PRODUCT INFORMATION - TARGIN® PROLONGED-RELEASE TABLETS

FOR HOSPITAL USE ONLY
This product may be habit-forming upon prolonged use

1. NAME OF THE MEDICINE
Oxycodone hydrochloride and naloxone hydrochloride dihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Targin® 5 mg/2.5 mg prolonged-release tablet contains 5 mg of oxycodone hydrochloride equivalent to 4.5 mg oxycodone, and 2.73 mg of naloxone hydrochloride dihydrate equivalent to 2.5 mg naloxone hydrochloride and 2.25 mg naloxone;

Targin® 10 mg/5 mg prolonged-release tablet contains 10 mg of oxycodone hydrochloride equivalent to 9.0 mg oxycodone, and 5.45 mg of naloxone hydrochloride dihydrate equivalent to 5.0 mg naloxone hydrochloride and 4.5 mg naloxone;

Targin® 20 mg/10 mg prolonged-release tablet contains 20 mg of oxycodone hydrochloride equivalent to 18.0 mg oxycodone, and 10.9 mg of naloxone hydrochloride dihydrate equivalent to 10.0 mg naloxone hydrochloride and 9.0 mg naloxone;

Targin® 40 mg/20 mg prolonged-release tablet contains 40 mg of oxycodone hydrochloride equivalent to 36.0 mg oxycodone, and 21.8 mg of naloxone hydrochloride dihydrate equivalent to 20.0 mg naloxone hydrochloride and 18.0 mg naloxone;

The inactive ingredients in ***Targin***® 5 mg/2.5 mg tablets are lactose monohydrate, hydroxypropylcellulose, ethylcellulose, stearyl alcohol, talc and magnesium stearate. The inactive ingredients in ***Targin***® 10 mg/5 mg, 20mg/10 mg and 40mg/20 mg tablets are lactose monohydrate, povidone K30, ethylcellulose, stearyl alcohol, talc and magnesium stearate. All tablets are coated with polyvinyl alcohol, titanium dioxide (E171), macrogol 3350 and talc. The tablet coat also contains brilliant blue FCF aluminium lake E133 (5mg/2.5 mg tablets), iron oxide red E172 (20mg/10 mg tablets) and iron oxide yellow E172 (40mg/20 mg tablets).

Excipients with known effect: contains sugars as lactose and sulfites.

May contain presence of sulfites from the manufacturing process.

3. PHARMACEUTICAL FORM
Targin® tablets are available as oblong, unscored film-coated tablets in blister pack sizes of 28 tablets as follows:

5 mg/2.5 mg light blue, marked “OXN” on one side and “5” on the other;
10 mg/5 mg white, marked “OXN” on one side and “10” on the other;
20 mg/10 mg pink, marked “OXN” on one side and “20” on the other;
40 mg/20 mg yellow, marked “OXN” on one side and “40” on the other

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
The management of moderate to severe chronic pain unresponsive to non-narcotic analgesics. The opioid antagonist naloxone in the fixed combination is added to counteract and/or prevent opioid-induced

constipation.

Second line symptomatic treatment of patients with severe to very severe idiopathic Restless Legs Syndrome (RLS) after failure of dopaminergic therapy.

4.2 DOSAGE AND METHOD OF ADMINISTRATION

Targin® **tablets are to be swallowed whole and are not to be broken, chewed or crushed. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone that could be fatal.**

Before initiating treatment with *Targin*®, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4- Special warnings and precautions for use).

Targin® **should not be used longer than necessary.**

Analgesia
Targin® tablets are intended for oral use only. The required dosage should be taken with sufficient liquid, with or without food, at 12-hourly intervals (e.g. 8 am and 8 pm). The analgesic efficacy of ***Targin***® tablets is equivalent to **OxyContin**® tablets.

The dosage for an individual patient is dependent upon the severity of the pain, functional status, sensitivity (side effects) and the patient's previous history of analgesic requirements, including opioid analgesics.

Adults and paediatric patients from 18 years of age
Prior to initiation and titration of doses, refer to the **PRECAUTIONS** section for information on *Special Risk Groups*.

The usual starting dose for opioid-naïve patients or patients presenting with moderate to severe chronic pain uncontrolled by weaker opioids is one ***Targin***® tablet 10mg/5 mg at 12-hourly intervals. One ***Targin***® tablet 5 mg/2.5 mg 12-hourly is suitable for patients with mild hepatic impairment and patients with renal impairment. The dose should then be cautiously titrated, as frequently as every 1-2 days if necessary, to achieve pain relief.

Patients already being treated with opioids may be started on higher doses of ***Targin***® tablets, depending upon their previous opioid exposure.

Patients receiving oral morphine prior to treatment with ***Targin***® tablets should have their daily dose of ***Targin***® tablets established based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It is emphasised that this is a guide to the required dose of ***Targin***® tablets only. Inter-patient variability in sensitivity and response to opioid analgesics requires that each patient is carefully

titrated to the appropriate dose.

Patients receiving other oral oxycodone formulations may be transferred to ***Targin***® tablets at the same total daily dosage, equally divided into two 12-hourly tablets doses.

Increasing severity of pain may require an increased dosage of ***Targin***® tablets using the 5mg/2.5 mg, or where appropriate, 10mg/5 mg tablet strengths, either alone or in combination, to achieve a stable dose providing adequate pain relief. The correct dosage for any individual patient is the minimum dose that controls the pain, provides functional improvement and is well tolerated, for a full 12 hours. Patients should be titrated to pain relief and functional improvement unless unmanageable adverse drug reactions prevent this.

Some patients taking ***Targin***® tablets according to a regular time schedule may require immediate release analgesics (e.g. immediate release oxycodone) as "rescue" medication for breakthrough pain. ***Targin***® tablets are a prolonged release formulation and are not intended to treat breakthrough pain. Should breakthrough pain treatment be necessary, it is generally recommended that a single dose of rescue medication should be approximately 1/6 to 1/12 of the equivalent daily dose of oxycodone hydrochloride. The need for more than two doses of "rescue" medication per day is usually an indication for the patient to be re-assessed and, if appropriate, the dosage of ***Targin***® tablets increased.

The maximum recommended daily dose of ***Targin***® tablets is 160/80mg (corresponding to 12-hourly administration of ***Targin***® tablets 80/40mg). Patients requiring higher dosages should be administered supplemental, single entity controlled release oxycodone at the same time intervals. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be impaired. After complete discontinuation of ***Targin***® tablets and a subsequent switch to another opioid, a worsening of bowel function can be expected.

Moderate to severe pain in the majority of patients is well managed by the symmetric administration (identical morning and evening doses) of ***Targin***® tablets at the established, stable, 12-hourly fixed dosage schedule. However, some patients may benefit from an asymmetric dosing schedule (higher dose in the morning or evening) tailored to their analgesic needs, depending on the nature of their variable, diurnal pain severity. In these patients, the lowest total daily analgesic dose that provides adequate pain relief should always still be prescribed.

Targin® tablets should not be prescribed and taken by the patient for longer than absolutely necessary to manage their pain. If long-term pain treatment is anticipated given the nature and severity of the illness, careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment with an opioid analgesic. When opioid treatment is no longer needed, the dose should be gradually reduced to minimise symptoms of withdrawal.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate in this patient population.

Non-Cancer Pain
Daily doses of up to 40 mg/20 mg ***Targin***® tablets are usually sufficient for the treatment of moderate to severe, chronic non-cancer pain, but higher doses may be required.

Use in paediatric patients
Not recommended for use in paediatric patients below 18 years of age.

