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

This medicine is sold with a doctor's prescription only

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

Prolonged release tablets

Active ingredients:

Product	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 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 your 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 that 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 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 the relief of moderate to severe pain. Targin has 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 throughout the entire day, for a few days or more. The naloxone was added to reduce the 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 other ingredients that these tablets contain (for the list of other 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 the use of opioids.
- You suffer from moderate to severe liver function impairment.

Special warnings regarding the use of this medicine:

Before treatment with Targin tell your doctor if:

- You are an elderly or debilitated (weak) patient.
- You suffer from bowel obstruction caused by the use of opioids; kidney impairment; liver impairment; severe lung impairment; frequent breathing stops during sleep which may cause you to feel very sleepy during the daytime (sleep apnea); sleepiness/falling asleep; thyroid gland function disorder (underactivity or myxedema that can be manifested in dryness, cold and swelling of the skin in your face or limbs); gallstones; low or high blood pressure; cardiovascular heart and blood vessels disease, enlarged prostate gland; inflammation of the pancreas.
- Your adrenal glands do not produce sufficient hormones (adrenal insufficiency, Addison's disease).
- You suffer from a mental disease accompanied by (partial) loss of contact with reality (psychoses), as a result of alcohol or a toxic effect of other substances (substance-induced psychosis); alcoholism or delirium tremens (psychosis caused by alcohol withdrawal).
- You suffer from a head injury, brain injury, increased intracranial pressure, reduced level of consciousness.
- You suffer from epilepsy or have a tendency to spasms/seizures.
- If you are taking a medicine from the MAOIs group - see 'Drug interactions' section below.
- You suffer or have suffered in the past from abuse of or addiction to alcohol, medicines or drugs, or from withdrawal symptoms following discontinuation of their use, such as: agitation, anxiety, tremor or sweating.
- You suffer from cancer associated with metastasis in the peritoneum or beginning of bowel obstruction in advanced stages of digestive or pelvic cancer .

Also tell your doctor 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), that may also cause blood oxygen levels to fall, resulting in phenomena such as fainting.
- The medicine may cause breathing problems while asleep. These problems can include pauses in breathing during sleep, waking up because of shortness of breath, difficulty remaining asleep, increased daytime drowsiness. If you feel these symptoms or someone else in your surroundings observes these symptoms in you, contact your doctor. The doctor may recommend reducing the dosage.
- Swallow the tablet whole, so as not to impair the prolonged release mechanism of oxycodone 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 (see section: 'If you have accidentally taken a higher dosage').

- If you experience severe diarrhea at the start of treatment this may be due to the effect of the naloxone. This diarrhea may occur within the first 3- 5 days of the treatment. If the diarrhea persists, or it bothers you, consult with your doctor.
- If you have used another opioid before treatment with Targin, there may be withdrawal symptoms upon switching to Targin (such as restlessness, sweating, muscle pains). If you experience withdrawal symptoms, you may need closer medical follow-up.
- 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, sweating, muscle pains). When you no longer need the treatment, the daily dose should be reduced gradually in consultation with your doctor.
- The active ingredient oxycodone has a potential for abuse, similar to other opioid analgesics. There is a risk of developing psychological dependence on the medicine (addiction). You should avoid treatment with the medicine if you suffer or have suffered in the past from alcohol, medicine or drug abuse or addiction.
- If you are about to undergo surgery, tell the doctor/medical staff you are taking this medicine.
- As with other opioids, the active ingredient oxycodone may affect the production of hormones in your body, for instance cortisol or the sex hormones, especially when you take high doses for prolonged periods. If you experience persistent symptoms such as nausea or vomiting, loss of appetite, fatigue, weakness, dizziness, changes in your menstrual cycle, impotence, infertility, decreased sex drive, consult your doctor. There may be need to monitor the hormones levels.
- The medicine may increase your sensitivity to pain, particularly with a high dose. Inform the doctor if you experience this. Your doctor may recommend reducing the dosage or changing the medicine.
- You may notice the remains of the tablet in the stool. This phenomenon is not a cause for concern, since the active ingredients in the tablet have already been released in the gastrointestinal system and absorbed into the body.

