PRODUCT MONOGRAPH

^{N}Targin®

Oxycodone Hydrochloride/Naloxone Hydrochloride
Controlled Release Tablets

5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg

Opioid Analgesic/Opioid Antagonist

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[N]Targin®

(oxycodone hydrochloride/naloxone hydrochloride controlled release tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Controlled Release Tablets 5 mg oxycodone hydrochloride/ 2.5 mg naloxone hydrochloride 10 mg oxycodone hydrochloride/ 5 mg naloxone hydrochloride 20 mg oxycodone hydrochloride/ 10 mg naloxone hydrochloride 40 mg oxycodone hydrochloride/ 20 mg naloxone hydrochloride	Ethylcellulose, FD&C Blue No. 1 (5/2.5 mg only), hydroxypropylcellulose (5/2.5 mg only), iron oxide (20/10 and 40/20 mg only), lactose monohydrate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, povidone K30 (10/20, 20/40 and 40/20 mg only), stearyl alcohol, talc, titanium dioxide

INDICATIONS AND CLINICAL USE

Adults

Targin® (oxycodone hydrochloride/naloxone hydrochloride) is a controlled release tablet having a dual therapeutic effect. The oxycodone component in **Targin** is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and,
- for which alternative treatment options are inadequate.

The naloxone component in **Targin** is indicated for the relief of opioid-induced constipation (OIC).

Targin is not indicated as an as-needed (prn) analgesic.

Geriatrics (>*65* years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and other drug therapy. The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Pediatrics (<18 years of age)
The safety and efficacy of **Targin** has not been studied in the pediatric population. Therefore, use of **Targin** is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) is contraindicated in:

- Patients who are hypersensitive to the active substances (oxycodone or naloxone) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Administration by the rectal route is contraindicated (see **WARNINGS AND PRECAUTIONS**).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain, including use in outpatient or day surgeries.
- The management of perioperative pain.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery.
- Opioid-dependent patients and for narcotic withdrawal treatment.
- Patients with moderate to severe hepatic impairment (Child-Pugh Class B & C).
- Patients with severe renal impairment.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with controlled release opioid formulations, Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
Targin poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Targin, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Targin should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Targin. Patients should be monitored for respiratory depression, especially during initiation of Targin or following a dose increase. Targin must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Targin can lead to rapid release and absorption of a potentially fatal dose of oxycodone (see WARNINGS AND PRECAUTIONS).

Accidental Exposure
Accidental ingestion of even one dose of Targin, especially by children, can result in a fatal overdose of oxycodone (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Targin during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

General
Targin® tablets must be swallowed whole. Taking broken, chewed, dissolved or crushed Targin tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

Targin should not be administered rectally due to the possible increased systemic availability of naloxone by this route and the potential for the occurrence of severe withdrawal effects (see CONTRAINDICATIONS).

Targin 40/20 mg tablets are for use in opioid tolerant patients only (see also DOSAGE AND ADMINISTRATION). A single dose greater than 40 mg of oxycodone, or total daily doses greater than 80 mg of oxycodone, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Patients for whom Targin is prescribed should not give Targin to anyone else as such inappropriate use may have severe medical consequences, including death.

Targin should not be used to treat patients with constipation not related to opioid use.

The 5/2.5 mg tablets allow for smaller dose increases and are intended for use in titration or adjustments of dosage. Note that proportional bioavailability of the 5/2.5 mg tablet to other **Targin** strengths has not been established. Multiple units of the 5/2.5 mg tablet should not be substituted for other **Targin** strengths.

Patients should be cautioned not to consume alcohol while taking **Targin**, as it may increase the chance of experiencing dangerous side effects.

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required.

There is no clinical experience in patients with cancer associated with peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of **Targin** in this population is not indicated.

Gastrointestinal Effects

Diarrhea is a possible effect of naloxone. If severe or persistent diarrhea lasts for more than 3 days during treatment, patients should be advised to contact their physician.

Addiction, Abuse and Misuse

Like all opioids, **Targin** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **Targin** should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as **Targin**, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

If abused parenterally, intranasally or rectally by individuals dependent on opioid agonists, **Targin** is expected to produce marked withdrawal symptoms – because of the systemic opioid receptor antagonist characteristics of naloxone by these routes – or to intensify withdrawal symptoms already present.

Targin consists of a dual polymer matrix intended for oral use only. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury, which may be fatal.

Dependence/Tolerance
As with other opioids, tolerance and physical dependence may develop upon repeated administration of **Targin** and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

Use in Drug and Alcohol Addiction
Targin is an agonist/antagonist combination product with no approved use in the management of addictive disorders.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioid during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of **Targin** is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic
Interactions with Other Central Nervous System Depressants (including alcohol): Targin should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation,

coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. **Targin** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of oxycodone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, oxycodone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, oxycodone must be used with extreme caution and only if it is judged essential.

Withdrawal Effects: Withdrawal symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

In patients under long-term opioid treatment, the switch to **Targin** may initially provoke withdrawal symptoms or diarrhea.

Cardiovascular

Targin should be used with caution in patients with pre-existing cardiovascular disease.

Oxycodone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume or concurrent administration of drugs, such as phenothiazines or certain anaesthetics. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of **Targin**, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with **Targin** and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of **Targin** are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the **Targin** dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

Peri-Operative Considerations

Targin is contraindicated for perioperative use, within 24 hours before or after surgery. Targin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with **Targin** within 24 hours before or after the operation. Thereafter, if **Targin** is to be continued after the patient recovers from the post-operative period, a new dose should be used in accordance with the changed need for pain relief.

Psychomotor Impairment

Targin may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients using **Targin** should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug. Patients should also be cautioned about the combined effects of **Targin** with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Patient Counselling Information

A patient information sheet should be provided to patients when **Targin** tablets are dispensed to them.

Patients receiving **Targin** should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

2. Patients should be advised that **Targin** contains two ingredients: oxycodone, an opioid pain medicine and naloxone, which reduces constipation.

3. Patients should be advised that **Targin** should only be taken as directed. The dose of **Targin** should not be adjusted without consulting with a physician.

4. **Targin** must be swallowed whole (not broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.

5. Patients should be warned not to administer **Targin** by the rectal route, as severe withdrawal effects may occur.

6. Diarrhea is a possible effect of naloxone. Patients should be advised to contact their physician if the diarrhea is severe or persistent.

7. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

8. Patients should not combine **Targin** with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.

9. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with **Targin**.

10. Patients should be advised that if they have been receiving treatment with **Targin** and cessation of therapy is indicated, it may be appropriate to taper the **Targin** dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

11. Patients should be advised of the most common adverse reactions that may occur while taking **Targin**: nausea, constipation, diarrhea, hyperhidrosis, fatigue, vomiting, headache and dizziness.

12. Patients should be advised that **Targin** may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on **Targin** or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of **Targin**.

13. Patients should be advised that **Targin** is a potential drug of abuse. They should protect it from theft or misuse.

14. Patients should be advised that **Targin** should never be given to anyone other than the individual for whom it was prescribed.

15. Patients should be advised that **Targin** 40/20 mg is for use only in individuals tolerant to the effect of equivalent doses of oxycodone.

16. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with **Targin**. Women who are breast-feeding or pregnant should not use **Targin.**

17. Patients should be advised that they may pass empty matrix tablet remnants in the stool, and that this should not be a concern since the analgesic medication, oxycodone, has already been released.

Special Populations

Special Risk Groups: Oxycodone should be administered with caution and in a reduced dosage to debilitated patients, and in patients with Addison's disease, cholelithiasis, hypotension, hypothyroidism, mild hepatic impairment, myxoedema, renal impairment, toxic psychosis, prostatic hypertrophy or urethral stricture.

Nursing Women: Oxycodone passes into the breast milk. It is not known whether naloxone is excreted in human milk. Since the safety of **Targin** in infants and newborns has not been studied, **Targin** is contraindicated in nursing mothers.

Pregnancy, Labour and Delivery: Oxycodone and naloxone pass into the placenta. **Targin** is contraindicated during pregnancy, labour and delivery due to impaired uterine contractility and the risk of neonatal respiratory depression (see **CONTRAINDICATIONS**). There are no adequate data from the use of **Targin** in pregnant women or during childbirth. Animal studies have not been performed with oxycodone and naloxone in combination. While animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone, safe use in pregnancy has not been established.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

Geriatrics (> *65* years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The dosage should be adjusted to the lowest **Targin** dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.

Pediatrics (< 18 years of age): Targin has not been studied in children and is not recommended for patients less than 18 years of age. The safety and efficacy of **Targin** in children have not been established.

Hepatic Impairment: A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Due to the potential for increased systemic availability of naloxone to result in withdrawal effects, a reduced initial dose followed by careful titration is recommended when administering **Targin** to patients with mild hepatic impairment undergoing prolonged opioid therapy (see **DOSAGE AND ADMINISTRATION**). **Targin is contraindicated in patients with moderate and severe hepatic impairment** (see **CONTRAINDICATIONS**).

Renal Impairment: A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Naloxone concentrations were affected to a higher degree than oxycodone. Due to the potential for increased systemic availability of naloxone to result in withdrawal effects, a reduced initial dose followed by careful titration is recommended when administering **Targin** to patients with mild to moderate renal impairment undergoing prolonged opioid therapy (see **DOSAGE AND ADMINISTRATION**). **Targin is contraindicated in patients with severe renal impairment** (see **CONTRAINDICATIONS**).

