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

The medicine is dispensed with a doctor's prescription only

Targin 5, Targin 10, Targin 20, Targin 30, Targin 40

Prolonged-release tablets

Active ingredients:

The medicine	Oxycodone hydrochloride (Oxycodone HCl)	Naloxone hydrochloride (Naloxone HCl)
Targin 5	5 mg	2.5 mg
Targin 10	10 mg	5 mg
Targin 20	20 mg	10 mg
Targin 30	30 mg	15 mg
Targin 40	40 mg	20 mg

For the list of the additional ingredients, see section 6. See also 'Important information about some of the medicine's ingredients' 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, please 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 it seems to you that their medical condition is similar to yours.

Medicines of the opioids group may cause addiction, especially with prolonged use, and they have a potential for misuse and overdose. A reaction to an overdose may be manifested by slow breathing and may even cause death.
Make sure you know the name of the medicine, the dosage you take, how often you take it, the duration of treatment, potential side effects and risks.
Additional information regarding the risk of dependence and addiction can be found at the following link:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

Taking this medicine along with medicines from the benzodiazepines group, other medicines which depress the central nervous system (including drugs) or alcohol, may cause a feeling of profound drowsiness, breathing difficulties (respiratory depression), coma and death.

1. What is the medicine intended for?

Targin is intended for relief of moderate to severe pain. Targin contains two active ingredients, oxycodone and naloxone. The oxycodone is intended for the relief of moderate to severe pain in adults who need opioid pain relief around-the-clock, for a few days or more. The naloxone was added to reduce constipation caused by the activity of the opioid oxycodone in the digestive system.

Therapeutic group: Oxycodone - opioid analgesic (painkiller), Naloxone - opioid antagonist.

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 that the tablets contain (for the list of the additional ingredients, see section 6).
- You suffer from respiratory depression (your breathing cannot supply sufficient oxygen to the blood and get rid of carbon dioxide); severe lung disease associated with narrowing of the airways (COPD), severe bronchial asthma.
- You suffer from cor pulmonale (a condition where the right side of the heart becomes enlarged due to increased pressure inside blood vessels in the lung, for instance).
- You suffer from bowel obstruction not caused by opioids use.
- You suffer from moderate to severe liver function impairment.

Special warnings regarding the use of this medicine:

Before the treatment with Targin tell the doctor if:

- You or anyone in your family is or was ever addicted to opioids, alcohol, prescription medicines or drugs.
- You are an elderly or debilitated (weak) patient.
- You suffer from bowel obstruction caused by opioids use; kidney function impairment; liver function impairment; severe lung function impairment (reduced breathing capacity); frequent breathing stops during sleep which may cause you to feel very sleepy during the day (sleep apnea); myxedema - thyroid gland function disorder accompanied by dryness, coldness and swelling of the skin of the face or the limbs.
- Your thyroid gland does not produce sufficient hormones (underactive thyroid gland or hypothyroidism).
- Your adrenal glands do not produce sufficient hormones (adrenal insufficiency, Addison's disease).
- You suffer from a mental illness accompanied by (partial) loss of reality (psychoses), as a result of alcohol or of a toxic effect of other substances (substance-induced psychosis).
- You suffer or have ever suffered from problems with your mood (depression, anxiety or personality disorder), or you are being treated or have been treated by a psychiatrist for other mental illnesses.
- You suffer from gallstone problems.
- You suffer from an enlarged prostate gland (prostate hypertrophy).
- You suffer from alcoholism or delirium tremens (a psychosis caused upon withdrawal from alcohol).
- You suffer from inflammation of the pancreas.
- You suffer from low blood pressure or high blood pressure.
- You have an existing cardiovascular disease.
- You are a smoker.
- You suffer from a head injury (due to the risk of increased brain pressure).
- You suffer from epilepsy or have a prone to spasms/seizures.
- You are taking a medicine belonging to the monoamine oxidase inhibitor group (MAOIs) (used to treat depression or Parkinson's disease), or you have taken this type of medicine during the last two weeks, e.g.: medicines containing tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid.
- You suffer from sleepiness or episodes of suddenly falling asleep.
- You suffer from any biliary tract problem (diseases affecting the bile ducts, gallbladder, etc.).

Tell the doctor also if you suffered from the above mentioned conditions in the past, and/or if they develop during treatment with the medicine.

