Patient package insert in accordance with the Pharmacists' Regulations (Preparations) – 1986

The medicine is dispensed according to a physician's prescription only

Name of preparation and form:
ZALDIAR® film-coated tablets

Active ingredients and quantity:
Tramadol Hydrochloride 37.5 mg
Paracetamol 325 mg
Inactive and allergic ingredients in the medicinal product – see section 6 and also "Important information about some ingredients of the medicine" in section 2.

! Read the entire leaflet carefully before using the medicine.
This leaflet contains concise information about the medicine. If you have any further questions, refer to the physician or the pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems like their disease is similar to yours.

Opioids may cause addiction, especially in prolonged use, and have potential for abuse and over-dosage. A response to over-dose can result in slow breathing and even death. Make sure that you know the name of the drug, the dosage you are taking and frequency, the duration of treatment, the side effects and potential effects.
More information about the risk of dependence and addition 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?

Zaldiar is a combination of two analgesics, tramadol and paracetamol, which work together to relieve pain.
Zaldiar is intended for use only by adults and children over the age of 14.

Therapeutic group:
The preparation contains a combination of tramadol – a pain reliever from the opioids group and paracetamol – a pain reliever and fever reducer from the anilide group and is intended to treat moderate to severe pain.

2. BEFORE USING THE MEDICINE:

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the additional ingredients contained in the medicine (listed in section 6).
- In cases of acute alcohol poisoning.
- You are taking sleeping pills, pain relievers or medicines that affect mood and emotions.
- You are also taking medicines called monoamine oxidase inhibitors (MAOIs) or have taken MAOIs in the last 14 days before treatment with Zaldiar. MAOIs are used in the treatment of depression or Parkinson's disease.
- You have a severe liver disorder.
- You have epilepsy that is not adequately controlled by your current medicine.
- In children under the age of 14.

! Special warnings regarding use of the medicine:
Before beginning Zaldiar treatment, inform your physician if:

- You take medicines containing paracetamol or tramadol.
- You have liver problems or disease, as your eyes and skin may turn yellow, which may suggest jaundice.
- You have kidney problems.
- You have severe difficulties in breathing, for example asthma or severe lung problems.
- You have epilepsy or have already experienced fits or seizures.
- if you suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see “Other medicines and Zaldiar”);

- You have recently suffered from a head injury, shock or severe headaches associated with vomiting (being sick).
- You are dependent on any medicine for example morphine.
- You take other medicines to treat pain that contain buprenorphine, nalbuphine or pentazocine.
- You are going to have an anaesthetic (tell your physician or dentist that you are taking Zaldiar).
- if you are taking or will be taking a certain group of penicillins (isoxazolyl penicillins such as flucloxacillin). There is a risk of blood and fluid abnormality (high anion gap metabolic acidosis, see section 3).

Sleep-related breathing disorders
Zaldiar contains an active substance that belongs to the group of opioids. Opioids can cause sleep-related breathing disorders, for example central sleep apnea (shallow/pause of breathing during sleep) and sleep-related hypoxemia (low level of oxygen in the blood).
The risk of experiencing central sleep apnea is dependent on the dose of opioids. Your physician may consider decreasing your total opioid dosage if you experience central sleep apnea.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”).

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 seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

If any of the above-mentioned points applied to you in the past or applies to you while you are taking Zaldiar, please make sure your doctor knows. He/she can then decide whether you should continue to use this medicine.

Talk to your doctor if you experience any of the following symptoms while taking Zaldiar:

Extreme fatigue, lack of appetite, severe abdominal pain, nausea, vomiting or low blood pressure. This may indicate that you have adrenal insufficiency (low cortisol

levels). If you have these symptoms, contact your doctor, who will decide if you need to take hormone supplement.

Other Medicines and Zaldiar

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

Do not exceed the maximum daily doses of paracetamol or tramadol from this or other medicines.
Do not take Zaldiar with MAOIs (see the section 'Before using the medicine').

Zaldiar is not recommended to be taken with the following:

- carbamazepine (a medicine used to treat epilepsy or some types of pain).
- buprenorphine, nalbuphine or pentazocine (opioid-type pain relievers).