***In Vitro* Dissolution Studies of Interaction with Alcohol**

In vitro data show that in presence of ethanol, at concentrations up to 40%, the controlled-release characteristics of the **Targin** formulation were maintained and no breakdown of the controlled release mechanism was observed.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The pre-marketing pivotal clinical program of **Targin®** (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) included exposure to 520 patients. A summary of adverse events occurring at an incidence of 1% or more is given below which includes all events, whether considered by the clinical investigator to be related to the study drug or not (see **CLINICAL TRIALS** for methodological details of the trials). Nausea was a very common adverse effect in patients taking **Targin**. Nausea is a common effect associated with other drugs with opioid-agonist activity and tends to reduce with time. Adverse effects, including constipation, diarrhea, fatigue, headache and hyperhidrosis, often observed with other drugs with opioid-agonist activity, were also seen with **Targin** treatment.

The following summary (Table 1) captures all adverse events in patients who were exposed to **Targin**, oxycodone controlled release or placebo.

Table 1: Adverse Event Reports in Targin Pivotal Clinical Trials (≥1%) OXN3401, 038-001, OXN3001 and OXN3006

System Organ Class Preferred Term	% of Patients on Targin n = 520	% of Patients on Oxycodone CR n = 446	% of Patients on Placebo[a] n = 235
Ear and labyrinth disorders			
Vertigo	1.7	1.8	5.1
Gastrointestinal disorders			
Abdominal pain	3.3	2.7	3.8
Abdominal pain upper	1.9	2.7	2.1
Constipation	6.5	10.5	8.9
Diarrhea	6.2	5.4	6.0
Dry mouth	2.5	1.6	2.1
Dyspepsia	1.4	3.4	3.0
Flatulence	1.2	0.5	0.9
Nausea	12.3	14.8	14.9
Vomiting	5.4	5.6	6.0
General disorders and administrative site conditions			
Asthenia	1.4	0.0	0.9
Chills	1.2	0.7	0.9
Drug withdrawal syndrome	0.2	1.4	0.4
Fatigue	5.4	5.8	4.3
Malaise	0.2	0.7	1.7
Edema peripheral	1.7	1.8	0.0
Pain	2.3	1.6	2.1
Pyrexia	0.4	0.0	1.3
Infections and infestations			
Bronchitis	1.5	1.1	0.0
Cystitis	0.2	1.4	1.3
Gastroenteritis	1.9	2.2	0.0
Influenza	1.2	1.6	0.4
Nasopharyngitis	2.9	4.7	4.3
Sinusitis	1.2	0.0	0.0
Upper respiratory tract infection	0.0	1.6	0.0
Urinary tract infection	3.5	2.2	1.3
Viral infection	1.5	1.4	1.3
Injury, poisoning and procedural complications			
Contusion	0.0	0.2	1.7
Investigations			
Blood cholesterol increased	0.0	0.0	1.7
Blood glucose increased	1.9	0.2	0.4
Blood triglycerides increased	0.6	2.0	1.7
Blood uric acid increased	0.2	0.2	2.6
Gamma-glutamyltransferase increased	0.6	1.1	0.4
Lymphocyte count decreased	0.0	0.2	1.3

Table 1: Adverse Event Reports in Targin Pivotal Clinical Trials (≥1%) OXN3401, 038-001, OXN3001 and OXN3006

System Organ Class Preferred Term	% of Patients on Targin n = 520	% of Patients on Oxycodone CR n = 446	% of Patients on Placebo[a] n = 235
Metabolism and nutrition disorders			
Anorexia	0.8	1.1	0.9
Decreased appetite	0.6	0.2	1.3
Hyperglycemia	1.2	1.4	0.0
Hyperlipidemia	1.2	0.2	0.0
Hypertriglyceridemia	1.4	0.2	1.3
Hyperuricemia	1.2	1.1	0.0
Musculoskeletal and connective tissue disorders			
Arthralgia	1.5	2.2	2.1
Back pain	3.3	2.5	0.0
Neck pain	0.0	1.4	0.0
Osteoarthritis	1.2	1.6	0.0
Pain in extremity	1.5	1.1	0.0
Nervous system disorders			
Dizziness	4.2	8.1	4.3
Headache	6.2	6.3	9.8
Migraine	1.4	0.2	0.4
Sciatica	1.5	0.0	0.0
Somnolence	1.2	1.1	0.0
Tremor	1.0	1.1	0.4
Psychiatric disorders			
Depression	1.9	2.5	0.0
Insomnia	2.1	2.5	3.4
Nervousness	0.6	0.0	1.3
Restlessness	0.8	0.2	2.6
Sleep disorder	0.6	0.2	1.7
Skin and subcutaneous tissue disorders			
Hyperhidrosis	6.5	4.3	6.4
Pruritus	2.9	4.0	3.0
Rash	1.2	0.5	0.0
Vascular disorders			
Hot flush	1.0	2.0	0.9
Hypertension	0.6	1.4	1.7

a. Placebo patients received immediate-release oxycodone or combination preparations with codeine 30mg as rescue medication in pivotal clinical trials.

Other less common (<1%) adverse drug reactions reported and considered in any way related to **Targin** in randomized pivotal clinical trials are summarized below.

Cardiac disorders: Angina pectoris, atrioventricular block first degree, bundle branch block right, palpitations.

Ear and labyrinth disorders: Cerumen impaction, deafness unilateral, tinnitus.

Eye disorders: Dry eye, lacrimation increased, photopsia, vision blurred, visual impairment.

Gastrointestinal disorders: Abdominal distension, abdominal pain lower, anal discomfort, anal fissure, aptyalism, diverticulum intestinal, food poisoning, gastric disorder, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux, glossitis, periodontitis.

General disorders and administration site conditions: Chest pain, feeling cold, influenza-like illness, localized edema, mucous membrane disorder, non-cardiac chest pain, swelling.

Hepatobiliary disorders: Bile duct obstruction, cholelithiasis, increased hepatic enzymes.

Infections and infestations: Candidiasis, cellulitis, furuncle, otitis externa, pneumonia, rhinitis.

Injury, poisoning and procedural complications: Accidental overdose, drug toxicity, fall, joint sprain, muscle strain, skin laceration.

Investigations: Alanine aminotransferase increased, blood bilirubin increased, blood lactate dehydrogenase increased, blood phosphorus decreased, electrocardiogram change, hematocrit decreased, hemoglobin decreased, heart rate increased, liver function test abnormal, platelet count decreased, red blood cell count decreased, weight decreased.

Metabolism and nutrition disorders: Gout, hyponatremia.

Musculoskeletal and connective tissue disorders: Gouty arthritis, joint swelling, muscle spasms, muscle twitching, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, polyarthritis, shoulder pain, tenosynovitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps): Lipoma.

Nervous system disorders: Balance disorder, disturbance in attention, dysgeusia, grand mal convulsion, memory impairment, nervous system disorder, neuromuscular blockade, polyneuropathy, poor quality sleep, restless legs syndrome, stupor, tension headache.

Psychiatric disorders: Abnormal dreams, anxiety, confusional state, depressed mood, disorientation, irritability, loss of libido, negative thoughts, panic attack, social avoidant behaviour, sopor.

Renal and urinary disorders: Pollakiuria, renal pain, urinary incontinence.

Reproductive system and breast disorders: Dysmenorrhea, vaginal hemorrhage.

Respiratory, thoracic and mediastinal disorders: Cough, dyspnea, dyspnea exertional, epistaxis, hemoptysis, yawning.

Skin and subcutaneous tissue disorders: Eczema, exanthem, night sweats, pruritus generalized, rash pruritic, skin reaction, stasis dermatitis.

Vascular disorders: Blood pressure decreased, blood pressure increased, hypertensive crisis, hypotension, peripheral coldness, thrombophlebitis superficial, thrombosis.

A subsequent study was conducted in patients suffering from chronic cancer pain (see **CLINICAL TRIALS** section for details of the study). The most common adverse events in this study were consistent with the expected opioid safety profile. Other commonly reported adverse events were considered by Investigators to be related to the underlying disease.

The following summary (Table 2) captures adverse events from this study for patients exposed to **Targin** or controlled-release oxycodone.

Table 2: Adverse Event Reports (≥5%) in Clinical Trial OXN2001

System Organ Class Preferred term	% of patients on Targin (n = 92)	% of patients on CR oxycodone (n = 92)
Blood and Lymphatic System Disorders		
Anaemia	5.4	6.5
Gastrointestinal Disorders		
Abdominal pain	7.6	5.4
Constipation	6.5	6.5
Nausea	7.6	13.0
Vomiting	6.5	5.4
General Disorders and Administration Site Conditions		
Asthenia	6.5	5.4
Drug Withdrawal Syndrome	7.6	2.2
Edema peripheral	5.4	9.8
Pain	3.3	6.5
Investigations		
Hemoglobin decreased	5.4	7.6
Metabolism and Nutrition Disorders		
Anorexia	7.6	5.4
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		
Cancer pain	12.0	8.7
Malignant Neoplasm Progression	8.7	10.9
Nervous System Disorders		
Headache	5.4	2.2

Other Adverse Drug Reactions Observed During the Premarketing and Postmarketing Clinical Trial Program for Targin

The following is a list of additional treatment-emergent adverse reactions, reported during controlled clinical trials with **Targin** (n = 832), which have not been captured in the preceding tables and lists. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥1/10); (Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Gastrointestinal Disorders
Uncommon: Eructation

General Disorders and Administration Site Conditions
Uncommon: Thirst

Immune System Disorders
Uncommon: Hypersensitivity

Nervous System Disorders
Uncommon: Lethargy, paresthesia, sedation speech disorder, syncope

Psychiatric Disorders
Uncommon: Abnormal thinking, drug dependence, euphoric mood, hallucinations, nightmares

Renal and Urinary Incontinence
Uncommon: Micturition urgency, urinary retention

Reproductive System and Breast Disorders
Uncommon: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders
Uncommon: Respiratory depression

In a two year non-interventional open-label, prospective, observational study (Study OXN9002) performed in Europe, 7,836 pain patients with severe pain for at least 4 months received **Targin** and were monitored over a period of 4 weeks. Approximately 25% of the patients (n = 1,963) were opioid naïve with the remaining 5,849 patients previously pre-treated with opioids. The most frequently reported adverse drug reactions in the total population were nausea (3.1%), constipation (3.1%), dizziness (2.4%), abdominal distension (1.9%), diarrhea (1.9%), abdominal pain (1.4%), vomiting (1.1%) and irregular bowel movements (1.1%). All these adverse drug reactions are consistent with the expected adverse event profile of the opioid analgesic class of drugs.