Additional warnings:

- The most serious result which may occur from opioid overdose is respiratory depression (slow and shallow breathing). This may also cause blood oxygen levels to fall, which will lead to fainting, etc.
- The medicine may cause breathing problems while sleeping. These problems can include pauses in breathing during sleep, waking up from shortness of breath, difficulty remaining asleep or increased daytime drowsiness. If you feel these symptoms or someone around you observes these symptoms in you, refer to the doctor. The doctor may recommend reducing the dosage.
- Swallow the prolonged-release tablet whole, so as not to damage the slow-release mechanism of oxycodone hydrochloride from the tablet. Do not break, chew, crush or halve the tablet! Taking tablets that are not whole may cause absorption of a life-threatening dose of oxycodone hydrochloride (see section 'If you accidentally took a higher dosage').
- If you experience severe diarrhea at the start of treatment, this may be the effect of the naloxone. It may be a sign that bowel function is returning to normal. Such diarrhea may occur within the first 3 to 5 days of the treatment. If the diarrhea persists for longer than 3-5 days, or if it bothers you, refer to the doctor.
- If you used another opioid before treatment with **Targin**, there may be withdrawal symptoms upon switching to Targin, such as: restlessness, bouts of sweating and muscle pains. If you experience such withdrawal symptoms, you may need closer medical monitoring.
- Taking this medicine regularly, particularly for a long time period, can lead to addiction that may result in a life-threatening overdose. If you are concerned that you may become dependent on **Targin**, it is important to consult your doctor. The doctor who prescribed the medicine for you must explain how long to take it, and when it is appropriate to stop, how to do so safely.
- Prolonged use may cause you to develop tolerance to the medicine (need for a higher dose to achieve the desired effect), as well as physical dependence. There may be withdrawal symptoms if the treatment is stopped suddenly (restlessness, bouts of sweating, muscle pains). When you no longer need treatment, the daily dose should be reduced gradually in consultation with the doctor.
- The active ingredient oxycodone hydrochloride has a potential for abuse, similar to other strong opioid painkiller. There is a risk of developing psychological dependence (addiction) on the medicine. Treatment with the medicine should be avoided if you suffer or have suffered in the past from alcohol, medicine or drug abuse or addiction.
- You suffer from cancer associated with metastasis in the peritoneum or in the case of the beginning of bowel obstruction in advanced stages of digestive or pelvic cancer.
- If you are about to undergo surgery, tell the doctor/medical staff that you are taking this medicine.
- Similar to other opioids, the active ingredient oxycodone may affect the production of hormones in the body, for instance, cortisol or the sex hormones, especially when taking high doses for prolonged periods. If you experience persistent symptoms such as nausea or vomiting, loss of appetite, fatigue, weakness, dizziness, changes in the menstrual cycle, impotence, infertility or decrease in sex drive, consult the doctor. Monitoring of the hormone levels may be required.
- The medicine may increase your sensitivity to pain, particularly with a high dose. Tell the doctor if this happens. A reduction in the dose or a change in the medicine may be necessary.
- You may notice remnants of the tablet in the stool. Do not worry, since the active ingredients in the tablet have already been released in the digestive system and absorbed into your body.

<u>Incorrect use of Targin:</u>

- **Targin** is not suitable for treatment of withdrawal symptoms.
  Never abuse **Targin**, especially if you have a drug addiction. If you are addicted to substances such as heroin, morphine or methadone, you may have severe withdrawal symptoms if you abuse the tablets since they contain naloxone. If you are already suffering from withdrawal symptoms, they may worsen.

- Never misuse the tablets by dissolving the tablets and injecting them (into a blood vessel for instance). Particularly since they contain talc, which can cause localized tissues destruction (necrosis) and changes in the lung tissue (pulmonary granuloma). Such abuse may cause other serious consequences and even death.
- The use of **Targin** may produce a positive result in doping controls.
- The use of **Targin** to improve athletic performance constitutes a health hazard.

Use in children and adolescents: There is no information on the safety and efficacy of the use in children and adolescents under the age of 18 years and therefore the use is not recommended.

Tests and monitoring: During long-term treatment, you should undergo periodic evaluations, to assess the continued need for the medicine.