The risk of side effects increases:

- if you are taking triptans (used for migraine) or selective serotonin re-uptake inhibitors (SSRIs, used for depression). Check with your physician if you experience confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles or diarrhea.
- if you are taking other pain relievers such as morphine and codeine (also as cough medicine), baclofen (a muscle relaxant), medicines used to lower blood pressure or medicines to treat allergies. Check with your physician if you feel drowsy or feel faint.
- Concomitant use of Zaldiar and sedative medicines such as benzodiazepines or related drugs 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 Zaldiar together with sedative medicines the dose and duration of concomitant treatment should be limited by your physician. Please tell your physician about all sedative 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 when experiencing such symptoms.
- if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk having a fit may increase if you take Zaldiar at the same time. Your physician will tell you whether Zaldiar is suitable for you.
- if you are taking certain antidepressants. Zaldiar may interact with these medicines and you may experience serotonin syndrome (see section 4 "Side effects").
- if you are taking warfarin or phenprocoumon (for blood thinning). The effectiveness of such medicines may be altered and bleeding may occur (see section 4).
- if you are taking a certain group of penicillins (isoxazolyl penicillins such as flucloxacillin). There is a risk of blood and fluid abnormality (high anion gap metabolic acidosis) which occurs when there is an increase in blood plasma acidity. You are at higher risk if you suffer from severe renal or hepatic impairment, sepsis or malnutrition, especially if you take the maximum daily dose of paracetamol for longer time. High anion gap metabolic acidosis is a serious disease that must have urgent treatment.

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The effectiveness of Zaldiar may be altered if you also take:

- Metoclopramide, domperidone or ondansetron (medicines used to treat nausea and vomiting/being sick).
- Cholestyramine (medicine used to reduce cholesterol in the blood).

Your physician will advise you which medicines are safe to use with Zaldiar.

Zaldiar with food and alcohol:
Do not drink alcohol while you are taking Zaldiar, as you may feel drowsier.

Zaldiar may be taken with or without food.

Pregnancy, breast-feeding and fertility:
Do not take Zaldiar while you are pregnant or breastfeeding.
Check with your physician if you become pregnant during treatment with Zaldiar and before taking any further tablets.
Breast-Feeding:
Tramadol is excreted into breast milk. For this reason, you should not take Zaldiar more than once during breast-feeding, or alternatively, if you take Zaldiar more than once, you should stop breast-feeding.
Based on human experience, tramadol is suggested not to influence female or male fertility. No data on the influence of the combination of tramadol and paracetamol on fertility are available.

Ask your physician or pharmacist for advice before taking the medicine.

Driving and using machines:
If you feel drowsy while taking Zaldiar, do not drive, use tools or use 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 ingredients of the medicine:

Zaldiar contains lactose
If you have been told by your physician that you have an intolerance to some sugars, contact your physician before taking this medicinal product.
Zaldiar contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine according to the physician’s instructions. You should check with the physician or pharmacist if you are not sure.

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.
Take Zaldiar for as short a time as possible, and no longer than your physician has told you.

The dosage and treatment will be determined only by the physician.

The usual dose is an initial dosage of up to 2 tablets. If required, further tablets may be taken, as instructed by your physician. The shortest time between doses must be at least 6 hours.

Do not take more than 8 tablets per day (300 mg tramadol, 2600 mg paracetamol). Do not use Zaldiar more often than your physician has told you.

Older people:
In elderly patients (above 75 years) the excretion of tramadol 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 Zaldiar. If in your case the insufficiency is mild or moderate, your physician may recommend prolonging the dosage interval.

Do not exceed the recommended dose.

Method of administration:
The tablets are for oral use.
Swallow the tablet whole with sufficient liquid.
Do not chew, divide, or crush the tablets!

If you think that the effect of Zaldiar is too strong (you feel very drowsy or have difficulty breathing) or too weak (you do not have enough pain relief), contact your physician.

If you take more Zaldiar than you should
If you mistakenly took more Zaldiar than instructed, contact your physician or pharmacist immediately, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.
In case of overdose, or if a child accidently swallowed the medicine, immediately refer to the emergency room of a hospital, and bring the medicine package with you.

Do not induce vomiting without a physician's specific instruction!

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

If you stop taking Zaldiar
Generally, there will be no side effects when treatment with Zaldiar is stopped. Rarely, people who have been using a medicine containing tramadol may become dependent on it, making it hard to stop taking it. If you have been taking Zaldiar for some time and want to stop, contact your physician because your body may have become used to Zaldiar.

People may:
- feel agitated, anxious, nervous or shaky
- be over active
- have difficulty sleeping
- have stomach or bowel disorders.

Very few people may also get:
- panic attacks
- hallucinations, unusual perceptions such as itching, tingling and numbness
- ringing in the ears.

If you experience any of these effects after stopping this medicine, please contact your physician.
Other side effect information is listed in section 4.