Additional Adverse Drug Reactions Reported with Oxycodone Products other than Targin

The following additional adverse drug reactions have been reported in association with the medicinal substance, oxycodone.

Eye Disorders
Uncommon: Miosis

Gastrointestinal Disorders
Uncommon: Dysphagia, dental caries, ileus

General Disorders and Administrative Site Conditions
Uncommon: Drug tolerance, edema
Not known: drug withdrawal syndrome neonatal

Hepatobiliary Disorders
Uncommon: Cholestasis

Immune System Disorders
Uncommon: Anaphylactic responses

Metabolism and Nutrition Disorders
Uncommon: Dehydration

Nervous System Disorders
Uncommon: Hypertonia, involuntary muscle contractions, hypoesthesia
Not known: Hyperalgesia

Psychiatric Disorders
Common: Agitation
Not known: Aggression

Reproductive System and Breast Disorders
Uncommon: Hypogonadism, amenorrhea

Skin and Subcutaneous Disorders
Uncommon: Dry skin, urticaria

Vascular Disorders
Uncommon: Vasodilatation

DRUG INTERACTIONS

Overview

Interactions with Central Nervous System (CNS) Depressants: Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) should be dosed with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are currently taking other central nervous system depressants (e.g., other opioids, sedatives, hypnotics, anti-depressants, phenothiazines, neuroleptics, anti-emetics) and beta-blockers, as they may enhance the CNS-depressant effect (e.g., respiratory depression) of **Targin**. **Targin** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Interactions with Anticholinergics: Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Drug-Drug Interactions

No interaction studies have been performed with **Targin**.

Drugs Metabolized by Cytochrome P450 Isozymes

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, **Targin** is not expected to cause clinically relevant interactions with other concomitantly administered drugs metabolized over the CYP isomers CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Oxycodone doses may need to be adjusted accordingly.

Inhibitors of CYP3A4: Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., clarithromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir) and grapefruit juice, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and C_{max} by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with **Targin** is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inducers of CYP3A4: CYP450 inducers, such as rifampin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or possibly the development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and C_{max} by

86% and 63% respectively. If co-administration with **Targin** is necessary, caution is advised when initiating therapy with, currently taking or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inhibitors of CYP2D6: Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine, common SSRIs such as paroxetine as well as polycyclic antidepressants), this blockade may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

Administration with Mixed Activity Agonist/Antagonist Opioids: Mixed activity agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure μ-opioid agonist analgesic, such as the oxycodone in **Targin**. In this situation, mixed activity agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

MAO Inhibitors: MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decrease respiration. **Targin** is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see **CONTRAINDICATIONS**).

Warfarin and Other Coumarin Anticoagulants: Clinically relevant changes in International Normalized Ratio (INR or Quick-value) in both directions have been observed in individuals when oxycodone and coumarin anticoagulants are co-administered.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

Dosing Considerations
Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

Targin must be swallowed whole. Cutting breaking, crushing, chewing, or dissolving Targin tablets can lead to the rapid release and absorption of a potentially fatal dose of oxycodone (see WARNINGS AND PRECAUTIONS).

Patients who are currently taking oral oxycodone can be switched to Targin based on an equivalent oxycodone dose. For conversion from other opioids/opioid preparations, patients should be initiated on the lowest available Targin strength, provided with adequate rescue medication, with dose titration to achieve satisfactory pain relief with acceptable side effects. Targin doses must be individualized and should be assessed at regular intervals.

Targin 40/20 mg tablets are for use in opioid tolerant patients only. A single dose greater than 40 mg of oxycodone, or total daily doses greater than 80 mg of oxycodone, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids at equivalent doses (see **WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS**).

Targin is contraindicated for rectal administration (see CONTRAINDICATIONS).

Targin is contraindicated in the perioperative period, within 24 hours before or after surgery. Targin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with **Targin** within 24 hours before or after the operation. Thereafter, if **Targin** is to be continued after the patient recovers from the post-operative period, a new dose should be used in accordance with the changed need for pain relief.

In steady-state studies, the analgesic efficacy of **Targin** is equivalent to the OxyContin® controlled release oxycodone formulation. In clinical studies with **Targin**, only patients who had previously been dosed on oxycodone were switched to **Targin.** To date, there is no clinical experience evaluating switching from other analgesics to **Targin**.

Targin doses must be individualized based upon the status of each patient and should be assessed at regular intervals. Proper optimization of doses scaled to the individual's pain should aim at the regular administration of the lowest dose of **Targin** which provides pain relief. The dosage of the drug must be individualized according to the response and tolerance of the patient.

Targin should be taken at the determined dosage twice daily (every 12 hours) according to a fixed time schedule. **Single doses should not exceed 40 mg oxycodone and 20 mg naloxone. The maximum daily dose of Targin is 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.** For patients requiring higher doses of **Targin,** administration of supplemental controlled-release oxycodone at the same time intervals should be considered. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be impaired. In general, the lowest effective opioid analgesic dose should be selected.

After discontinuation of therapy with **Targin**, with a subsequent switch to another opioid, symptoms associated with reduced bowel motility can be expected.

The controlled release tablets may be taken with or without food with sufficient liquid (with 4 to 6 oz. of water).

The empty matrix tablet remnants may be visible in the stool.

Adults (over 18 years)

Patients Not Receiving Opioids at the Time of Initiation of **Targin** Treatment (Opioid-Naïve)
The usual initial adult dose for patients who have not previously received opioid analgesics is **Targin** 10/5 mg every 12 hours.

The 5/2.5 mg tablets allow for smaller dose increases and are intended for use in titration or adjustments of dosage. Note that proportional bioavailability of the 5/2.5 mg tablet to other **Targin** strengths has not been established. Multiple units of the 5/2.5 mg tablet should not be substituted for other **Targin** strengths.

Patients Currently Receiving Opioids
Patients who are currently taking oxycodone can be switched to Targin based on an equivalent oxycodone dose. Discontinue all other around-the-clock oxycodone analgesic medications when Targin therapy is initiated. In clinical studies with **Targin**, only patients who had previously been dosed on oxycodone were switched to **Targin.** Patients receiving other oral oxycodone formulations may be transferred to **Targin** tablets at the same total daily dosage, equally divided into two 12-hourly **Targin** tablet doses and reassessed with dose adjustments made accordingly. To date, there is no clinical experience to refer to for switching other opioid analgesics to **Targin**.

Patients already receiving oxycodone, and tolerant to the respiratory depressant effects, may be started on higher dose than the usual initial adult dose of 10/5 mg every 12 hours depending on their previous oxycodone dose. Not to exceed the maximum daily dose of **Targin**, 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.

For conversion from other opioids/opioid preparations, discontinue all other round-the-clock opioid analgesic preparations. Patients should be initiated on the lowest available Targin strength, provided with adequate rescue medication, with dose titration to achieve satisfactory pain relief with acceptable side effects. Targin doses must be individualized and should be assessed at regular intervals.

Targin should be gradually titrated until adequate pain relief and acceptable side effects have been achieved. **The maximum daily dose of Targin is 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.**

Dose Titration: Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of **Targin** which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects. Dose adjustments may be made every 1-2 days until a stable dose is reached (see also Managing Expected Opioid Adverse Experiences).

Subsequent increases in **Targin** dosage must be individualized according to the pain relief and tolerance of the patient with adequate rescue medication, as required (see Management of Patients Requiring Rescue Medication). **If pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration.**

The maximum daily dose of Targin is 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.

Management of Patients Requiring Rescue Medication
Some patients taking **Targin** according to a fixed time schedule may require immediate-release analgesics as "rescue" medication for pain. In clinical trials with **Targin**, immediate-release oxycodone or combination preparations with codeine 30 mg were used as rescue medications. Selection of rescue medication should be based on individual patient conditions. **Targin** is a controlled release formulation and therefore is not intended for use as rescue medication.

For the treatment of pain with an immediate-release opioid, a single dose of "rescue medication" should approximate one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two rescue medication doses per day (24 hours) is usually an indication that the dose of **Targin** requires upward adjustment. This adjustment may be made every 1-2 days until a stable dose is reached. The aim is to establish a patient-specific 12 hour dose that will maintain adequate analgesia and minimize side effects for as long as pain therapy is necessary. Reducing the dosing frequency from every 12 hours is not recommended.

Managing Expected Opioid Adverse Experiences
Many patients receiving opioids, especially those who are opioid-naïve, will experience side effects. Clinical trials have shown that these effects are generally most bothersome during initial treatment and can be minimized by starting **Targin** at 10/5 mg every 12 hours and gradually increasing the dose as needed.

Other opioid related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Patients with Hepatic Impairment
Targin is contraindicated in patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS**). When administering **Targin** to patients with mild hepatic impairment, reduce the initial dose to 1/3 to 1/2 the usual starting dose followed by careful dose titration (see **ACTION AND CLINICAL PHARMACOLOGY**).