Misuse of Targin:

- Targin is not suitable for treatment of withdrawal symptoms.
  Never abuse the tablets, 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 use the tablets improperly by dissolving them and injecting them (into blood vessels, for instance). Particularly since they contain talc, which can cause localized damage of tissues (necrosis) and changes in the lung tissue (pulmonary granuloma). Such abuse may cause additional serious results and even death.
- Use of the medicine may cause a positive result in a drugs test.
- The use of the medicine in order to improve sports performances constitutes a health risk.

Use in children and adolescents: There is no information about 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 follow up: During long-term treatment, you should undergo periodic evaluations to assess the continuing need for the medicine.

Drug interactions:

- **The risk of side effects increases, if you take antidepressants** (from the SSRIs or SNRIs group such as citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine) **or other serotonergic medicines.** These medicines may cause a drug interaction with oxycodone (serotonin syndrome/poisoning) and make you experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye; changes in your mental

condition (such as agitation, hallucinations) excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C, coma, tachycardia (rapid heartbeats), changes in blood pressure, lack of coordination, muscle stiffness, digestive system symptoms (nausea, vomiting, diarrhea). Contact 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. If your doctor has decided to prescribe sedatives for you together with Targin, the doctor may limit the dosage and the duration of the concomitant treatment. Inform the doctor of all the sedatives you are taking. Examples of such medicines include: other strong medicines for the relief of pain (opioids); gabapentinoids (such as gabapentin, pregabalin) for treatment of epilepsy, pain and anxiety; sedatives and sleep-inducing medicines (including benzodiazepines, anti-anxiety); antidepressants; anti-allergy medicines , travel sickness or nausea/vomiting (antihistamines or anti-nausea/vomiting); medicines for treatment of mental/psychiatric problems (antipsychotic medicines including phenothiazines and neuroleptic medicines).

Please follow your doctor’s dosage recommendation strictly. Recommended to ask friends and relatives to be on the alert for the symptoms mentioned above. Contact 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:

- Anticoagulants (such as coumarin derivatives); antibiotics of the macrolide group (such as clarithromycin, erythromycin, telithromycin); antifungal medicines of the azole group (such as ketoconazole, voriconazole, itraconazole, posaconazole).
- Protease inhibitors (anti-HIV virus) such as ritonavir, indinavir, nelfinavir, saquinavir; cimetidine (for the treatment of heartburn, stomach ulcer, indigestion); rifampicin (for the treatment of tuberculosis); carbamazepine (for the treatment of seizures and certain pain conditions), phenytoin (for the treatment of seizures).
- The hypericum plant (also known as St. John's Wort); quinidine (for the treatment of heart rhythm disturbances).
- Medicines of the monoamine oxidase inhibitors group (MAOIs), such as tranylcypromine, phenelzine, isocarboxazid, moclobemide, linezolid, used also as antidepressants or to treat Parkinson's. Also tell your doctor if you have taken this medicine during the last two weeks.
- No drug interaction is expected between Targin and paracetamol, acetylsalicylic acid (aspirin) and naltrexone.

Use of this 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 with this medicine.
Drinking alcohol during the treatment period with the medicine may cause you to feel sleepier or increase the risk of serious side effects, such as shallow breathing with a risk of cessation of breathing and loss of consciousness.

Pregnancy and breastfeeding: Consult your doctor if you are pregnant, think you are pregnant, plan to become pregnant or are breastfeeding.

- **Pregnancy**: Avoid use of this medicine if you are pregnant (unless your doctor instructs otherwise). 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 passes into the breastmilk. There may be a risk for the breastfeeding baby. (It is unknown whether naloxone passes into the breastmilk).

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 sleep or 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 your doctor if necessary.

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

3. How should you use the medicine?

Always use according to the doctor's instructions. You should check with your doctor or pharmacist if you are not sure regarding the dosage and manner of treatment with the medicine.
The dosage and manner of treatment will be determined by the doctor only. Targin tablets have a prolonged release mechanism. The active ingredients are released for 12 hours.
Swallow the tablet whole, so as not to impair the prolonged release mechanism of oxycodone from the tablet. Do not break, chew, crush or halve the tablet! Taking tablets that are not whole may cause absorption of a potentially life-threatening dose of oxycodone (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 your 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 your doctor switches Targin to another opioid, your bowel function may worsen.
If you experience pain between two doses of Targin contact your doctor. You may need to get a rapid acting pain-reliever. Targin is not suitable for this.
If you feel that the effect of the tablets is too strong or too weak, contact your doctor.