Drug interactions:

- **The risk of side effects increases if you use antidepressants** (such as citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine). These medicines may have a drug interaction with oxycodone and you may experience symptoms such as involuntary, rhythmic muscle contractions, including the muscles that control eye movement, agitation, hallucinations, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38 °C, coma, tachycardia (rapid heartbeat), changes in blood pressure, lack of coordination, muscle stiffness, digestive system symptoms (nausea, vomiting, diarrhea). refer to the doctor if you experience these symptoms.
- **Taking opioids concomitantly with sedatives (medicines that sedate, calm or induce sleep) such as benzodiazepines or similar medicines** increases the risk of drowsiness, breathing difficulties (respiratory depression) and coma, and might be life-threatening. Therefore, concomitant use should be considered only if there are no other treatment options available. Nevertheless if your doctor has decided to prescribe sedatives for you together with **Targin**, he will have to limit the dosage and the duration of the combined treatment. Tell the doctor of all the sedatives you are taking. Examples of these or similar medicines include: other strong medicines for pain relief (opioids); medicines to treat epilepsy, pain and anxiety such as gabapentin and pregabalin; sedatives and sleep-inducing medicines (including benzodiazepines, hypnotics, anxiolytics); medicines to treat depression; medicines to treat allergies, travel sickness or nausea (antihistamines or antiemetics); medicines to treat psychiatric or mental disorders (antipsychotics including phenothiazines and neuroleptics).

Please strictly follow the doctor's recommendations regarding the dosage. It is recommended to ask friends and relatives to pay attention to the symptoms mentioned above. Refer to the doctor if you experience these symptoms.

If you are taking or have recently taken any other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:

- Medicines to prevent blood clotting (such as coumarin derivatives);
- Antibiotics from the macrolide group (such as clarithromycin, erythromycin, telithromycin);
- Antifungals from the azole group (such as ketoconazole, voriconazole, itraconazole, posaconazole);
- Protease inhibitors (anti-HIV virus) such as: ritonavir, indinavir, nelfinavir, saquinavir;
- Cimetidine (to treat heartburn, stomach ulcer, indigestion);
- Rifampicin (to treat tuberculosis);

- Carbamazepine (to treat convulsions and certain pain conditions); phenytoin (to treat convulsions);
- The hypericum plant (also known as St. John's Wort);
- Quinidine (to treat irregular heartbeat);
- Medicines of the monoamine oxidase inhibitors group (MAOIs), such as: tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid, used to treat depression or Parkinson's disease. Also tell the doctor if you have taken a medicine of this type during the last two weeks.

No drug interaction is expected between **Targin** and paracetamol, acetylsalicylic acid (aspirin) or naltrexone.

Use of the medicine and food: You may take the medicine regardless of mealtimes.
Avoid drinking grapefruit juice when using this medicine.

Use of the medicine and alcohol consumption: Do not drink alcohol during the treatment period with this medicine.
Drinking alcohol during the treatment period with the medicine may cause you to feel more sleepy or increase the risk of serious side effects, such as shallow breathing with a risk of stopping breathing and loss of consciousness.

Pregnancy and breastfeeding: Consult the doctor if you are pregnant, think you are pregnant, planning a pregnancy or are breastfeeding.

- **Pregnancy:** Avoid using the medicine if you are pregnant (unless otherwise instructed by the doctor). Prolonged use during pregnancy may cause withdrawal symptoms in the newborn. Use during childbirth may cause respiratory depression (slow and shallow breathing) in the newborn.
- **Breastfeeding**: Do not breastfeed during the treatment period. Oxycodone hydrochloride passes into the breastmilk. It is not known whether naloxone also passes into the breastmilk. Therefore, a risk for the breastfeeding infant cannot be excluded, in particular following intake of multiple doses of **Targin**.

Driving and use of machinery: The use of this medicine may impair your ability to drive or operate machinery, as it may cause you to fall asleep and feel drowsy (especially at the beginning of treatment, when the dosage is increased, when switching from another medicine or in combination with other medicines that affect the central nervous system). If you feel drowsiness and/or any other effect that may affect driving, do not drive, operate machinery or participate in activities that require alertness. Consult with the doctor if necessary.

Important information about some of the medicine's ingredients: The tablets contain lactose. If you have intolerance to certain sugars, inform the doctor before taking this medicine (see section 6).

3. How to use the medicine?

Always use according to the doctor's instructions. You should check with the doctor or pharmacist if you are not sure regarding the dosage and the manner of treatment with the medicine. **The dosage and the manner of treatment will be determined by the doctor only**.
Targin tablets have a prolonged-release mechanism - the active ingredients are released over an extended period. Their action lasts for 12 hours.
Swallow the tablet whole, so as not to impair the prolonged release mechanism of oxycodone hydrochloride from the tablet. Do not break, chew, crush or halve the tablet!