Patients with Renal Impairment
Targin is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS**). When administering **Targin** to patients with mild or moderate renal impairment, reduce the initial dose to 1/3 to 1/2 the usual starting dose followed by careful dose titration (see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose
If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

Disposal
Targin should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. **Targin** should not be used in front of children, since they may copy these actions.

Unused or expired **Targin** should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. **Targin** should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

Targin should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

Discontinuation
Careful and regular monitoring are required to establish required maintenance of treatment. When the patient no longer requires therapy with **Targin**, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Withdrawal symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose, given every 12 hours or immediate release oxycodone every 6 hours for the first two days, followed by a 25% reduction every two days.

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

Symptoms: Depending on the history of the patient, an overdose of **Targin®** (oxycodone hydrochloride/ naloxone hydrochloride controlled release tablets) may be manifested by symptoms that are either triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist).

Symptoms of oxycodone overdose include miosis, respiratory depression, somnolence progressing to stupor, hypotonia, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more severe cases and may lead to a fatal outcome.

Symptoms of a naloxone overdose alone are unlikely due to the low systemic availability of naloxone by the oral route. Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely-supervised environment.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. Clinical symptoms suggestive of an oxycodone overdose may be treated by the administration of opioid antagonists (e.g., naloxone 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone in 500 mL of 0.9% sodium chloride or 5% dextrose (0.004 mg/mL naloxone). The infusion should run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

Supportive measures (artificial ventilation, oxygen, vasopressors and infusions) should be employed, as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g., intestine). Oxycodone acts as opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the CNS. Oxycodone acts on the gut opioid receptors and induces constipation. Naloxone is a pure antagonist acting on all types of opioid receptors. Naloxone acts locally on the gut opioid receptors and counteracts the opioid-induced constipation.

Because of the extensive first-pass metabolism in the liver, the bioavailability of naloxone upon oral administration is <3%, therefore a clinically relevant systemic effect is unlikely. Due to the competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone's local opioid antagonist effect reduces the constipation that is typical with opioid treatment.

Preclinical studies show differing effects of natural opioids on components of the immune system. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects on the immune system to natural opioids.

Pharmacodynamics

For a complete listing of pharmacodynamic results on analgesia and bowel function, please refer to the **CLINICAL TRIALS** section of the Product Monograph.

Oxycodone Hydrochloride

Oxycodone retains at least one-half of its analgesic activity when administered orally and with acute dosing is approximately twice as potent as orally administered morphine.

While there is no intrinsic limit to the analgesic effect of oxycodone, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

Cardiovascular System: Oxycodone may produce release of histamine with or without associated peripheral vasodilatation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Central Nervous System: Oxycodone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation. Oxycodone depresses the cough reflex by direct effect on the cough centre in the medulla.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

Endocrine System: Opioids can influence the hypothalamic-pituitary-prostal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may manifest from these hormone changes.

Gastrointestinal Tract and Other Smooth Muscle: Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Immune System: *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Oxycodone Hydrochloride

Absorption: Oxycodone has a high absolute bioavailability of up to 87% following oral administration. The high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Distribution: Following absorption, oxycodone is distributed throughout the entire body. Plasma protein binding is approximately 45%. Oxycodone crosses the placenta and may be detected in breast milk.

Metabolism: Unlike morphine, oxycodone does not undergo high first pass metabolism, possibly due to the protective effect of a methoxy group in the 3 position which is a site of morphine glucuronidation. Oxycodone is metabolized in the gut and liver to noroxycodone, oxymorphone, noroxymorphone and their glucuronides. The formation of oxymorphone and noroxycodone is mediated by cytochrome P450 2D6 and its cytochrome P450 3A4, respectively. In addition, noroxymorphone formation is mediated by both cytochrome P450 2D6 and cytochrome P450 3A4. Therefore, the formation of these metabolites can, in theory, be affected by other drugs (see **DRUG INTERACTIONS**). *In vitro* studies suggest that therapeutic doses of cimetidine are not likely to significantly influence the production of noroxycodone. Quinidine reduced the production of oxymorphone in man without substantially influencing the pharmacodynamics of oxycodone. The contribution of the metabolites to the overall pharmacodynamic effect is insignificant.

The *in vitro* drug-drug interaction studies with noroxymorphone using human liver microsomes resulted in no significant inhibition of CYP2D6 and CYP3A4 activities, which suggest that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4. Noroxymorphone has been shown to bind to μ-opioid receptor. However, due to its low lipophilicity and its low ability to cross the blood-brain barrier, tissue levels in the brain are minimal. Although oxymorphone has been shown to be active, the analgesic effects of the metabolites are thought to be clinically insignificant.

Oxymorphone is known to possess analgesic activity but concentrations in the plasma are very low and not as closely correlated to opioid effects as oxycodone concentrations. Although the AUC ratio of noroxycodone to oxycodone is about 0.6 following oral dosing, noroxycodone is reported to be a considerably weaker analgesic than oxycodone and is unlikely to contribute significantly to the analgesic effect of oxycodone. The analgesic activity profile of other metabolites is not known.

Elimination: Oxycodone and its metabolites are excreted in both urine and feces.

The plasma concentrations of oxycodone are only nominally affected by age, i.e., 15% higher concentrations in elderly patients than in young subjects. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a bodyweight-adjusted basis.

Naloxone Hydrochloride

Absorption: Following oral administration, naloxone has a very low systemic availability of <3%.

Distribution: Naloxone passes into the placenta. It is not known whether naloxone also passes into breast milk.

Metabolism: Naloxone is metabolised in the liver. The principal metabolites are naloxone glucuronide, 6β-Naloxol and its glucuronide.

Elimination: Naloxone and its metabolites are excreted in the urine.

Oxycodone Hydrochloride/Naloxone Hydrochloride Combination **(Targin)**

The pharmacokinetic characteristics of controlled release oxycodone from **Targin®** (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) are equivalent to those of controlled release oxycodone hydrochloride tablets (OxyContin®) administered together with oral controlled release naloxone hydrochloride tablets. The pharmacokinetics of oxycodone were not influenced by the co-administration of naloxone.

Dose proportionality of some strengths of **Targin** (10/5mg, 20/10 mg and 40/20 mg) has been demonstrated. Note that proportional bioavailability of the lowest 5/2.5 mg tablet to other **Targin** strengths has not been established. This lowest dosage strength is intended solely for use in dose titration and multiple units of the 5/2.5 mg tablet should not be substituted for other **Targin** strengths.

After the oral administration of **Targin** in healthy subjects, the plasma concentrations of naloxone are very low.

After ingestion of **Targin** following a high-fat breakfast, the bioavailability and peak plasma concentration (C_{max}) of oxycodone were increased by an average of 16% and 30%, respectively compared to administration in the fasting state. This was evaluated as not clinically relevant therefore, **Targin** controlled release tablets may be taken with or without food (see **DOSAGE AND ADMINISTRATION**).

Targin (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) is contraindicated for administration by the rectal route. If naloxone is administered rectally, increases in systemic availability of naloxone are possible due to partial bypass of hepatic metabolism. As well, rectal administration of oxycodone independently of naloxone has been reported to result in increased bioavailability. Rectal administration of **Targin** has not been studied but may potentially result in withdrawal effects.

Naloxone has a rapid absorption rate when administered intranasally. Both properties mean that **Targin** will not have the intended effect of intranasal abuse. In oxycodone-dependent rats, the intravenous administration of oxycodone/naloxone at a ratio of 2:1 resulted in withdrawal symptoms.

Special Populations and Conditions

Pediatrics: Targin has not been studied in children and is not recommended for patients less than 18 years of age.

Geriatrics: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The dosage should be adjusted to the lowest **Targin** dose that will achieve the goal of satisfactory pain relief with acceptable side effects.

Gender: No differences in plasma concentrations were detected between males and females treated with **Targin**.

Race: No data available.

Hepatic Impairment: Oxycodone pharmacokinetics from **Targin** were significantly altered by hepatic impairment, especially in subjects with moderate or severe hepatic impairment. Following oral administration of a single 10/5 mg dose of **Targin** to 18 patients with varying degrees of hepatic impairment, mean oxycodone AUC was 99.1, 143, 319 and 314 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in oxycodone AUC was approximately 43%, 219%, and 210% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects. Mean oxycodone C_{max} was 9.00, 10.8, 18.1 and 17.2 ng/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in oxycodone C_{max} was approximately 20%, 101%, and 91% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects.

Naloxone pharmacokinetics from **Targin** were also significantly altered by hepatic impairment, especially in subjects with moderate or severe hepatic impairment. Mean naloxone AUC_{0-t} was 0.238, 0.908, 14.1 and 13.7 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in naloxone AUC was approximately 311%, 11418%, and 10566% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects. Mean naloxone C_{max} was 0.0278, 0.0537, 1.47 and 1.46 ng/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in naloxone C_{max} was approximately 93%, 5192%, and 5152% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects.

Renal Impairment: Following oral administration of a single 20/10 mg dose of **Targin** to 12 patients with varying degrees of renal impairment, mean oxycodone AUC was 111, 171, 186 and 253 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in oxycodone AUC was approximately 53%, 66% and 124% for subjects with mild, moderate and severe renal impairment, respectively, as compared with that for healthy subjects. Mean oxycodone C_{max} was 10.6, 11.7, 14.4 and 17.8 ng/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment,

respectively. The mean increase in oxycodone C_{max} was approximately 10%, 35%, and 67% for subjects with mild, moderate, and severe renal impairment, respectively, as compared with that for healthy subjects.

