex OD can be taken with drink or food.
It is forbidden to halve, chew, crush, or dissolve the tablet as it is in a prolonged release form. Take the tablets once every 24 hours.
Do not take the medicine for longer than required. If you need to be treated for a long period, the doctor will check at regular and short time intervals (with treatment intermissions, as needed) whether you can continue to take the medicine and at what dosage.
If you feel that the effect of the medicine is too strong or too weak, refer to a doctor or a pharmacist.

If you have accidentally taken a higher dosage
If you have taken an overdose, refer to a doctor immediately. If a child has accidently swallowed the medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine
If you forgot to take this medicine at the designated time, do not take a double dose to make up for a forgotten dose. Take the next dose at the regular time and consult the doctor.

Continue with the treatment as recommended by the doctor.
Even if there is an improvement in your health, do not stop taking this medicine without consulting the doctor.

If you stop taking the medicine
Do not suddenly stop taking the medicine unless the doctor has instructed you to do so. If you want to stop using the medicine, consult the doctor first, particularly if you have used the medicine for a long time. Your doctor will advise you how and when to stop. It may be by lowering the dosage gradually to reduce the chance of developing side effects (withdrawal symptoms).
Rarely, when some of the patients stop taking **Tramadex OD** after long-term use, they suffer from withdrawal symptoms. They may suffer from the following side effects: agitation, anxiety, nervousness or shakiness, hyperactivity, and difficulty falling asleep.
These effects usually disappear within a few days. Tell the doctor upon the appearance of these symptoms.

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 further questions on the use of this medicine, consult the doctor or pharmacist.

4. Side effects

Like any medicine, the use of **Tramadex OD** 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.
All medicines may cause allergic reactions, but serious allergic reactions are very rare.
Refer to the doctor immediately with the sudden appearance of wheezing while breathing, breathing difficulties, swelling of the eyelids, face or lips, rash or itching (especially if affecting the whole body).

Serious side effects
Stop using the medicine and refer immediately to a doctor with the appearance of:
- fits (convulsions)
- breathing difficulties
- rash or allergic reaction of any kind

Additional side effects
Very common side effects (effects that appear in more than one in ten users):
- nausea
- dizziness

Common side effects (effects that appear in 1-10 out of 100 users):
- constipation, dry mouth, vomiting
- sweating
- headache, drowsiness
- fatigue

Uncommon side effects (effects that appear in 1-10 out of 1,000 users):
- gastrointestinal irritation (a feeling of pressure in the stomach and gas)
- cardiac and vascular problems (increased heart rate, low blood pressure when standing up, feeling unwell with drop in blood pressure)
- skin reactions (itching, rash, hives)

Rare side effects (effects that appear in 1-10 out of 10,000 users):
- muscle weakness
- changes in appetite
- numbness, itching or feeling of pins and needles, tremors
- slow heart rate or breathing
- blurred vision, constriction of the pupils (miosis).
- difficulty in passing urine
- mood changes (such as an unusual feeling of happiness), changes in activity (such as a decrease in activity) and changes in thought
- hallucinations (seeing or hearing things), confusion, sleep disturbances, anxiety, nightmares, confused thinking and reduced awareness (delirium)
- allergic reactions
- worsening of asthma
- dependence on the medicine (addiction to or reliance on this medicine) may occur
- when treatment is stopped abruptly, withdrawal symptoms may appear (see section 3 "If you stop taking the medicine").
- epileptic fits
- increased liver enzymes in a few isolated cases

Side effects with unknown frequency (effects for which a frequency has not yet been determined):
- low levels of blood sugar
- hiccups
- 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").

If a side effect appears, if one of the side effects worsens or if you suffer from a side effect which is not mentioned in this leaflet, consult the doctor.
Side effects can be reported to the Ministry of Health via the link "דיווח על תופעות לוואי עקב טיפול תרופתי" that can be found on the home page of the Ministry of Health website (www.health.gov.il) directing to the online form of adverse events reporting or via the following link: https://sideeffects.health.gov.il

5. How to store the medicine

- Avoid poisoning! This medicine and any other medicine must be stored 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 the doctor.
- Do not use the medicine after the expiry date (תאריך תפוגה) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store below 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Polyvinyl acetate, xanthan gum, hydroxypropyl distarch phosphate (E1442) (Contramid®), povidone, hydrogenated vegetable oil, magnesium stearate, silica colloidal anhydrous, sodium laurilsulfate.

What the medicine looks like and what the package contains:
A round, white to off-white colored tablet.
Approved package sizes: 2, 5, 10, 20, 30, 150 tablets. Not all package sizes may be marketed.

Manufacturer and address: Dexcel Ltd., 1 Dexcel St., Or Akiva 3060000, Israel.

Drug registration number at the national drug registry of the Ministry of Health:
Tramadex OD 100: 139-25-31580
Tramadex OD 200: 139-26-31581
Tramadex OD 300: 139-27-31582

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Tramadex OD PIL PB0222-03

Registration holder:

Dexcel Pharma Technologies Ltd.

1 Dexcel St., Or Akiva 3060000, Israel