Restless legs syndrome

Targin® tablets are indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). ***Targin***® tablets should be used after failure of previous dopaminergic treatment. Dopaminergic treatment failure is defined as inadequate initial response, a response that has become inadequate with time, occurrence of augmentation or unacceptable tolerability despite adequate doses. Previous treatment with at least one dopaminergic medicinal product should have lasted in general 4 weeks. A shorter period might be acceptable in case of unacceptable tolerability with dopaminergic therapy.

The dosage should be adjusted to the sensitivity of the individual patient.

Treatment of patients with RLS with ***Targin***® tablets should be under the supervision of a clinician with experience in the management of RLS.

Unless otherwise prescribed, ***Targin***® tablets should be administered as follows:

Adults
The usual starting dose is 5mg/2.5mg of oxycodone hydrochloride/naloxone hydrochloride at 12 hourly intervals.

Titration on a weekly basis is recommended in case higher doses are required. The mean daily dose in the pivotal study was 20mg/10mg oxycodone hydrochloride/naloxone hydrochloride.

Some patients may benefit from higher daily doses up to a maximum of 60 mg/30 mg oxycodone hydrochloride/naloxone hydrochloride.

Targin® tablets is taken at the determined dosage twice daily according to a fixed time schedule. While symmetric administration (the same dose mornings and evenings) subject to a fixed time schedule (every 12 hours) is appropriate for the majority of patients, some patients, depending on the individual situation, may benefit from asymmetric dosing tailored to the individual patient. In general, the lowest effective dose should be selected.

For doses not realizable / practicable with this strength other strengths of this medicinal products are available.

Children and adolescents (under 18 years)
Targin® tablets is not recommended for use in children and adolescents below the age of 18 years due to a lack of data on safety and efficacy.

Elderly patients
Dosage should be adjusted to the intensity of RLS symptoms and the sensitivity of the individual patient.

Patients with impaired hepatic function
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. The clinical relevance of a relative high naloxone exposure in hepatic impaired patients is yet not known. Caution must be exercised when administering ***Targin***® to patients with mild hepatic impairment. In patients with moderate and severe hepatic impairment ***Targin***® is contraindicated.

Patients with impaired renal function
A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment. Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering ***Targin***® to patients with renal

impairment.

4.3 CONTRAINDICATIONS

Hypersensitivity to opioids, naloxone and any of the excipients or any situation where opioids are contraindicated; moderate to severe hepatic impairment; elevated carbon dioxide levels in the blood; severe respiratory disease, acute respiratory disease and respiratory depression; *cor pulmonale*; cardiac arrhythmias; uncontrolled bronchial asthma; severe chronic obstructive pulmonary disease; non-opioid induced paralytic ileus; pregnancy; lactation; severe CNS depression; increased cerebrospinal or intracranial pressure; brain tumour or head injury (due to the risk of increased intracranial pressure); uncontrolled convulsive disorders; suspected surgical abdomen; delayed gastric emptying; alcoholism; *delirium tremens*; concurrent administration of MAO-inhibitors and for 2 weeks after their cessation. History of opioid abuse for restless legs syndrome.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and Harmful use

Targin® contains the opioid oxycodone hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed ***Targin***® at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed ***Targin***®.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see *section 6.4 Special precautions for storage* and *section 6.6 Special precautions for disposal*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Repeated use of ***Targin***® can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of ***Targin***® may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with ***Targin***® and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2- Dose and method of administration). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

If abused parenterally or intranasally by individual's dependent on opioid agonists, such as heroin, morphine or methadone, ***Targin***® are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone, or to intensify already present withdrawal symptoms.

Parenteral injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

Patients should be advised not to share ***Targin***® with anyone else.

Respiratory depression
Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of ***Targin***®, but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients in patients with renal and hepatic impairment and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 Dose and method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications).

Respiratory depression occurs most frequently in overdose situations in those suffering from conditions accompanied by hypoxia when even moderate doses may dangerously decrease respiration.

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and prolonged release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to prolonged release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response. (see section 4.2- Dosage and method of administration).

Sleep related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use can increase the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8- Adverse effects).

Targin® should be used with extreme caution in patients with sleep apnoea and patients with a substantially decreased respiratory reserve. Severe pain antagonises the respiratory depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest.

Risks from Concomitant Use with Benzodiazepines
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of oxycodone with benzodiazepines.

Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when oxycodone is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Section 4.5 Interactions with other medicines and other forms of interactions).

Use of opioids in chronic (long-term) non-cancer pain (CNCP)
Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Section 4.4 Special warnings and precautions; see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a prolonged-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly, and the dose tapered off slowly if opioid treatment is no longer appropriate (see Section 4.4 Special warnings and precautions; Ceasing Opioids).

Tolerance, dependence and withdrawal
Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia,

mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate. ***Targin***® are not suitable for the treatment of symptoms of opioid withdrawal.

When discontinuing ***Targin***® in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Section 4.4 Special warnings and precautions *Ceasing opioids)*

In patients undergoing opioid treatment, the switch to ***Targin***® can initially provoke withdrawal symptoms or diarrhoea. These patients require specific attention.

Accidental ingestion/exposure
Accidental ingestion or exposure of ***Targin***®, especially by children, can result in a fatal overdose of oxycodone. Patients and their caregivers should be given information on safe storage and disposal of unused ***Targin***® (see *section 6.4 Special precautions for storage*).

Hyperalgesia
Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Section 4.4 Special warnings and precautions *Tolerance, dependence and withdrawal*). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids
Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Section 4.4 Special warnings and precautions Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Adrenal insufficiency
Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with ***Targin***® should be considered.

Endocrine effects
Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes

observed are an increase in serum prolactin and a decrease in levels of cortisol and testosterone. Clinical symptoms may accompany these hormonal changes.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea or infertility.

Neonatal withdrawal syndrome
Chronic use of oxycodone by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section 4.6- Fertility, Pregnancy and Lactation).

Gastrointestinal toxicity
Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

Restless Legs Syndrome
Sleep apnoea is more common in patients with restless leg syndrome and caution is advised in treating such patients with ***Targin***® tablets due to the additive risk of respiratory depression.

There is no clinical experience with ***Targin***® tablets in the treatment of RLS beyond 1 year (see section 4.2- Dosage and Administration).

There is no clinical experience of concomitant dopaminergic agents with ***Targin***® tablets in the management of RLS. Additive or synergistic adverse CNS effects such as nausea, dizziness and confusion may occur and the combination was not tested in the clinical trial OXN3502 in RLS patients.

The combination of ***Targin***® tablets with dopaminergic agents for the management of RLS is not recommended.

Clinical abuse potential studies
1. Study in Opioid-Dependent Subjects
The likeability of ***Targin***® tablets chewed or intact was compared with oxycodone solution and placebo in a randomised, double-blind, placebo and positive-controlled study in 29 opioid-dependent, methadone-maintained subjects. ***Targin***®, either chewed or intact, was associated with statistically significant lower maximum "Drug Liking" scores ($p < 0.001$) and statistically significant lower scores for "Take Drug Again" ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median maximum scores for "Drug Liking" and "Take Drug Again", compared to placebo treatment. This indicates that ***Targin***® tablets are expected to result in less potential for abuse by all routes of administration in opioid-dependent subjects compared with immediate release oxycodone.

2. Studies in non-dependent opioid abusers
Additional studies via the intranasal (IN) and intravenous (IV) routes indicate that ***Targin***® is expected to reduce abuse via the IN and IV routes of administration. ***Targin***®, administered via the IN and IV routes was statistically significantly less preferred over oxycodone HCl powder. No reduction in abuse potential was noted following chewed oral administration in this patient group.
Despite the abuse deterrent properties demonstrated in these studies, abuse and diversion by these and other routes are still possible. As with other opioids, patients should be carefully monitored for signs of abuse and addiction. Abuse or misuse of ***Targin***® by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and

death.