Naloxone pharmacokinetics from **Targin** were also significantly altered by renal impairment, especially in subjects with severe renal impairment. Mean naloxone AUC_{0-t} was 0.115, 1.02, 0.459 and 1.12 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in naloxone AUC was approximately 2750%, 3810% and 7512% in subjects with mild, moderate, and severe renal impairment, respectively, as compared with that for healthy subjects. Mean naloxone C_{max} was 0.0345, 0.0435, 0.0347 and 0.0678 ng/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in naloxone C_{max} was approximately 976%, 758%, and 1575% for subjects with mild, moderate, and severe renal impairment, respectively, as compared with that for healthy subjects.

Genetic Polymorphism: No data available.

Drug Abuse Studies

***In Vitro* Studies:** *In vitro* physical and chemical tablet manipulation studies were performed to evaluate the success of separating the oxycodone component from naloxone, a potent opioid antagonist. Laboratory test data demonstrate that **Targin** can be crushed and dissolved in solution. However, complete inactivation of naloxone and complete separation of naloxone from oxycodone was not achieved despite using various techniques and conditions. The clinical significance of these results is not known.

In vitro physical and chemical tablet manipulation studies were not performed with the 5/2.5 mg tablet.

***In Vivo* Studies:** A series of clinical studies designed to explore the abuse/misuse potential of **Targin**, were conducted in dependent or non-dependent recreational opioid users. The studies included both subjective measures, e.g., Drug Liking VAS and objective measures, e.g., pupillometry. Collectively for these studies, the subjective results produced were supported by similar results in objective measures, and were consistent with the established pharmacology of naloxone. One comparison demonstrated reduced Drug Liking for **Targin** relative to oxycodone powder when each was administered intranasally. In another comparison, solutions containing a 2:1 ratio by weight of oxycodone HCl to naloxone HCl were administered by the intravenous route to explore the abuse and misuse potential of **Targin.** In this comparison, the oxycodone/naloxone solutions demonstrated reduced Drug Liking relative to the oxycodone solution alone when each was administered intravenously. The clinical significance of these results has not yet been established. If abused parenterally or intranasally by individuals dependent on opioid agonists, **Targin** is expected to produce marked withdrawal symptoms – because of the systemic opioid receptor antagonist characteristics of naloxone by these routes – or to intensify withdrawal symptoms already present.

STORAGE AND STABILITY

Store at room temperature (15°C- 30ºC). Protect from light, heat and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Targin® (oxycodone hydrochloride/ naloxone hydrochloride controlled release tablets) 5/2.5 mg are blue, oblong tablets with a film-coating, marked OXN on one side and 5 on the other.

Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) 10/5 mg are white, oblong tablets with a film coating, marked OXN on one side and 10 on the other.

Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) 20/10 mg are pink, oblong tablets with a film coating, marked OXN on one side and 20 on the other.

Targin® (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) 40/20 mg are yellow, oblong tablets with a film coating, marked OXN on one side and 40 on the other.

Composition

Targin 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg tablets contain the following nonmedicinal ingredients:

Tablet Core: ethylcellulose, hydroxypropyl cellulose (5/2.5 mg only), lactose monohydrate, magnesium stearate, povidone K30 (10/5, 20/10and 40/20 mg only), stearyl alcohol, talc.

Tablet Coating

5/2.5 mg: Opadry II Blue: FD&C Blue No. 1-Aluminum Lake (E133), polyethylene glycol (Macrogol 3350), polyvinyl alcohol, talc, titanium dioxide (E171)

10/5 mg: Opadry II White: polyethylene glycol (Macrogol 3350), polyvinyl alcohol, talc, titanium dioxide (E171)

20/10 mg: Opadry II Pink: iron oxide red (E172), polyethylene glycol (Macrogol 3350), polyvinyl alcohol, talc, titanium dioxide (E171)

40/20 mg: Opadry II Yellow: iron oxide yellow (E172), polyethylene glycol (Macrogol 3350), polyvinyl alcohol, talc, titanium dioxide (E171)

Packaging

All strengths will be available in blisters (10s, 14s, 20s, 28s, 30s, 50s, 56s, 60s, 98s and 100s) and opaque plastic bottles of 50, 60, 100 and 250's.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance(s)

Oxycodone:

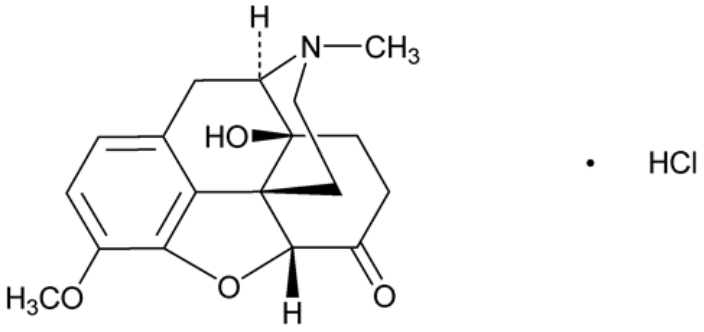
Proper Name: Oxycodone Hydrochloride

Chemical Name: 4,5αEpoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular Formula and Molecular Mass: $C_{18}H_{21}NO_4$•HCl / 351.83

Structural Formula:

Figure 1: Oxycodone Hydrochloride



Physicochemical Properties: Oxycodone is an opioid analgesic. White or off-white odourless, crystalline powder. Soluble in water, slightly soluble in alcohol.

Naloxone:

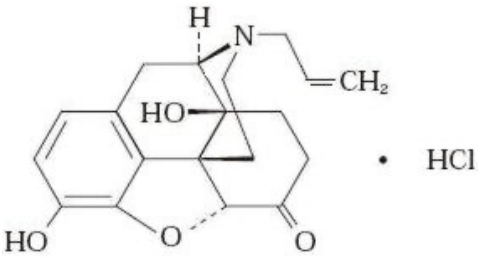
Proper Name: Naloxone hydrochloride

Chemical Name: 17-Allyl-4,5 α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Molecular Formula and Molecular Mass: $C_{19}H_{21}NO_4$•HCl / 363.84

Structural Formula:

Figure 2: Naloxone Hydrochloride



Physicochemical Properties: Naloxone is an opioid antagonist. White to off-white powder. Soluble in water and alcohol, practically insoluble in ether.

CLINICAL TRIALS

The safety and efficacy of **Targin®** (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) has been evaluated in pivotal clinical trials for the management of various types of moderate to severe pain.

Study Demographics and Trial Design

Table 3: Summary of Patient Demographics for Pivotal Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = number)	Mean age (Range)	Gender
PIVOTAL PAIN STUDIES					
OXN3401	Multicentre, randomized, double-blind, placebo- and active -controlled, double-dummy, parallel group	**Targin** 10/5, 20/10 mg (q12h) vs. Oxycodone CR 10 and 20 mg (q12h) vs. placebo tablets (q12h), oral Duration: 12 weeks Dose range: 20/10 to 40/20 mg/day	N = 463	56 (22-85)	M = 178 F = 285
038-001	Multicentre, randomized, double-blind, placebo-controlled, double-dummy, parallel group	**Targin** 10/5, 20/10 and 40/20 mg tablets vs. Placebo tablets (q12h), oral Duration: 4 weeks / phase Dose range: 40/20 to 80/40 mg/day	N = 83	51 (39-63)	M = 39 F = 44

Table 3: Summary of Patient Demographics for Pivotal Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = number)	Mean age (Range)	Gender
PIVOTAL BOWEL FUNCTION STUDIES					
OXN3001	Multicentre, randomized, double-blind, double-dummy, active controlled, parallel group	**Targin** 10/5, 20/10 mg (q12h) vs. Oxycodone CR 10 and 20 mg tablets (q12h), oral Duration: 12 weeks Dose range: 20 /10 to 50/25 mg /day	N = 322	59 (25-87)	M = 126 F = 196
OXN3006	Multicentre, randomized, double-blind, double-dummy, active controlled, parallel group	**Targin** 10/5, 20/10, 40/20 mg (q12h) vs. Oxycodone CR 10, 20 and 40 mg tablets (q12h), oral Duration: 12 weeks Dose range: 60/30 to 80/40 mg/day	N = 265	56 (32-84)	M = 84 F = 181
Pooled Analysis of Bowel Function Studies (OXN3001 and 3006)					
OXN9001 (Pooled Analysis for OXN3001 and 3006)	Multicentre, randomized, double-blind, double-dummy, active controlled, parallel group	**Targin** 10/5, 20/10 mg (q12h) vs. Oxycodone CR 10 and 20 mg tablets (q12h), oral Duration: 12 weeks Dose range: 20/10 to 80/40 mg/day	N = 587	58 (25-87)	M = 210 F = 377
PIVOTAL STUDY WITH PAIN AND BOWEL FUNCTION AS CO-PRIMARY ENDPOINTS					
OXN2001	Multicentre, randomized, double-blind, active-controlled, double-dummy, parallel group study with co-primary endpoints (pain and bowel function)	**Targin** 5/2.5, 10/5, 20/10 and 40/20 mg tablets vs. oxycodone CR 5, 10, 20 and 40 mg tablets (q12h) Oral Duration: 4 weeks Dose range: 20/10 to120/60 mg/day	N = 184	63 (36-84)	M = 94 F = 90

Study Results

Pivotal Pain Studies

Study OXN3401 – Four-hundred and sixty three patients with chronic back pain were randomly assigned to receive **Targin** (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets), oxycodone controlled release (CR) or placebo twice daily in a 12 week randomized, double-blind, parallel study. Adult patients with chronic moderate to severe back pain requiring around-the-clock opioid therapy were enrolled. All patients were converted from an effective immediate release oxycodone dose (15 to 45 mg/day). Immediate release oxycodone (q4-6h) was given as needed.

The primary objective of this study was to demonstrate the superiority of **Targin** over placebo on the time from the initial dose of study medication to multiple (i.e., recurring) pain events (inadequate analgesia) during the Double-Blind Phase.