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

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.

Duration of use: Do not take the tablets for a longer period than necessary. In prolonged treatment, the doctor will perform follow-up tests 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 package of the medicine with you. Symptoms of overdose may include: constriction of the pupils in the eye, respiratory depression (slow and weak breathing), drowsiness up to loss of consciousness, low muscle tone, decrease in pulse rate, drop in blood pressure. In severe cases there may be coma, fluid in the lungs, collapse of the blood system (shock). These symptoms can cause death and require urgent medical attention. Avoid activities requiring high alertness, such as driving.

If you forgot to take the medicine, follow the instructions below:
If 8 hours or more remain until taking the next dose: Take the forgotten dose immediately. Take the next dose at the regular time.
If less than 8 hours remain until taking the next dose: Take the forgotten dose and wait 8 hours for the next dose.
Afterwards try to get back to your regular dosing times. Consult your 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 this medicine without consulting your doctor.
If you stop taking the medicine: If you do not need any further treatment, consult your 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, sweating, muscle pains.
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 concerning the use of the medicine, consult your 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 a hospital emergency room immediately if the following side effects appear:

- Respiratory depression (slow and shallow breathing). Respiratory depression is the main risk in overdose cases. This phenomena may occur particularly in the elderly and in 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/exhaustion, skin reactions such as itchiness or rash, excessive 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/pain (especially if you already suffer from a coronary heart disease), decrease or increase in blood pressure, withdrawal symptoms such as agitation; fainting, lack of energy, thirst, altered taste, palpitations (feeling heartbeats), biliary pain (colic), angina pectoris, generally feeling unwell, pain, swelling of the hands, ankles or feet; concentration difficulties, speech impairment, shaking, shortness of breath or breathing difficulties, restlessness, chills, increase in liver 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, convulsions (especially in epileptic patients or patients with tendency to seizures).

Rare side effects (appear in 1-10 users out of 10,000): increase in pulse rate, dental changes, weight gain, yawning, dependence on the medicine.
Side effects of unknown frequency (effects whose frequency has not yet been determined): feeling of extreme happiness (euphoria), severe drowsiness (sedation), erectile problems, nightmares, hallucinations, shallow breathing, difficulty in passing urine (urinary retention), tingling, belching, aggressiveness, breathing problems during sleep (sleep apnea).

Other side effects observed in the use of medicines containing oxycodone only as an active ingredient:
Reduction in eye pupils size, decreased cough reflex, contraction of the bronchial muscles.
Common side effects (appear in 1-10 users out of 100): changes in behavior/personality or mood, increased or decreased activity, hiccups.
Uncommon side effects (appear in 1-10 users out of 1,000): 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, ulcers/inflammation in the mouth, difficulties in swallowing, sore gums, perception disturbances, flushing of skin, widening of blood vessels, dehydration, agitation, a decrease in sex hormones 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): urticaria (itchy rash), infections such as herpes or cold sores (may appear as blisters around the mouth or genitals), increased appetite, black (bloody) stools, bleeding gums.
Side effects of unknown frequency (effects whose frequency has not yet been determined): severe general allergic reaction (anaphylactic reaction), increase in sensitivity to pain, absence of menstrual periods in women, withdrawal symptoms in the newborn, 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 with your 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.
When you no longer need the tablets, consult the pharmacist on how to dispose of them.

- Do not use the medicine after the expiry date (exp. date) stated 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, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, hydroxypropylcellulose, brilliant blue FCF (E133).
Targin 10: Each tablet contains about 62 mg lactose and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, povidone.
Targin 20: Each tablet contains about 52 mg lactose and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, povidone, iron oxide red (E172).

Targin 30: Each tablet contains about 37 mg lactose and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, povidone, iron oxide yellow (E172) iron oxide black (E172) iron oxide red (E172).
Targin 40: Each tablet contains about 104 mg lactose and in addition:
Stearyl alcohol, ethylcellulose, talc, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, povidone, 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 blisters.
Registration holder: Rafa Laboratories Ltd., PO 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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