Formulation
Targin® tablets consist of a dual-polymer matrix, intended for oral use only. ***Targin***® tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take ***Targin***® tablets. The empty tablet matrix may be visible in the stool. ***Targin***® tablets may produce positive results in sports agency drug testing procedures.

Use in hepatic impairment
Targin® tablets should be used with caution in patients with mild hepatic impairment (refer to section 5.2- Pharmacokinetic Properties). Whilst the administration of ***Targin***® tablets to these patients does not result in significant levels of oxycodone active metabolites, the plasma concentrations in this patient population may be increased compared with patients having normal hepatic function. Therefore, initiation of dosing in patients with mild hepatic impairment should be reduced to ⅓ to ½ of the usual dose with cautious titration and careful medical monitoring.

Because of the observed increase in naloxone plasma concentrations, and until the clinical relevance of this is established, ***Targin***® tablets are contraindicated in patients with moderate to severe hepatic impairment.

Use in renal impairment
Targin® tablets should be used with caution in patients with renal impairment (CKD stages 2 to 5) (refer to section 5.2- Pharmacokinetic Properties). Whilst the administration of ***Targin***® tablets to these patients does not result in significant levels of oxycodone active metabolites, the plasma concentrations in this patient population may be increased compared with patients having normal renal function. Therefore, initiation of dosing in patients with renal impairment (CKD stages 2 to 5) should be reduced to ⅓ to ½ of the usual dose with cautious titration and careful medical monitoring.

As patients with severe renal impairment (CKD stages 4 and 5) may be at greater risk for opioid withdrawal-related adverse events, consideration should be given to alternative products without naloxone.

Use in the elderly
As with other opioid initiation and titration, doses in elderly patients who are infirm or debilitated should be reduced to ⅓ to ½ of the usual doses.

The plasma concentrations of oxycodone are only nominally affected by age, being approximately 18% greater in elderly as compared with young subjects. There were no differences in adverse event reporting between young and elderly subjects. The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating ***Targin***® and when ***Targin***® are given concomitantly with other drugs that depress respiration

As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Exercise caution when administering ***Targin***® tablets to elderly, infirm or debilitated patients, patients with mild hepatic impairment, patients with renal impairment, patients with severely impaired pulmonary function and opioid-dependent patients. Precaution is required in hypotension, hypertension, hypovolaemia, diseases of the biliary tract (e.g. cholelithiasis), pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, myxoedema, opioid-induced paralytic

ileus, pre-existing cardiovascular disease and in epileptic disorders or predisposition to convulsions.

As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive ***Targin***® tablets for 24 hours before surgery. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with ***Targin***® tablets is then indicated, the dosage should be adjusted to the new post-operative requirement.

Targin® tablets are not recommended for immediate pre-operative use and post-operative use for the first 24 hours after surgery. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual health status of the patient, the exact timing for initiating treatment with ***Targin***® tablets depends on a careful risk-benefit assessment for each individual patient.

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***® tablets in this population is not recommended.

Biliary tract disorders
Oxycodone can cause an increase in intrabiliary pressure and spasm as a result of its effects on the sphincter of Oddi; therefore, monitor patients with diseases of the biliary tract for worsening symptoms while administering oxycodone. Therefore, ***Targin***® tablets have to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Paediatric use
Targin® is not recommended for use in patients under 18 years of age.

Serotonin Svndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of oxycodone is with serotonergic drugs (see Section 4.5 Interactions with other medicines). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see Section 4.5 Interactions with other medicine). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that.
Discontinue oxycodone is if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility. (See Postmarketing Experience)

4.5 INTERACTIONS WITH OTHER MEDICINES

Alcohol

Dissolution studies with ***Targin***® tablets were conducted in Standard Gastric Fluid sine pepsin (SGFsp) dissolution media, modified with ethanol at concentrations up to 40%v/v, representative of the most extreme conditions likely to be encountered *in vivo*. The prolonged release characteristics of ***Targin***® tablets were maintained under these test conditions, and no breakdown of the controlled release mechanism of the formulation was observed.

Anticholinergic agents

Concurrent use 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 effects, e.g. an increased risk of severe constipation and/or urinary retention. The presence of naloxone in ***Targin***® tablets, however, may serve to reverse the additive constipative effect, at least in part.

Antihypertensive agents

Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.

CNS depressants

Concurrent use of CNS depressants *(including antidepressants, sedatives (incl. benzodiazepines), antipsychotics, hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids, gabapentinoids such as pregabalin, anxiolytics, anti-histamines, anti-emetics and neuroleptic drugs, etc.)* with oxycodone may enhance the CNS-depressant effect resulting in increased risk of respiratory depression, hypotension, profound sedation, coma or death. Caution is recommended and the dosage of one or both agents should be reduced.

Intake of alcoholic beverages while being treated with oxycodone should be avoided because this may lead to more frequent undesirable effects such as somnolence and respiratory depression. Oxycodone hydrochloride containing products should be avoided in patients with a history of or present alcohol, drug or medicines abuse.

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Section 4.4 Special warnings and precautions)

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue oxycodone if serotonin syndrome is

suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see Section 4.4 Special warnings and precautions).

Coumarin derivatives
Opiate agonists have been reported to potentiate the anticoagulant activity of coumarin derivatives. Clinically relevant changes in International Normalised Ratio (INR or Quick-value) in both directions were observed when oxycodone and coumarin anticoagulants were co-administered.

CYP2D6 and CYP3A4 inhibitors and inducers
Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, or dietary elements. ***Targin***® tablets doses may need to be adjusted accordingly.

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone.

CYP3A4 inhibitors, such as macrolide antibiotics (eg. clarithromycin), azole-antifungal agents (eg. ketoconazole), protease inhibitors (eg. ritonavir), and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

CYP3A4 inducers, such as rifampin, carbamazepine, phenytoin and St. John's wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations.

Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with ***Targin***® tablets.

In vitro metabolic studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, ***Targin***® tablets are not expected to cause clinically relevant interactions with other concomitantly administered drugs metabolised over the CYP isomers, CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4. In addition, the likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal. *In vitro* data also suggest that the dopamine agonists, ropinirole, (S)-pramipexole and levodopa have little or no effect on either oxycodone or naloxone major metabolic pathways. Rotigotine had little effect on oxycodone metabolism, and inhibited naloxone metabolism only at concentrations considerably greater than anticipated clinical plasma rotigotine concentrations associated with RLS treatment.

CNS adverse effects associated with dopamine agonists and oxycodone are similar and concurrent use for the treatment of RLS was not assessed in the pivotal RLS study.

Metoclopramide
Concurrent use with oxycodone may antagonise the effects of metoclopramide on gastrointestinal motility.

Monoamine Oxidase Inhibitors (MAOIs)
Non-selective MAOIs intensify the effects of opioid drugs which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients

concurrently administered MAOIs and pethidine. Oxycodone should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. As it is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and oxycodone, caution is advised with this drug combination.

Neuromuscular blocking agents
Oxycodone may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Opioid agonist analgesics (including morphine, pethidine)
Additive CNS-depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

Opioid agonist-antagonist analgesics (including pentazocine, butorphanol, buprenorphine)
Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms.