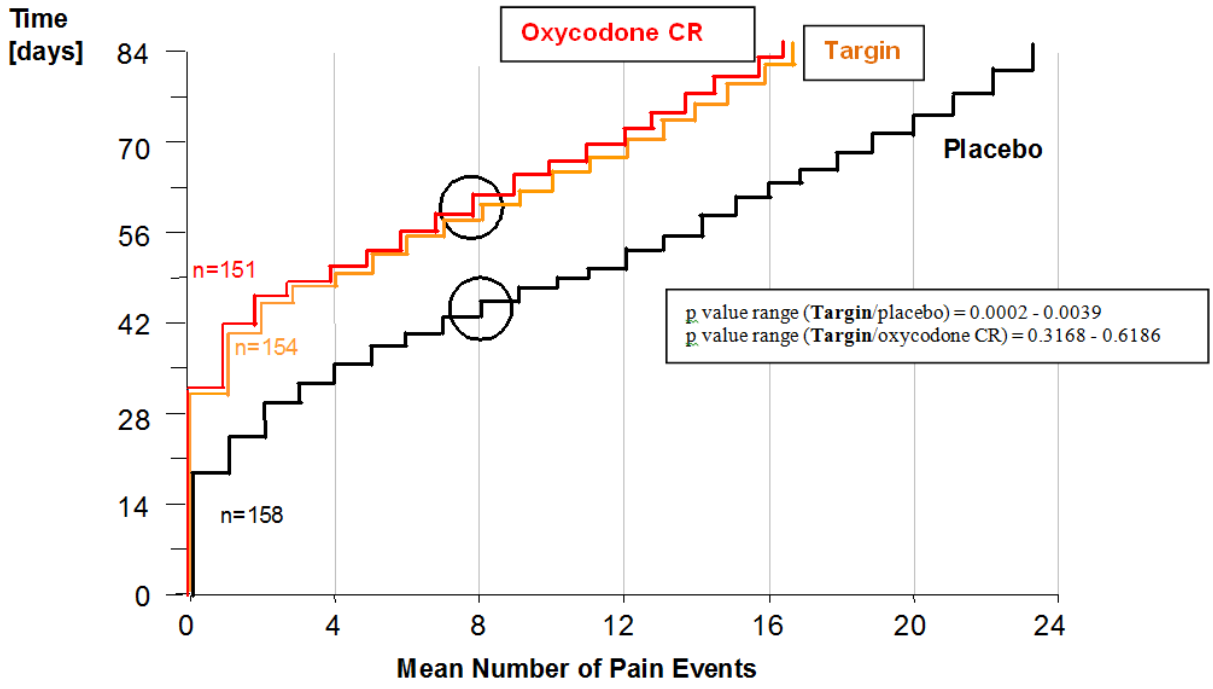
The primary efficacy results showed that the appearance of pain events was significantly reduced for **Targin** compared to placebo. The appearance of pain events was comparable for **Targin** compared to oxycodone CR.

The time from the initial dose of study medication to recurrent pain events during the 12 week period was evaluated. A pain event was demonstrated by unacceptable pain control for two consecutive days. Pain events in the **Targin** group occurred 12 to 15 days later than in the placebo group. Pain events in the controlled release oxycodone group occurred 14 to 16 days later than in placebo group. The time to pain events were significantly shorter in the placebo group compared to the **Targin** group ($p < 0.0001$ and 0.0003). No statistical significant differences were seen between **Targin** and the controlled release oxycodone group. Refer to Figure 3 below.

Secondary efficacy measures for pain were generally supportive of the primary efficacy outcome.

Bowel function was a secondary efficacy parameter. After 12 weeks of treatment, the results of the BFI scores and number of CSBMs showed improvement in bowel function (bowel function is measured by a combination of Bowel Function Index (BFI) and Complete Spontaneous Bowel Movements [CSBM]) with **Targin** treatment compared to oxycodone CR treatment.

Figure 3: OXN3401 - Time to Recurrent Pain Events over Mean Number of Pain Events by Treatment Group



Study 038-001 - Eighty three patients with chronic back pain were randomly assigned to receive **Targin** or placebo twice daily in a 8 week randomized, double-blind, cross-over study. Adult patients with chronic low back pain requiring around-the-clock opioid therapy were enrolled. All patients underwent a 2-7 day washout from all opioid analgesics before randomization to 10/5 mg **Targin** or placebo. Patients were titrated weekly according to efficacy and tolerability to 20/10, 30/15 and 40/20 mg or placebo twice daily. A codeine (30 mg)/ acetaminophen combination preparation was provided (q4-6h) as needed for rescue analgesia.

The primary efficacy outcome in this trial was for pain, measured by use of a Pain Intensity Scale (VAS and 5-point ordinal).

Targin demonstrated superiority to placebo in the treatment of chronic low back pain. Significant improvements in pain intensity were observed. The mean VAS scores and 5-point ordinal pain intensity score in the last week of treatment were significantly lower in the **Targin** group (48.6 and 2.1) than in the placebo group (55.9 and 2.4), respectively. Refer to Table 4 for a summary of the data.

Table 4: Results of Study 038-001

Endpoints	Associated value and statistical significance for Targin	Associated value and statistical significance for Placebo plus PRN codeine/acetaminophen
Pain Intensity (100 mm VAS) 4 Weeks of Treatment	Baseline 61.4 **Targin** 48.6	Baseline 61.4 Placebo and PRN codeine/acetaminophen 55.9
	Targin vs. Placebo plus PRN codeine/acetaminophen, p = 0.0296	
Pain Intensity (Ordinal Scale – 0-4) 4 Weeks of Treatment	Baseline 2.5 **Targin** 2.1	Baseline 2.5 Placebo and PRN codeine/acetaminophen 2.4
	Targin vs. Placebo plus PRN codeine/acetaminophen, p = 0.0415	

Pivotal Bowel Function Studies

Study OXN3001 – Three-hundred and twenty-two patients with chronic back pain were randomly assigned to receive **Targin** or oxycodone controlled release (CR) twice daily in a 12 week randomized, double-blind, parallel study. Adult patients with chronic moderate to severe pain requiring around-the-clock opioid therapy (oxycodone equivalent of 20 to 50 mg/day) who had constipation (less than 3 CSBM [complete spontaneous bowel movements] in the last 7 days) caused or aggravated by an opioid were enrolled. Dosing range was 20/10 mg to 50/25 mg **Targin** per day.

Rescue medication: Oxycodone immediate release (q4-6h) was given as needed; oral bisacodyl 10 mg/day 72 hours after their most recent bowel movement (BM) as rescue medication for constipation. Exception was allowed if the constipation was overwhelming.

The primary efficacy outcome measured in this trial was bowel function:

Bowel Function Index (BFI). BFI is a validated instrument based on the Rome criteria and has a three-item questionnaire measuring constipation on a NAS scale of 0-100 (ease of defecation, feeling of incomplete bowel evacuation, and judgement of constipation).

Secondary efficacy variables included:
- Complete Spontaneous Bowel Movements (CSBMs/week).
- Pain Intensity Score (0-10) “Average Pain over the last 24 hours” score.

Targin demonstrated a statistically significant difference in BFI after 4 weeks (primary end point) of treatment (-15.2) in comparison to oxycodone CR (Mixed-Model Repeated Measures analysis, $p < 0.0001$). The difference was comparable after 12 weeks of treatment (-13.5). The reduction in mean BFI score in the **Targin** group continued until the end of the study (12 weeks) with a 12-week mean BFI of 27.5 and an overall BFI reduction of 30.5 points compared to baseline (see Figure 4).

Overall CSBMs/week improved after 4 weeks of treatment from a mean of 1.1 to 3.5 with an improvement of one extra bowel movement per week in the use of **Targin** compared to oxycodone CR. Similar improvement was found at 1, 2 and 3 weeks of treatment. Refer to Table 5 for a summary of the data.

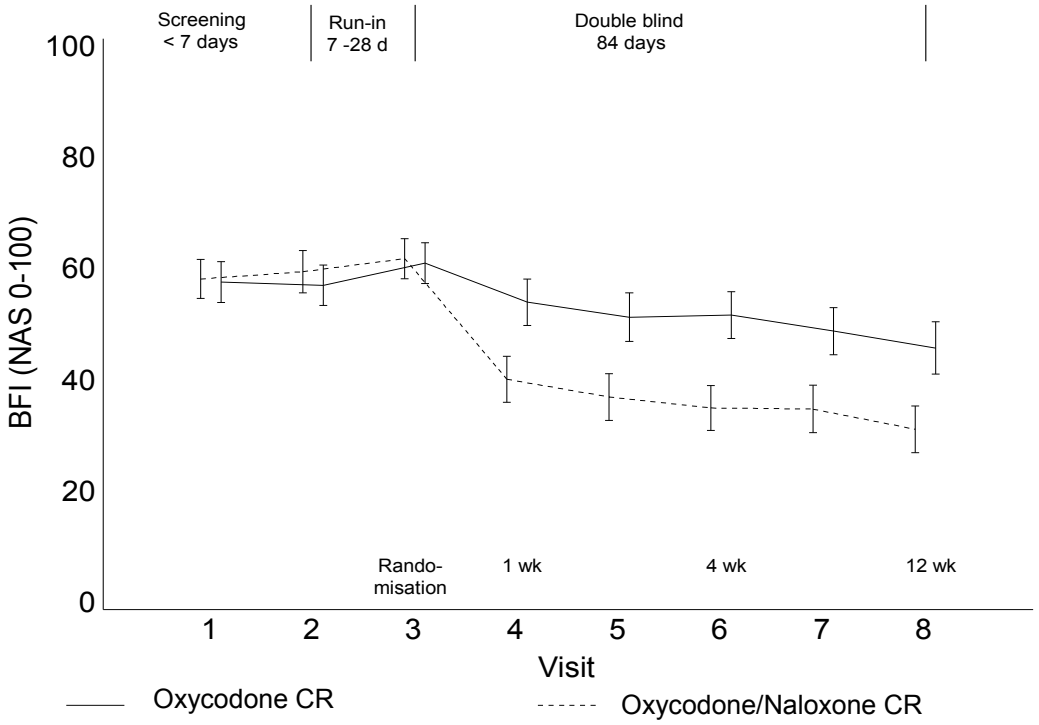
Table 5: Results of Study OXN3001

Endpoints	**Associated value and statistical significance for Targin**	**Associated value and statistical significance for Controlled Release Oxycodone**
Bowel Function Index (0-100)	Baseline 61.8	Baseline 61.0
4 Weeks of Treatment	**Targin** 34.9	Controlled Release Oxycodone 51.6
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	
12 Weeks of Treatment	**Targin** 31.1	Controlled Release Oxycodone 45.7
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	
Complete Spontaneous Bowel Movement (mean) – CSBM/week	Baseline 1.1	Baseline 1.1
4 Weeks of Treatment	**Targin** 3.5	Controlled Release Oxycodone 2.4
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	

- The proportion of subjects in the **Targin** group (31%) that required laxative (bisacodyl tablets) was significantly less than in the oxycodone CR group (55%) after 4 weeks of treatment.