Taking tablets that are not whole may cause absorption of a life-threatening dose of oxycodone hydrochloride (see section: 'If you have accidentally taken a higher dosage').

The standard dosage is usually:
Take the tablets at set intervals (usually every 12 hours), as determined by the attending doctor. The doctor will adjust your dosage according to your condition and the intensity of your pain. The doctor will prescribe the minimum dose needed to control your pain.

Do not exceed the recommended dose.
If the doctor switches your **Targin** to another opioid painkiller, your bowel function may worsen.
If you experience pain between two doses of **Targin** refer to the doctor. You may need to receive a rapid-acting painkiller. **Targin** is not suitable for that.
If you feel that the effect of the tablets is too strong or too weak, refer to the doctor.

Elderly patients: If the liver and kidney functions are normal, there is usually no need for a dosage adjustment.
Patients with liver or kidney problems: if you suffer from kidney function problems or mild liver function problems, the doctor may take precautions (for instance prescribe a lower dose). Do not use the medicine if you suffer from moderate or severe liver problems.

Manner of use: for oral administration. Take the tablets whole with a sufficient amount of water (about half a glass) every 12 hours (for example at 8 am and 8 pm). The medicine can be taken regardless of mealtimes. Do not break, chew crush or halve the prolonged-release tablet (see section 2 'Special warnings regarding the use of this medicine').

Duration of use: Do not take the tablets for a longer period than necessary. In long-term treatment, the doctor will perform follow-up to verify the need for continued treatment.

If you have accidentally taken a higher dosage or if a child or any other person has accidentally swallowed the medicine, proceed **immediately** to a doctor or to a hospital emergency room and bring the medicine package . Symptoms of overdose may be manifested in: constriction of the pupils, slow and weak breathing (respiratory depression), drowsiness up to loss of consciousness, low muscle tone, slowing of pulse rate and drop in blood pressure.
In severe cases, there may be loss of consciousness (coma), fluid in the lungs, collapse of the blood system (shock), which may cause death in some cases (conditions that require urgent medical attention).
Do not perform activities which require a high level of alertness, such as driving.

If you forgot to take the medicine, follow the instructions below:
<u>If 8 hours or more remain until taking the next dose:</u> Take the forgotten dose immediately. Take the next dose at the regular time.
<u>If less than 8 hours remain until taking the next dose:</u> Take the forgotten dose and wait 8 hours until the next dose.
Afterwards, try to get back to your regular dosing times. Consult the doctor if you are not sure. Make sure there is an interval of at least 8 hours between doses. Do not take a double dose to make up for the forgotten dose.
Adhere to the treatment according to your doctor’s recommendation. Even if your state of health improves, do not stop the treatment with the medicine without consulting your doctor.
If you stop taking the medicine: If you do not need any further treatment, consult the doctor who will guide you on how to gradually decrease the daily dose in order to reduce the risk of withdrawal symptoms, such as: restlessness, bouts of sweating and muscle pains.
Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.

If you have further questions concerning the use of the medicine, consult the doctor or pharmacist.

4. Side Effects

As with any medicine, the use of **Targin** 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.

Proceed to a doctor or to an emergency room immediately if the following side effects appear:

- Slow and shallow breathing (respiratory depression). Respiratory depression is the main risk in overdose cases, it occurs mainly in elderly and debilitated (weak) patients.
- Severe drop in blood pressure.

Additional side effects:

Common side effects (appear in 1-10 users out of 100): abdominal pain, constipation, diarrhea, dry mouth, indigestion, vomiting, nausea, flatulence, decrease in appetite up to loss of appetite, dizziness or spinning sensation, headache, hot flashes, unusual weakness, tiredness or exhaustion, skin reactions such as itching or rash, sweating, vertigo, sleeping difficulties, drowsiness.

Uncommon side effects (appear in 1-10 users out of 1,000): abdominal bloating, abnormal thoughts, anxiety, confusion, depression, nervousness, chest tightness (especially if you already suffer from a coronary heart disease), drop or rise in blood pressure, withdrawal symptoms such as agitation, fainting, lack of energy, thirst, altered sense of taste, palpitations (feeling heartbeats), bile-related pains (colic), chest pains, generally feeling unwell, pain, swelling of the hands, ankles or feet, concentration difficulties, speech impairment, shaking, breathing difficulties, restlessness, chills, increase in hepatic enzymes, reduced sexual drive, runny nose, cough, hypersensitivity or allergic reactions, weight loss, increased risk for injuries from accidents, increased urge to urinate, muscle pain, muscle cramps or twitches, vision impairment, epileptic seizures (especially in epileptic patients or patients with a predisposition to seizures).