Dopaminergic agents
Concomitant use of dopaminergic agents and ***Targin***® tablets for the treatment of RLS is not recommended because efficacy and safety have not been assessed in the clinical study and both medicines are CNS depressants. If dopaminergic agents are used for the management of Parkinson's disease in patients taking ***Targin***® tablets then the dose of each medicine may need to be reduced.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies have been conducted on the reproductive toxicity of the combination of oxycodone and naloxone. In reproductive toxicology studies of oxycodone alone, no evidence of impaired fertility was seen in male or female rats at oral oxycodone doses of 8 mg/kg/day, approximately half the oxycodone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis. There were also no effects on fertility in rats following oral administration of naloxone at doses up to 800 mg/kg/day, which is about 90-fold the naloxone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis.

No human data on the effect of oxycodone and naloxone on fertility are available.

Despite these fertility studies in animals, prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes, and irregular menses in women.

Use in pregnancy
Targin® tablets are contraindicated in pregnancy. Oxycodone and naloxone pass into the placenta. There are no adequate and well-controlled studies on the use of ***Targin***® tablets in pregnant women and during childbirth. Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn child, and may cause respiratory depression during childbirth. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

No studies have been conducted on the reproductive toxicity of the combination of oxycodone and naloxone. There was no evidence of teratogenicity following oral administration of oxycodone during the period of organogenesis to rats at doses up to 7.2 mg/kg/day (approximately half the oxycodone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis) or to rabbits at doses of up to 112 mg/kg/day (approximately 12-fold the oxycodone dose at the maximal recommended clinical dose of ***Targin***® tablets). There was also no evidence of teratogenicity following oral administration of naloxone during the period of organogenesis to rats and rabbits at

respective doses up to 800 and 400 mg/kg/day, which are more than 80-fold the naloxone dose at the maximal recommended clinical dose of ***Targin***® tablets on a body surface area basis.

Because animal reproduction studies are not always predictive of human responses, this drug should not be used during pregnancy.

Use in lactation
Targin® tablets are contraindicated during lactation. Oxycodone passes into breast milk. A milk:plasma ratio of 3.4:1 was measured, and withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped.

Oral administration of oxycodone to rats from early gestation to weaning did not affect postnatal development parameters at doses up to 6 mg/kg/day (about one-third the oxycodone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis). Oral administration of naloxone to rats from prior to mating to weaning, or from late gestation to weaning, did not affect reproductive or developmental indices up to 800 mg/kg/day (about 90-fold the naloxone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis).

It is not known if naloxone also passes into breast milk. ***Targin***® tablets should not be taken by breastfeeding mothers prior to the infant being weaned

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Targin® tablets may impair the ability to drive and operate machinery, particularly at the commencement of treatment, after dosage increase or opioid rotation, and if ***Targin***® tablets are combined with alcohol or other CNS depressants. The degree of driving impairment can depend upon the dosage and individual susceptibility, and some patients stabilised on a specific dosage may not be affected. All patients should consult with their physician and should not drive or operate machinery if their ability is impaired.

Patients who have experienced somnolence and/or an episode of sudden sleep onset must not drive or operate machinery. Additionally, a dose reduction or termination of therapy may be considered. Because of possible addictive effects, caution should be advised when patients are taking other sedating medicinal products in combination with ***Targin***® tablets (see section 4.5 Interaction with other medicine).

4.8 ADVERSE EFFECTS

Analgesia
Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time. The naloxone in ***Targin***® tablets reduces bowel function disorders such as constipation that typically arise during oxycodone analgesic treatment. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability. A reduction in pre-existing laxatives may be appropriate when initiating ***Targin***® tablets in opioid-treated patients.

The following adverse events were reported in the pivotal trials, during the double-blind phase, without attributing causality.

The incidence of adverse events for ***Targin***® tablets and active comparator reported in ≥ 1% of subjects by system organ class (≥ 10%) and preferred term in the double-blind phase of pivotal clinical study **OXN3001**:

TABLE 2

Adverse Events in Study OXN3001:	***Targin*® tablets dose:** Equivalent to ***OxyContin*®** tablets		**Active Comparator:** ***OxyContin*®** tablets 20-50 mg/day	
	(N=162)	(%)	(N=160)	(%)
Gastrointestinal disorders				
Dyspepsia	1	(0.6%)	4	(2.5%)
Diarrhoea	9	(5.6%)	11	(6.9%)
Constipation	1	(0.6%)	8	(5.0%)
Abdominal pain	2	(1.2%)	7	(4.4%)
Abdominal pain upper	2	(1.2%)	2	(1.3%)
Nausea	10	(6.2%)	17	(10.6%)
Vomiting	2	(1.2%)	7	(4.4%)
Infections & infestations				
Urinary Tract Infection	9	(5.6%)	4	(2.5%)
Bronchitis	3	(1.9%)	1	(0.6%)
Cystitis	0	(0.0%)	4	(2.5%)
Nasopharyngitis	4	(2.5%)	8	(5.0%)
Lower Respiratory Tract Infection	3	(1.9%)	3	(1.9%)
Gastroenteritis	3	(1.9%)	3	(1.9%)
Musculoskeletal & connective tissue disorders				
Neck pain	2	(1.2%)	3	(1.9%)
Myalgia	3	(1.9%)	2	(1.3%)
Back pain	7	(4.3%)	5	(3.1%)
Arthralgia	4	(2.5%)	5	(3.1%)
Nervous system disorders				
Dizziness	5	(3.1%)	9	(5.6%)
Headache	5	(3.1%)	6	(3.8%)
Tremor	2	(1.2%)	3	(1.9%)

Incidence of adverse events for ***Targin*®** tablets and active comparator reported in ≥ 1% of subjects by system organ class (≥ 10 %) and preferred term in the double-blind phase of pivotal clinical study **OXN3006**:

TABLE 3

Adverse Events in Study OXN3006:	***Targin*® tablets dose:** Equivalent to OxyContin® tablets		**Active Comparator:** OxyContin® tablets 60-80 mg/day	
	(N=130)	(%)	(N=135)	(%)
Gastrointestinal disorders				
Abdominal pain	10	(7.7%)	2	(1.5%)
Abdominal pain upper	4	(3.1%)	3	(2.2%)
Constipation	1	(0.8%)	2	(1.5%)
Diarrhoea	6	(4.6%)	4	(3.0%)
Dry mouth	1	(0.8%)	2	(1.5%)
Nausea	13	(10.0%)	9	(6.7%)
Vomiting	4	(3.1%)	1	(0.7%)
General disorders & admin. site conditions				
Chest pain	2	(1.5%)	1	(0.7%)
Chills	3	(2.3%)	2	(1.5%)
Drug withdrawal syndrome	0	(0.0%)	4	(3.0%)
Fatigue	2	(1.5%)	4	(3.0%)

Feeling cold	3	(2.3%)	0	(0.0%)
Pain	10	(7.7%)	5	(3.7%)
Infections & infestations				
Gastroenteritis	2	(1.5%)	4	(3.0%)
Influenza	1	(0.8%)	4	(3.0%)
Nasopharyngitis	1	(0.8%)	3	(2.2%)
Sinusitis	2	(1.5%)	2	(1.5%)
Urinary Tract Infection	4	(3.1%)	2	(1.5%)
Musculoskeletal & connective tissue disorders				
Arthralgia	2	(1.5%)	1	(0.7%)
Back pain	5	(3.8%)	5	(3.7%)
Osteoarthritis	1	(0.8%)	3	(2.2%)
Nervous system disorders				
Dizziness	1	(0.8%)	2	(1.5%)
Headache	7	(5.4%)	5	(3.7%)
Sciatica	5	(3.8%)	0	(0.0%)

Incidence of adverse events for ***Targin***® tablets, active comparator and placebo reported in ≥ 2% of subjects by system organ class (>10 %) and preferred term in the double-blind phase of pivotal clinical study **OXN3401**:

TABLE 4

Adverse Events in Study OXN3401:	***Targin***® **tablets dose:** Equivalent to *OxyContin*® tablets		**Active Comparator:** *OxyContin*® tablets 20-40 mg/day		**Placebo**
	(N=154)	(%)	(N=151)	(%)	(N=158) (%)
Ear & labyrinth disorders					
Vertigo	2	(1.3%)	5	(3.3%)	5 (3.2%)
Gastrointestinal disorder					
Constipation	13	(8.4%)	18	(11.9%)	8 (5.1%)
Diarrhoea	8	(5.2%)	4	(2.6%)	7 (4.4%)
Dyspepsia	3	(1.9%)	7	(4.6%)	3 (1.9%)
Nausea	10	(6.5%)	12	(7.9%)	11 (7.0%)
Vomiting	8	(5.2%)	7	(4.6%)	5 (3.2%)
General disorders & admin. site conditions					
Fatigue	4	(2.6%)	8	(5.3%)	4 (2.5%)
Infections and infestations					
Nasopharyngitis	2	(1.3%)	5	(3.3%)	4 (2.5%)
Investigations					
Blood triglycerides increased	3	(1.9%)	5	(3.3%)	3 (1.9%)
Nervous system disorders					
Dizziness	2	(1.3%)	9	(6.0%)	6 (3.8%)
Headache	5	(3.2%)	6	(4.0%)	11 (7.0%)
Skin & subcutaneous tissue disorders					
Hyperhidrosis	5	(3.2%)	2	(1.3%)	7 (4.4%)
Pruritus	5	(3.2%)	3	(2.0%)	4 (2.5%)

Adverse drug reactions attributable to ***Targin***® tablets were reported at the frequencies below:
Very common: ≥ 10%
Common: ≥ 1% and < 10%

Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01% or
Not known: (cannot be estimated from the available data)

The adverse drug reactions listed below are taken cumulatively from clinical trial data and post-marketing data.

Cardiac disorders
Uncommon palpitations (in the context of withdrawal symptoms)

Ear and labyrinth disorders
Common vertigo

Endocrine disorders
Not known adrenal insufficiency, androgen deficiency

Eye disorders
Uncommon visual impairment

Gastrointestinal disorders
Common abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting
Uncommon flatulence
Not known eructation, pancreatitis

General disorders and application site conditions
Common asthenic conditions, fatigue
Uncommon chest pain, chills, malaise, peripheral oedema, thirst
Not Known drug withdrawal syndrome

Hepatobiliary disorders
Uncommon hepatic enzymes increased

Immune system disorders
Uncommon hypersensitivity

Injury, poisoning and procedural complications
Uncommon injuries from accidents

Metabolism and nutrition disorders
Common decreased appetite

Musculoskeletal and connective tissue disorders
Uncommon muscle spasms, muscle twitching, myalgia

Nervous system disorders
Common dizziness, headache, somnolence
Uncommon disturbance in attention, dysgeusia, speech disorder, tremor, convulsion (particularly in persons with epileptic disorder or predisposition to convulsions), syncope, lethargy
Not known sedation, paraesthesia, sleep apnoea syndrome

Psychiatric disorders
Common insomnia
Uncommon anxiety, confusional state, depression, nervousness, restlessness, abnormal thinking,

	libido decreased
Not known	nightmares, euphoric mood, hallucinations, aggression, drug dependence (see section 4.4- Special warnings and precautions for use)

Renal and urinary disorders

Uncommon	micturition urgency
Not known	urinary retention

Reproduction system and breast disorders

Not known	erectile dysfunction

Respiratory, thoracic and mediastinal disorders

Uncommon	dyspnoea
Not known	respiratory depression, central sleep apnoea syndrome

Skin and subcutaneous tissue disorders

Common	hyperhidrosis, pruritus, rash

Vascular disorders

Common	hot flush
Uncommon	increase in blood pressure, decrease in blood pressure

The following additional adverse events are known for oxycodone:
Due to its pharmacological properties, oxycodone may cause respiratory depression, miosis, bronchial spasm, and spasms of non-striated muscles as well as suppress the cough reflex.

Ear and labyrinth disorders

Uncommon	tinnitus

Eye disorders

Uncommon	miosis

Gastrointestinal disorders

Common	gastritis, hiccup
Uncommon	colic, dysphagia, gastrointestinal disorder, ileus, stomatitis
Not known	dental caries

General disorders and administration site conditions

Common	fever
Uncommon	facial flushing, lymphadenopathy, neck pain, oedema
Not known	drug withdrawal syndrome neonatal, drug tolerance

Hepatobiliary disorders

Uncommon	biliary spasm
Not known	cholestasis, sphincter of Oddi dysfunction

Immune system disorders

Uncommon	allergic reaction, anaphylactoid reaction
Not known	anaphylactic reaction

Metabolism and nutrition disorders

Uncommon	dehydration, hyponatraemia
Rare	increased appetite

Musculoskeletal and connective tissue disorders
Uncommon involuntary muscle contractions, muscular rigidity

Nervous system disorders
Common faintness
Uncommon amnesia, drowsiness, gait abnormal, hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, stupor
Not known hyperalgesia

Psychiatric disorders
Common mood changes
Uncommon agitation, affect lability, disorientation, dysphoria

Renal and urinary disorders
Common ureteric spasm, urinary abnormalities, urinary tract infection

Reproductive system and breast disorders
Uncommon hypogonadism
Not known amenorrhoea

Respiratory, thoracic and mediastinal disorders
Common bronchospasm, pharyngitis, voice alteration

Skin and subcutaneous tissue disorders
Uncommon dry skin, exfoliative dermatitis
Rare urticaria

Vascular disorders
Common orthostatic hypotension
Uncommon migraine, vasodilatation

Drug dependence
The frequencies in the above table regarding drug dependence, drug withdrawal syndrome and drug tolerance reflects that although risk is low with short term and low dose use, it is highly variable.

Repeated use of ***Targin***® can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4- Special warnings and precautions for use).

Management of common adverse effects
If nausea and vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation must be treated with appropriate laxatives. Overdose may produce respiratory depression. Compared with other opioids, oxycodone is associated with low histamine release although urticaria and pruritus may occur.

Restless Legs Syndrome
Adverse drug reactions reported in clinical Study OXN3502 are consistent with the expected safety profile of opioid analgesics. These adverse events are not unexpected in a study of an active opioid treatment and inactive placebo, and consistent with observations from studies of dopaminergic agents versus placebo in RLS.

Adverse drug reactions associated with ***Targin***® in pain and not observed in RLS study population were added with the frequency of not known.

TABLE 5

Adverse Event Reports (≥ 5%) in Clinical Trial OXN3502			
System Organ Class Preferred Term	***Targin***® (N=150) n(%)	Placebo (N=154) n(%)	Total (N=304) n(%)
Subjects with at least one related AE	109 (72.7%)	66 (42.9%)	175 (57.6%)
Definitely	25 (16.7%)	3 (1.9%)	28 (9.2%)
Possibly	30 (20.0%)	29 (18.8%)	59 (19.4%)
Probably	45 (30.0%)	26 (16.9%)	71 (23.4%)
Unlikely	9 (6.0%)	8 (5.2%)	17 (5.6%)
GASTROINTESTINAL DISORDERS	55 (36.7%)	25 (16.2%)	80 (26.3%)
Constipation	29 (19.3%)	7 (4.5%)	36 (11.8%)
Dry mouth	12 (8.0%)	3 (1.9%)	15 (4.9%)
Nausea	26 (17.3%)	14 (9.1%)	40 (13.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	49 (32.7%)	29 (18.8%)	78 (25.7%)
Fatigue	44 (29.3%)	20 (13.0%)	64 (21.1%)
INVESTIGATIONS	20 (13.3%)	16 (10.4%)	36 (11.8%)
NERVOUS SYSTEM DISORDERS	42 (28.0%)	27 (17.5%)	69 (22.7%)
Dizziness	13 (8.7%)	4 (2.6%)	17 (5.6%)
Headache	20 (13.3%)	11 (7.1%)	31 (10.2%)
Somnolence	16 (10.7%)	7 (4.5%)	23 (7.6%)
PSYCHIATRIC DISORDERS	14 (9.3%)	9 (5.8%)	23 (7.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	30 (20.0%)	11 (7.1%)	41 (13.5%)
Hyperhidrosis	18 (12.0%)	6 (3.9%)	24 (7.9%)
Pruritus	11 (7.3%)	4 (2.6%)	15 (4.9%)

AE: Adverse event. N: Number of subjects in population.
n: Number of subjects with data available. %: Percentage based on N.