- The change from baseline in the proportion of subjects reaching ≥ 3 CSBM after 4 weeks of treatment was higher in the **Targin** (58%) group as compared to 40% in the oxycodone CR group. Changes in the proportion of subjects were detected at 1, 2 and 3 weeks of the study.
- The average pain over the last 24 hours over the 12 week study was comparable between **Targin** and oxycodone CR.

Figure 4: OXN3001 – Bowel Function Index (BFI) Comparison between Targin and Controlled Release Oxycodone – 12 weeks



Study OXN3006 – Two-hundred and sixty-five patients with chronic back pain were randomly assigned to receive **Targin** or oxycodone controlled release (CR) twice daily in a 12 week randomized, double-blind, parallel study. Adult patients with chronic moderate to severe pain requiring around-the-clock opioid therapy (oxycodone equivalent of 60 to 80mg/day) who had constipation (less than 3 CSBM [complete spontaneous bowel movements] in the last 7 days) caused or aggravated by an opioid were enrolled. Patients were randomized to **Targin** or oxycodone CR in a 1:1 ratio. Dosing levels up to 80/40 mg of **Targin** per day were used. Immediate release oxycodone (q4-6h) was given as needed.

The primary efficacy outcome measured in this trial was bowel function:

- Bowel Function Index (BFI). BFI is a validated instrument based on the Rome criteria and has a three-item questionnaire measuring constipation on a NAS scale of 0-100 (ease of defecation, feeling of incomplete bowel evacuation, and judgement of constipation).

Secondary efficacy variables included:

- Complete Spontaneous Bowel Movements (CSBMs/week);
- Pain Intensity Score (0-10) "Average Pain over the last 24 hours" score.

Targin demonstrated a statistically significant difference in BFI after 4 weeks (primary end point) of treatment (-14.9) in comparison to controlled release oxycodone (Mixed-Model

Repeated Measures Analysis, $p < 0.0001$). The difference was maintained after 12 weeks of treatment (-14.6).

The reduction in mean BFI score in the **Targin** group continued to the end of the study with a 12 week mean BFI of 34.0 and an overall BFI reduction of 33.4 points compared to baseline (see Figure 5 and Table 6).

Overall CSBMs/week improved after 4 weeks of treatment from a mean of 0.9 to 3.1, with an improvement of one extra bowel movement per week in the use of **Targin** compared to oxycodone CR. Similar improvements were found at 1, 2 and 3 weeks of treatment.

Table 6: Results of Study OXN3006

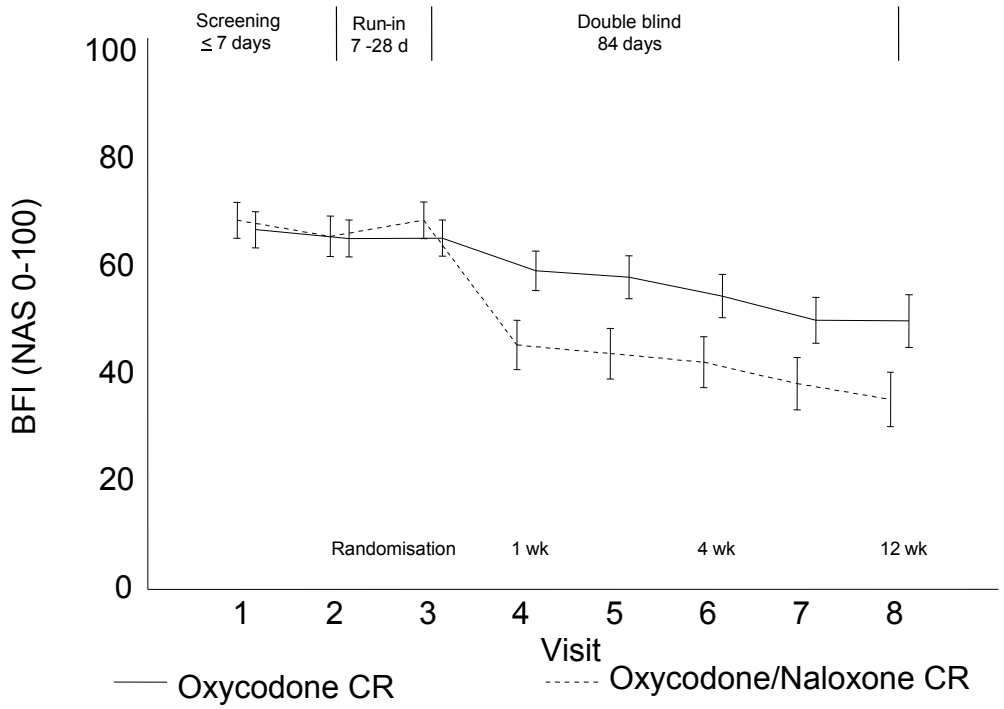
Endpoints	**Associated value and statistical significance for Targin**	**Associated value and statistical significance for Controlled Release Oxycodone**
Bowel Function Index (0-100)	Baseline 67.4	Baseline 64.1
4 Weeks of Treatment	**Targin** 40.9	Controlled Release Oxycodone 53.3
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	
12 Weeks of Treatment	**Targin** 34.0	Controlled Release Oxycodone 48.6
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	
Complete Spontaneous Bowel Movement (mean) – CSBM/week	Baseline 0.93	Baseline 0.92
4 Weeks of Treatment	**Targin** 3.1	Controlled Release Oxycodone 1.8
	Targin vs. Controlled Release Oxycodone, $p < 0.0001$	

- The proportion of subjects in the **Targin** group (43%) that required laxative (bisacodyl tablets) was significantly less than in the oxycodone CR group (64%) after 4 weeks.

- The change from baseline in the proportion of subjects reaching ≥ 3 CSBM after 4 weeks of treatment was higher in the **Targin** (51%) group as compared to 25% in the oxycodone CR group. Changes in the proportion of subjects were detected at 1, 2 and 3 weeks of the study

- The average pain over the last 24 hours over the 12 week study was comparable between **Targin** and oxycodone CR.

Figure 5: OXN3006 – Bowel Function Index (BFI) Comparison between Targin and Controlled Release Oxycodone – 12 weeks



Study OXN9001 - A pooled-analysis was conducted combining the two randomized, double-blind, parallel group studies 3001 and 3006 to demonstrate the non-inferiority of **Targin** to oxycodone controlled release (CR) in 12 week analgesic efficacy. A total of five-hundred and eighty seven subjects were included in this assessment. The results revealed that throughout the 12 weeks of the double-blind phase, no statistically significant difference was noted between the two groups in the mean pain intensity, and that non-inferiority of **Targin** to oxycodone CR was demonstrated (**Targin** vs oxycodone CR 0.08, non-inferiority: $p < 0.0001$). The actual observed difference of the means at 12 weeks was 0.1 on a VAS (0 to 10) scale (**Targin** 3.6, oxycodone CR 3.5) (see Table 7).

Table 7: Results of Study OXN9001

Endpoints	Associated value and statistical significance for Targin	Associated value and statistical significance for Controlled Release Oxycodone
Average Pain Intensity (Scale – 0-10) 12 Weeks of Treatment	Baseline 3.4 **Targin** 3.6	Baseline 3.3 Controlled Release Oxycodone 3.5
	Targin vs. Controlled Release Oxycodone, non-inf : 0.08; 95% CI -0.07 to 0.23	

Pivotal Study with Pain and Bowel Function as Co-Primary Endpoints

Study OXN2001 - One hundred and eighty-five patients, with moderate to severe chronic cancer pain, were randomly assigned to receive **Targin** or controlled-release oxycodone twice daily and evaluated in a 4-week randomized, double-blind, double-dummy, parallel group study. The study had three phases: a screening phase, a 4-week double-blind phase, and a 24 week extension phase. Following screening, subjects stopped their pre-study opioid and laxative medication and were randomised to receive either **Targin** or controlled-release oxycodone in the double-blind phase. Adult patients with a documented history of cancer pain requiring around-the-clock opioid therapy and who had constipation (less than 3 bowel evacuations in the last 7 days or the medical need for laxatives in order to have at least 3 bowel evacuations per week) caused or aggravated by an opioid were enrolled.

The co-primary endpoints of this study were the Brief Pain Inventory (BPI) and the Bowel Function Index (BFI).