Rare side effects (appear in 1-10 users out of 10,000): increase in pulse rate, dependence on the medicine, dental changes, weight gain, yawning.

Side effects of unknown frequency (effects whose frequency has not yet been determined): feeling of extreme happiness (euphoria), severe drowsiness, erectile problems, nightmares, hallucinations, shallow breathing, difficulty in passing urine (urinary retention), aggression, tingling skin (pins and needles), belching, breathing problems during sleep (sleep apnea syndrome) - for further information see section 2 'Special warnings regarding the use of this medicine'.

Other side effects observed in the use of medicines containing only oxycodone hydrochloride as an active ingredient, not combined with naloxone hydrochloride:
Oxycodone can cause breathing problems (respiratory depression), reduction in the size of the eye pupils, cramping of the bronchial muscles and cramping of the smooth muscles, as well as depression of the cough reflex.

Common side effects (appear in 1-10 users out of 100): changes in behavior/personality or mood (such as depression, feeling of extreme happiness), increase or decrease of activity, difficulties in passing urine, hiccups.

Uncommon side effects (appear in 1-10 users out of 1,000): impaired concentration, migraines, increase in muscle tension, involuntary muscle contractions, bowel obstruction, dry skin, drug

tolerance, reduced sensitivity to pain or touch, impaired coordination, vocal changes, fluid retention (edema), hearing impairment, mouth ulcers, difficulties swallowing, sore gums, perception disturbances (such as, hallucinations, derealization), flushed skin, dehydration, agitation, reduced sex hormone levels, which may affect sperm production in men or the menstrual cycle in women.

Rare side effects (appear in 1-10 users out of 10,000): itchy rash (urticaria), infections such as herpes or cold sores (may appear as blisters around the mouth or genitals), increased appetite, black (tarry) stools, bleeding gums.

Side effects of unknown frequency (effects whose frequency has not yet been determined): severe generalized allergic reaction (anaphylactic reaction), increase in sensitivity to pain, absence of a menstrual period in women, withdrawal symptoms in newborns, increase in severity of symptoms associated with pancreas inflammation (e.g. worsening of abdominal pains) or colicky abdominal pain or discomfort, problems with bile flow, tooth decay.
If a side effect appears, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult the doctor.

Side effects may be reported to the Ministry of Health by clicking on the link "Report on side effects following medicinal treatment" on the homepage of the Ministry of Health website (www.health.gov.il) which leads to an 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 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 throw away medicines into wastewater or household waste. When you no longer need the medicine, consult with the pharmacist on how to dispose of it to protect the environment.

- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- **Storage conditions: Targin 10, 20, 30 and 40** store below 25 °C. **Targin 5** store below 25 °C in the original package.

6. Additional information

- **In addition to the active ingredients, the tablets also contain:**

Targin 5: Each tablet contains about 69 mg lactose, and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, hydroxypropylcellulose, polyvinylalcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350, brilliant blue FCF aluminum lake (E133).
Targin 10: Each tablet contains about 62 mg lactose, and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, povidone K30, polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350.
Targin 20: Each tablet contains about 52 mg lactose, and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, povidone K30, polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350, iron oxide red (E172).
Targin 30: Each tablet contains about 37 mg lactose, and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, povidone K30, polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172).
Targin 40: Each tablet contains about 104 mg lactose, and in addition:

Stearyl alcohol, ethylcellulose, talc, magnesium stearate, povidone K30, polyvinyl alcohol partially hydrolysed, titanium dioxide (E171), macrogol 3350, iron oxide yellow (E172).

- **What does the medicine look like and what does the package contain?**

Oblong coated tablets (caplets). “OXN” is embossed on one side and the tablet strength on the other side (5, 10, 20, 30 or 40, respectively). **Color of the tablets**: **Targin 5** - blue, **Targin 10** - white, **Targin 20** - pink, **Targin 30** - brown, **Targin 40** - yellow.
Each box contains 20 tablets in blister packs.
Manufacturer and Registration Holder: Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301.
Medicine registration number in the National Medicines Registry of the Ministry of Health:
Targin 5 - 1439833120; **Targin 10** - 1399531636; **Targin 20** - 1399631637;
Targin 30 - 1604335262; **Targin 40** - 1439933122

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