Immune system disorders
Not known: Hypersensitivity

Metabolism and nutrition disorders
Common: Decreased appetite up to loss of appetite

Psychiatric disorders
Common: Insomnia, depression
Uncommon: Libido decreased, sleep attacks
Not known: Abnormal thinking, anxiety, confusion, nervousness, restlessness, euphoric mood, hallucination, nightmares

Nervous system disorders
Very common: Headache, somnolence
Common: Dizziness, disturbance in attention, tremor, paraesthesia
Uncommon: Dysgeusia
Not known: Convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), sedation, speech disorder, syncope

Eye disorders

Common: Visual impairment

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Not known: Angina pectoris in particular in patients with history of coronary artery disease, palpitations, tachycardia

Vascular disorders
Common: Hot flush, blood pressure decreased, blood pressure increased

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Not known: Cough, rhinorrhoea, respiratory depression, yawning

Gastrointestinal disorders
Very common: Constipation, nausea
Common: Abdominal pain, dry mouth, vomiting
Uncommon: Flatulence
Not known: Abdominal distension, diarrhoea, dyspepsia, eructation, tooth disorder

Hepatobiliary disorders
Common: Hepatic enzymes increased (alanine aminotransferase increased, gamma glutamyltransferase increased)
Not known: Biliary colic

Skin and subcutaneous tissue disorders
Very common: Hyperhidrosis
Common: Pruritus, skin reactions

Musculoskeletal and connective tissue disorders
Not known: Muscle spasms, muscle twitching, myalgia

Renal and urinary disorders
Not known: Micturition urgency, urinary retention

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

General disorders and administration site conditions
Very common: Fatigue
Common: Chest pain, chills, thirst, pain
Uncommon: Drug withdrawal syndrome, oedema peripheral
Not known: Malaise

Investigation
Not known: Weight decreased, weight increased

Injury, poisoning and procedural complications
Uncommon: Injuries from accidents

Postmarketing Experience:
Serotonin syndrome (see section 4.4 Special warnings and precaution for use)

Adrenal insufficiency (see section 4.4 Special warnings and precaution for use)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypotha/amic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

4.9 OVERDOSAGE

Depending upon the history of the patient, an overdose of ***Targin***® tablets may be manifested by symptoms triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist). However, symptoms of naloxone overdosage are unlikely (treat symptomatically in a closely-supervised environment).

Symptoms of oxycodone overdosage

Acute overdose with oxycodone can be manifested by miosis (dilated if hypoxia is severe), cold and/or clammy skin, respiratory depression (reduced respiratory rate and/or tidal volume, cyanosis), extreme somnolence progressing to stupor or coma, hypotonia, bradycardia and hypotension. Toxic leukoencephalopathy has been observed with oxycodone overdose. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more serious cases, and may lead to a fatal outcome.

The features of overdosage may be delayed with a controlled release product such as ***Targin***® tablets.

Treatment of oxycodone overdosage

Primary attention should be given to immediate supportive therapy with the establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Adequate body temperature and fluid balance should be maintained.

Oxygen, intravenous fluids, vasopressors, infusions and other supportive measures 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 and fluid and electrolyte metabolism maintained.

Activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. Administration of activated charcoal should be restricted to patients who are fully conscious with an intact gag reflex or protected airway. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Whole bowel irrigation (e.g. 1 or 2 litres of polyethylene glycol solution orally per hour until rectal effluent is clear) may be useful for gut decontamination. Whole bowel irrigation is contraindicated in patients with bowel obstruction, perforation, ileus, haemodynamic instability or compromised, unprotected airways and should be used cautiously in debilitated patients and where the condition may be further compromised. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the effectiveness of the charcoal (there may be competition for the charcoal binding site between the polyethylene glycol and the ingested drugs) but the clinical relevance is uncertain.

Prolonged periods of observation (days) may be required for patients who have overdosed with long-acting preparations.

If there are signs of clinically significant respiratory or cardiovascular depression, an opioid antagonist should be considered. Naloxone hydrochloride at a dose of 0.4-2 mg intravenously is a specific antidote for respiratory depression due to overdosage or as a result of unusual sensitivity to oxycodone (please refer to naloxone product information for further information). Concomitant efforts at respiratory resuscitation should be carried out. Administration of naloxone should be repeated at 2-3 minute intervals, as clinically necessary. An infusion of 2 mg naloxone in 500 mL of 0.9% sodium chloride or 5% dextrose (0.004 mg/mL naloxone), run at a rate aligned to previously administered bolus doses and to the patient's response, is also a possible alternative.

The duration of action of oxycodone may exceed that of the antagonist. Consequently, the patient should remain under continued surveillance and dosing of the antagonist continued as needed to maintain adequate respiration.

In an individual physically dependent on opioids, administering opioid antagonists may precipitate a withdrawal syndrome and should be avoided if possible. Withdrawal syndrome may lead to agitation, hypertension, tachycardia and risk of vomiting with possible aspiration. The severity of withdrawal depends on the degree of dependence and the antagonist dose. If required for serious respiratory depression, the antagonist should be administered with extreme care, commencing with 10 to 20% of the usual recommended initial dose and titrating.

Toxicity
Due to the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Crushing and taking the contents of a controlled release dosage form leads to the release of oxycodone in an immediate fashion; this might result in a fatal overdose. The toxic effects and signs of overdosage may be less pronounced than expected, when pain and/or tolerance are manifest.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Actions
Oxycodone is a full opioid receptor agonist whose principal therapeutic action is analgesia. It has an affinity for endogenous mu, kappa and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Binding of oxycodone to endogenous opioid receptors in the central nervous system (CNS) results in pain relief. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the CNS (respiratory depression, antitussive, anxiolytic, sedative and miosis), smooth muscle (constipation, reduced gastric, biliary and pancreatic secretions, sphincter of Oddi spasm and transient elevations in serum amylase), and cardiovascular system *via* histamine release and peripheral vasodilation (pruritus, flushing, red eyes, sweating and orthostatic hypotension).

Non-clinical studies have demonstrated differing immunomodulatory effects of naturally occurring opioids e.g. morphine, codeine. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects.

Naloxone also has an affinity for endogenous opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). However, in contrast to oxycodone, naloxone is a competitive opioid antagonist at opiate receptors, which can prevent or reverse the effects of opioid agonists.

Naloxone reduces bowel function disorders such as constipation that typically arise during opioid

analgesic treatment with e.g. oxycodone, due to its local competitive antagonism of the opioid receptor-mediated oxycodone effect in the gut. Diarrhoea may be a possible effect of naloxone, especially at the beginning of treatment, and tends to be transient. Oral administration of naloxone is unlikely to result in a clinically relevant systemic effect due to a pronounced first-pass effect and its very low oral bioavailability upon oral administration (<3%).