Efficacy results showed:

Pain: At the end of the 4-week treatment phase the average pain scores were 3.52 and 3.50 for controlled-release oxycodone and **Targin** respectively, down from baseline values of 4.18 and 4.16 respectively. The Least Squares Mean difference (-0.011, 90% CI -0.474, 0.452, $p < 0.001$) confirmed the non-inferiority of **Targin** compared to controlled-release oxycodone.

Bowel function: For improvements in symptoms of constipation, after four weeks the Bowel Function Index (BFI) values decreased to a mean value of 39.47 in subjects receiving **Targin** and 49.68 in subjects receiving controlled-release oxycodone from mean baseline values of 63.97 and 62.40 respectively. A comparison of the change in BFI values at the end of the double-blind phase, demonstrated that the improvement was statistically significant (LS Mean Difference = -12.36, 95% CI -19.05, -5.670, $p \leq 0.001$) and clinically relevant (Δ BFI > 12) in favour of subjects receiving **Targin**.

DETAILED PHARMACOLOGY

Oxycodone Hydrochloride

Pharmacodynamics: Oxycodone has affinity for kappa, mu and delta opioid receptors in the brain, spinal cord and peripheral organs (e.g., intestine). The major effects on the CNS and on the bowel include analgesia, drowsiness, changes in mood, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

Oxycodone receptor selectivity has not been extensively studied or characterized, and there appears to be a discrepancy between its weak affinity for opioid receptors and its potent antinociceptive activity.

Oxycodone has been shown to be 2 - 4 times more potent than morphine after both subcutaneous and intraperitoneal administration in rats. In clinical studies in patients with acute post-operative pain, oxycodone has been demonstrated to be twice as potent as morphine.

Naloxone Hydrochloride

Pharmacodynamics: Naloxone is a potent antagonist at mu, delta and kappa-opioid receptors in the brain, spinal cord and peripheral organs (e.g., intestine). In the CNS naloxone produces opioid withdrawal effects in opioid-dependent subjects. In the gut naloxone can relieve the constipating effect of opioids.

Naloxone in the combination tablet (oxycodone/naloxone CR) has no clinically significant systemic effect when administered orally because of its poor absorption and short half-life relative to oxycodone. Due to the local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone reduces the constipation that is typical with opioid treatment.

In a non-clinical pharmacology study conducted in opioid dependent rats**,** intravenous administration of oxycodone/naloxone (2:1) ratio precipitated opioid-antagonist effects and withdrawal symptoms similar in magnitude to those produced by naloxone alone.

TOXICOLOGY

There are no data from studies on reproductive toxicity of the combination of oxycodone and naloxone.

Teratogenicity: Studies with the single components showed that oxycodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual fetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the

pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone was not teratogenic and/or embryo/fetotoxic, and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone produced increased pup deaths in the immediate post-partum period at dosages that produced significant toxicity in maternal rats (e.g., body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Mutagenicity: Oxycodone and naloxone as single entities show a clastogenic potential in *in vitro* assays. No similar effects were observed, however, under *in vivo* conditions, even at toxic doses. The results indicate that the mutagenic risk of **Targin** (oxycodone hydrochloride/naloxone hydrochloride controlled release tablets) to humans at therapeutic concentrations may be ruled out with adequate certainty.

Carcinogenicity: For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is not carcinogenic under these conditions. Long-term carcinogenicity studies with oxycodone/naloxone in combination or oxycodone as single entity have not been performed.

REFERENCES

1. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P and Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med 2012;26(1):50-60. Epub 2011 Sep 21. PubMed PMID: 21937568. [Study OXN2001]

2. Lowenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, Uhl R et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opin Pharmacother 2009;10(4):531-43. [Study OXN3006]

3. Lowenstein O, Leyendecker P, Lux EA, Blagden M, Simpson KH, Hopp M, et al. Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC Clin Pharmacol 2010;10:12. [Study OXN9001]

4. Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes C, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur J Pain 2008;13(1):56-64. [Study OXN2401]

5. Sandner-Kiesling A, Leyendecker P, Hopp M, Tarau L, Lejcko J, Meissner W, et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. Int J Clin Pract, May 2010;64:763-74.

6. Simpson K, Leyendecker P, Hopp M, Müller-Lissner, Löwenstein O, De Andrés J, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. Curr Med Res Opin 2008;24(12):3503-12. [Study OXN3001]

7. Smith K, Hopp M, Mundin G, Leyendecker P, Bailey P, Grothe B, et al. Single- and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist/antagonist prolonged-release combination in healthy adult volunteers. Clin Therapeutics 2008;30 (11):2051-68.

8. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain 2008;9(12):1144-54. [Study OXN3401]

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N}Targin®

(oxycodone hydrochloride/naloxone hydrochloride controlled release tablets)

Read this carefully before you start taking **Targin** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Targin.**

Serious Warnings and Precautions

- **Even if you take Targin as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**
- **Life-threatening breathing problems can happen while taking Targin, especially if not taken as directed.**
- **Never give anyone your Targin. They could die from taking it. If a person has not been prescribed Targin, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken Targin (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is Targin used for?

Targin is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively manage your pain

Targin is also used to lessen the effect of constipation from opioid pain medication treatment.

Targin is NOT used ("as needed") to treat pain that you only have once in a while.

How does Targin work?

As its active substances, **Targin** contains oxycodone and naloxone.

Oxycodone is a pain medication belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

Naloxone is a medicine used to prevent opioid medications from binding to receptors in the gastrointestinal tract, to help reduce constipation.

What are the ingredients in Targin?

Medicinal ingredients: oxycodone hydrochloride and naloxone hydrochloride

Non-medicinal ingredients: ethylcellulose, FD&C Blue No. 1 (5/2.5 mg only), hydroxypropylcellulose (5/2.5 mg only), iron oxide (20/10 and 40/20 mg only), lactose monohydrate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, povidone K30 (10/20, 20/40 and 40/20 mg only), stearyl alcohol, talc, titanium dioxide

Targin comes in the following dosage forms:

Controlled Release Tablets: 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg

Do not use Targin if:

- you are allergic to oxycodone hydrochloride, naloxone hydrochloride, other opioids, or any of the other ingredients of **Targin**
- your pain can be controlled by the occasional use of pain medications, including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines (e.g., paralytic ileus)
- you have severe pain in your abdomen
- you have a head injury or other risks for seizures
- you have moderate to severe liver dysfunction
- you suffer from alcoholism
- you are being treated for narcotic withdrawal
- you are pregnant or plan to become pregnant, breast-feeding, or in labour
- you are under 18 years of age
- you take monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with **Targin**.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Targin. Talk about any health conditions or problems you may have, including if you:

- have severe kidney disease
- have low blood pressure
- you are going to have, or recently had, a planned surgery

- have a history of illicit or prescription drug or alcohol abuse
- have past or current depression
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems

Other warnings you should know about:

Targin should not be administered rectally due to the possible increased systemic availability of naloxone by this route and the potential for the occurrence of severe withdrawal effects.

You may see tablets in your stools (bowel movements) when using **Targin.** Do not be concerned, your body has absorbed the medicine.

There are important differences between physical dependence and addiction, and each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to **Targin**. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Targin:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking **Targin**. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **Targin**
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- most antidepressants (for depression and mood disorders)
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- antihistamines (for allergies)
- anticholinergics (for asthma, incontinence, gastrointestinal cramps and muscular spasms)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (beta blockers)
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, azole-anti-fungal and macrolide-antibiotic drugs
- grapefruit juice

How to take Targin:

Targin tablets are designed to work properly over 12 hours when swallowed whole.

Swallow whole. Do not cut, break, chew, dissolve or crush Targin tablets before swallowing since this can lead to the release and absorption of an excessive dose of oxycodone which can seriously harm you.

Do not take the 40/20 mg strength or a single dose of 80/40 mg or more of Targin unless you are "opioid tolerant". Your doctor will tell you when you are "opioid tolerant" to a certain dose of Targin.

Targin can be taken with or without food with sufficient fluid (e.g., 4 to 6 oz. of water), to treat pain and assist with decreasing constipation.

Do not use for rectal administration.

Usual Adult Starting Dose:

Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

The usual initial adult dose for patients who have not previously received opioid analgesics is **Targin** 10/5 mg every 12 hours. **The maximum daily dose of Targin should be limited to 80/40 mg/day or 40/20 mg every 12 hours.** If you need a higher dose, your doctor may give you an additional oxycodone preparation without naloxone.

Review your pain regularly with your doctor to determine if you still need **Targin**. Be sure to use **Targin** only for the condition for which it was prescribed.

Should your pain increase or any other complaint as a result of taking **Targin**, tell your doctor immediately.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much **Targin**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (e.g., 8 o'clock in the morning and 8 o'clock in the evening). If you miss several doses in succession, talk to your doctor before restarting your medication.

Discontinuation:

You should not stop taking **Targin** all at once if you have been taking it for more than a few days.

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, unexplained fever, weakness and yawning.

Refilling Prescriptions for Targin:

A new written prescription is required from your doctor each time you need more **Targin**. Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using Targin?

These are not all the possible side effects you may feel when taking **Targin**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- nausea and/or vomiting
- constipation
- diarrhea
- sweating
- fatigue
- headache
- dizziness

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			√
	Respiratory Depression: slow, shallow or weak breathing.			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep unused or expired Targin in a secure place to prevent theft, misuse or accidental exposure.

Store at room temperature (15°C- 30˚C). Protect from light, heat and humidity.

Keep Targin under lock, out of sight and reach of children and pets.

Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Targin, get emergency help right away.

Disposal:

Targin should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about Targin:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website; the manufacturer's website http://www.purdue.ca, or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

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