Do not take medicines in the dark!

Check the label and dose each time you take the medicine. Wear glasses, if you need them.

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

4. SIDE EFFECTS

As with all medicines, this medicine may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Some side effects could be serious. Contact your physician immediately if any of the following occur:

- rarely cases of skin rash, indicating an allergic reaction, may develop with sudden swelling of the face and neck, difficulties breathing or drop of blood pressure and fainting. If this happens to you, stop treatment. Do not take the medicine again.
- prolonged or unexpected bleeding, from the use of Zaldiar with medicines used to thin the blood (e.g. warfarin, phenprocoumon).
- Paracetamol may, in rare cases, cause severe skin diseases. The possible signs are: skin redness, rashes, blisters, extensive dermal injury. Severe dermal side effects may also appear even if you have previously taken preparations that contain the active agent paracetamol without any problem.

Additional Side Effects:
Additionally, if any of the following side effects get serious, contact your physician or pharmacist:

Very common: may affect more than 1 in 10 people

- nausea
- dizziness, drowsiness.

Common: may affect up to 1 in 10 people

- vomiting (being sick), digestion problems (constipation, flatulence, diarrhoea), stomach pain, dry mouth
- itching, sweating (hyperhidrosis)
- headache, shaking
- confusional state, sleep disorders, mood changes (anxiety, nervousness, feeling of high spirits).

Uncommon: may affect up to 1 in 100 people

- increase in pulse or blood pressure, heart rate or heart rhythm disorders
- tingling, numbness or feeling of pins and needles in the limbs, ringing in the ears, involuntary muscle twitching
- depression, nightmares, hallucinations (hearing, seeing or sensing things that are not really there), memory lapses
- difficulty breathing
- difficulty swallowing, blood in the stools
- skin reactions (for example rashes, hives)
- increase in liver enzyme values
- presence of albumin in urine, difficulties or pain on passing urine
- shivering, hot flushes, pain in the chest.

Rare: may affect up to 1 in 1,000 people

- fits, uncoordinated movements, transient loss of consciousness (syncope)
- drug dependence
- delirium

- vision blurred, constriction of the pupil (miosis)
- speech disorders
- excessive dilation of the pupils (mydriasis).

Frequency unknown:
- decrease in blood sugar level (hypoglycaemia).

In addition, the following side effects have been reported by people using medicines that contain only tramadol or only paracetamol:
- feeling faint when getting up from a lying or sitting position, slow heart rate, fainting
- changes in appetite
- muscle weakness, slower or weaker breathing
- mood changes, changes in activity, changes in perception
- worsening of existing asthma
- Paracetamol intake in very rare cases may induce a blood and fluid abnormality (high anion gap metabolic acidosis) when there is an increase in blood plasma acidity

- nose bleeds or bleeding gums, which may result from a low blood platelet count
- very rare cases of serious skin reactions have been reported with paracetamol
- rare cases of respiratory depression have been reported with tramadol.
- Frequency not known: 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”).
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If a side effect has appeared, if any of the side effects gets worse, or if you suffer from any 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 SHOULD THE MEDICINE BE STORED?

Prevent poisoning!
This medicine, like all medicines, must be stored in a closed place out of the sight and reach of children and/or infants, to avoid poisoning. Do not induce vomiting without a physician’s specific instruction.

Do not use this medicine after the expiry date (exp. date), which is printed on the box and on the blister. The expiry date refers to the last day of the indicated month.

The medicine is to be stored at a temperature not higher than 30°C.

6. ADDITIONAL INFORMATION

In addition to the active ingredients, the medicine also contains:
Tablet core:
Powdered cellulose, Maize starch, Pregelatinized starch, Sodium starch glycolate, Magnesium stearate.
Film-coating:
Hypromellose, Lactose monohydrate, Titanium dioxide, Macrogol 6000, Yellow iron oxide, Propylene glycol, Talc.

Each tablet contains 1.878 mg Lactose monohydrate.

What the medicine looks like and contents of the pack:
Zaldiar tablets are pale yellow film-coated tablets, marked with the manufacturer's logo on one side and "T5" on the other. Zaldiar is packed in blister packs of 10 tablets.
Zaldiar comes in packages of 10 and 20 film-coated tablets.

Not all pack sizes may be marketed.

Registration Owner: Tec-O-Pharm Libra Ltd., POB 45054 Jerusalem.

Manufacturer: Grunenthal GmbH, Aachen, Germany.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 1359031296.

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