The addition of naloxone at doses from 10 to 100 mg daily to methadone-stabilised opioid addicts increased the frequency of bowel movements in a dose-dependent manner, with an effect seen starting from a naloxone dose of 20 mg daily. Oral naloxone also induced withdrawal symptoms in these methadone-stabilised opioid addicts with a positive correlation between the methadone dose and the naloxone dose at which withdrawal occurred (p=0.02). Overall, the median dose of oral naloxone that induced clear symptoms of withdrawal appeared to be 70 mg daily. The onset of bowel movement and withdrawal was usually within the first 6 hours of naloxone administration.

Clinical Trials

Analgesia

1. Study 3001:

This 12-week randomised, double-blind, parallel-group study, in patients with non-malignant pain experiencing opioid-induced constipation, assessed constipation symptoms (as measured by the Bowel Function Index [BFI]) in patients taking ***Targin***® tablets compared with those taking oxycodone controlled release (CR) tablets. 272 patients were randomised to the double-blind phase (136 in each group), with the oxycodone dose between 20-50 mg/day. A secondary objective was to estimate the Average Pain over the last 24 hours (as measured by the Pain Intensity Scale) at each double-blind visit.

Patients in the ***Targin***® tablets group showed an improved bowel function compared with those on oxycodone CR tablets from one week after the start of the double-blind phase (Visit 4), continuing until the end of the study (Visit 8). Statistical significance was seen by four weeks/Visit 6 (15.2; p<0.0001; CI -18.2 to -12.2). The mean pain intensity scores for Average Pain over the last 24 hours were comparable between the two groups, which was maintained until the end of the study with no significant treatment differences seen (0.014; 95% CI; -0.2026 to 0.2304). The safety profile of ***Targin***® tablets is consistent with those of other strong opioids.

2. Study 3006:

This 12-week randomised, double-blind, parallel-group study, in patients with non-malignant pain experiencing opioid-induced constipation, also assessed constipation symptoms (measured by BFI) in patients taking ***Targin***® tablets compared with those taking oxycodone CR tablets. 278 patients were randomised to the double-blind phase (130 on ***Targin***® tablets, 135 on oxycodone CR tablets, 13 were excluded because of study questionnaire irregularities), and the oxycodone dose for each group was between 60 and 80 mg/day.

Throughout the first 4 weeks of the double-blind phase (Visits 3-6), the difference between the mean BFI scores for the two groups was statistically significant in favour of ***Targin***® tablets (-14.9; p<0.0001; CI -17.9 to -11.9). The actual observed difference of the means was -12.3 (***Targin***® tablets 40.94; oxycodone CR 53.27). Patients in the ***Targin***® tablets group had a reduced mean observed BFI score from one week after randomisation into the double-blind phase (Visit 4), continuing to the end of the study (Visit 8), but this was not seen for the oxycodone CR tablet group. The mean pain intensity scores for Average Pain over the last 24 hours were comparable between the groups at baseline (Visit 3), and this was maintained throughout the double-blind phase until the end of the study (Visit 8), with no significant treatment differences seen between the two groups (model estimated treatment difference: 0.010; 95% CI; -0.14 to 0.34). The safety profile of ***Targin***® tablets is consistent with those of other strong opioids.

3. Study OXN1006:

This open-label, single-dose, parallel-group study, compared the pharmacokinetics of oxycodone and

naloxone from an oxycodone/naloxone (OXN) prolonged-release (PR) tablet 10/5 mg in patients with varying degrees of hepatic impairment and healthy volunteers.
Significant differences in pharmacokinetic parameters between subjects with hepatic impairment (rated as mild, moderate or severe) and healthy volunteers were seen as summarised in the following table (values indicate % of healthy volunteer result):

TABLE 6

	Mild (x% (90% CI))	Moderate (x% (90% CI))	Severe (x% (90% CI))
Oxycodone			
▪ AUC_{INF}	143% (111, 184)	319% (248, 411)	310% (241, 398)
▪ C_{max}	120% (99, 144)	201% (166, 242)	191% (158, 231)
▪ $t_{1/2Z}$	108% (70, 146)	176% (138, 215)	183% (145, 211)
Naloxone			
▪ AUCt	411% (152, 1112)	11518% (4259, 31149)	10666% (3944, 28847)
▪ C_{max}	193% (115, 324)	5292% (3148, 8896)	5252% (3124, 8830)
	$t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not able to be calculated due to insufficient amount of data available. The bioavailability comparisons for naloxone were therefore based on AUCt values.		
Naloxone-3-glucuronide			
▪ AUC_{INF}	157% (89, 279)	128% (72, 227)	125% (71, 222)
▪ Cmax	141% (100, 197)	118% (84, 166)	98% (70, 137)
▪ $t_{1/2Z}$[1]	117% (72, 161)	77% (32, 121)	94% (49, 139)

[1] Terminal phase half-life

4. Study OXN1007:
This open-label, single-dose, parallel-group study, compared the pharmacokinetics of oxycodone and naloxone from an oxycodone/naloxone (OXN) prolonged release (PR) tablet 10/5 mg in patients with varying degrees of renal impairment and healthy volunteers.
Significant differences in pharmacokinetic parameters between subjects with renal impairment (rated as mild, moderate or severe) and healthy volunteers were seen as summarised in the following table (values indicate % of healthy volunteer result):

TABLE 7

	Mild (x% (90% CI))	Moderate (x% (90% CI))	Severe (x% (90% CI))
Oxycodone			
▪ AUC_{INF}	153% (130, 182)	166% (140, 196)	224% (190, 266)
▪ C_{max}	110% (94, 129)	135% (115, 159)	167% (142, 196)
▪ $t_{1/2Z}$	149%	123%	142%
Naloxone			
▪ AUCt	2850% (369, 22042)	3910% (506, 30243)	7612% (984, 58871)
▪ C_{max}	1076% (154, 7502)	858% (123, 5981)	1675% (240, 11676)
	Due to insufficient amount of data available, $t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values. The ratios may have been influenced by the inability to fully characterise the naloxone plasma profiles for healthy subjects.		
Naloxone-3-glucuronide			
▪ AUC_{INF}	220% (148, 327)	370% (249, 550)	525% (354, 781)
▪ C_{max}	148% (110, 197)	202% (151, 271)	239% (179, 320)
▪ $t_{1/2Z}$	No change	No change	No change

5. Study OXN3506:

The efficacy of ***Targin***® tablets doses up to 160/80 mg daily was assessed in a randomised, doubleblind, double-dummy, parallel-group, multiple-dose study in 243 patients with non-malignant or malignant pain requiring high doses of opioids and suffering from constipation caused/ aggravated by opioids. Patients were treated with ***Targin***® tablets (in the range of 50/25 to 80/40mg twice daily) or oxycodone controlled release (CR) tablets (in the range of 50 – 80mg twice daily) for up to 5 weeks. The primary objectives were to demonstrate that subjects taking ***Targin***® tablets have improvement in symptoms of constipation as measured by the Bowel Function Index (BFI) compared to subjects taking oxycodone CR tablets alone, and to demonstrate non-inferiority of ***Targin***® tablets compared to oxycodone CR tablets with respect to the analgesic efficacy based on the subject's 'Average Pain over last 24 Hours'

TABLE 8

Number of Patients Receiving ≥ 100 mg/d by Treatment Group

Dose level (mg/d)	***Targin***® (N=121)	Oxycodone (N=116)
100	40 (33.1%)	42 (36.2%)
120	26 (21.5%)	30 (25.9%)
140	15 (12.4)	13 (11.2%)
160	31 (25.6)	28 (24.1%)

The results show a clinically relevant and statistically significant improvement of the BFI scores in the ***Targin***® group compared to oxycodone CR tablets. The improvements consistently appeared in the Full Analysis (FA) as well as the Per Protocol (PP) population, in all the subgroups, in sensitivity analysis with Last Observation Carried Forward (LOCF) imputation, and in all 3 single BFI parameters.

TABLE 9

BFI observed values (FA population)					
Time point		***Targin***®		oxycodone CR	
		Value	Change from baseline	Value	Change from baseline
Baseline	n	121		116	
	Mean (SD)	68.1 (19.27)		66.7 (21.86)	
	Median	70.0		70.0	
	Min, Max	0, 100		0, 100	
Week 5	n	104	104	101	**101**
	Mean (SD)	37.0 (24.43)	-32.5 (26.96)	52.4 (27.39)	-14.2 (22.65)
	Median	33.3	-30.0	58.3	-10.0
	Min, Max	0, 97	-93, 20	0, 100	**-80, 27**

In the FA population at week 1 the mean BFI decreased by -28.3 in the ***Targin***® group and by -13.1 in the oxycodone CR tablets group. A median decrease of -23.3 in the ***Targin***® group compared with -6.7 in the oxycodone CR tablets group was observed.

At week 5, the mean BFI scores for the two groups was statistically significant ($p<0.001$, CI: -22.23, -9.86) and clinically relevant in favour of ***Targin***® group (mean difference -16.05 ±3.14) and an improvement in BFI was confirmed with ***Targin***® compared with oxycodone CR tablets ($p<0.001$, CI: -20.60, -8.40).

The pain value at the beginning of the double-blind phase served as the baseline value. No clinically relevant change to baseline was observed throughout the double-blind phase. At week 5 the mean

change to baseline was 0.1 in the ***Targin***® group and 0.0 in the oxycodone CR tablets group.

The average pain intensity over the last 24 hours was comparable between the two groups and was maintained until the end of the study. ***Targin***® was not more than 20% less effective than oxycodone CR alone in providing analgesia ($p<0.001$).

Restless Legs Syndrome
Study OXN3502:
This 12-week randomised, double-blind placebo-controlled, parallel-group, multicentre study, assessed the efficacy and safety in the symptomatic treatment of patients with moderate to severe idiopathic RLS with daytime symptoms and an inadequate responses to dopaminergic treatment. Dopaminergic agents were not permitted during the study.

The study comprised a pre-randomisation phase of up to 24 days (including a wash-out period of 7 - 10 days), a double-blind treatment phase of 12 weeks, and an open-label extension phase of 40 weeks.

The study's primary objective was to demonstrate superior efficacy of ***Targin***® compared to placebo in the improvement of symptom severity of RLS as measured by the International Restless Legs Syndrome Study Group Rating Scale total score (IRLS scale).
(IRLS scale: 0 to 10 = mild; 11 to 20 = moderate; 21 to 30 = severe; 31 to 40 = very severe)

The primary endpoint was the change in the IRLS score from baseline (Visit 3) to the final maintenance period assessment.

The secondary efficacy endpoints were scores measures of Clinical Global Impression (CGI), RLS-6-Rating Scale, Pain- Numeric Rating Scale (NRS) and the Quality of Life (QoL).

The 132 patients were initially treated with 5 mg oxycodone hydrochloride/ 2.5mg naloxone hydrochloride twice daily, but up-titrated to higher dose levels of ***Targin***® tablets (10/5 mg, 20/10 mg and 40/20 mg twice daily) if needed. Significant improvement of RLS during the entire treatment period was shown with a decrease in the mean IRLS score of 8.15 points with a statistically significant difference of 95% CI: 5.46, 10.85, $p<0.001$; compared to placebo (n=144) at week 12.

The onset of efficacy was demonstrated from as early as week 1 of treatment, with a decrease in the mean IRLS score of more than 10 points between baseline and week 1. Similar results were shown for the RLS symptom severity improvement (as measured by the RLS-6-Rating scale), in quality of life as measured by a QoL-RLS questionnaire, in sleep quality (measured by MOS sleep scale), and for the proportion of IRLS score remitters. No subject had a confirmed case of augmentation during the study.

Primary efficacy results presented by IRLS sum score are summarised in the following table:

TABLE 10

Visit	Statistic	***Targin***® (N=132)	Placebo (N=144)
1 (screening)	n Mean (SD) Median Min, Max	132 28.64 (5.38) 29.0 16, 38	144 27.63 (5.46) 28.0 15, 39
3 (Baseline/Randomisation)	n Mean (SD) Median	132 31.70 (4.37) 33.0	144 31.55 (4.66) 33

	Min, Max	21, 39	21, 40
4 (1 week)	n Mean (SD) Median Min, Max	128 21.02 (9.81) 22.0 0, 40	137 26.71 (7.17) 27.0 2, 39
8 (8 weeks)	n Mean (SD) Median Min, Max	102 11.55 (8.67) 11.0 0, 38	76 17.20 (10.15) 16.0 0, 38
9 (12 weeks)	n Mean (SD) Median Min, Max	129 15.11 (10.59) 12.0 0, 37	140 22.09 (12.15) 23.0 0, 40

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic characteristics of oxycodone from ***Targin***® tablets are comparable to those from controlled release ***OxyContin***® tablets, and demonstrate bioequivalence between these two long-acting oxycodone formulations. In addition, dose proportionality has been established for the ***Targin***® 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) facilitating reliable dose titration and interchangeability between tablet strengths.

Absorption

Oxycodone has a mean bioavailability of approximately 50% following oral administration in healthy volunteers. In cancer patients, an oral bioavailability of up to 87% has been reported. Following absorption, oxycodone is distributed throughout the body. Approximately 45% is bound to plasma protein.

In a study of ***Targin***® tablets in elderly subjects (≥ 65 years), plasma concentrations of oxycodone were only nominally affected by age, being approximately 18% greater in elderly compared with young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a bodyweight-adjusted basis.

Following ingestion of a high-fat breakfast, the maximum plasma concentration (C_{max}) and bioavailability of oxycodone from ***Targin***® tablets were nominally increased compared with fasting state administration, and not considered clinically relevant. ***Targin***® tablets may be taken with or without food.

Following ingestion, oral naloxone is subject to a significant first-pass metabolism and its oral bioavailability is less than 3%.

Metabolism

Oxycodone has an elimination half-life of approximately 4.8 hours and is metabolised principally in the liver *via* CYP3A4 and CYP2D6 to noroxycodone, oxymorphone, noroxymorphone, 6α and β oxycodol and conjugated glucuronides. Oxymorphone and noroxymorphone have some analgesic activity. However, oxymorphone is present in plasma at low concentrations and noroxymorphone, due to its low lipophilicity, does not penetrate the blood-brain barrier to a significant extent. Consequently, the contribution of these metabolites to the overall analgesic effect is insignificant. Oxycodone and its metabolites are excreted in urine and faeces.

After parenteral administration, naloxone has a plasma half-life of approximately one hour. Naloxone is metabolised in the liver to its principal metabolites, naloxone glucuronide, 6β-naloxol and its glucuronide,

and excreted in the urine.

Impaired hepatic function
A study has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone plasma concentrations were affected to a greater extent than oxycodone. The clinical relevance of a relatively high naloxone exposure in hepatically impaired patients is not yet known. Caution must be exercised in administering ***Targin***® tablets to patients with mild hepatic impairment. ***Targin***® tablets are contraindicated in patients with moderate to severe hepatic impairment.

Impaired renal function
A study has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment. Naloxone plasma concentrations were affected to a greater extent than oxycodone. The clinical relevance of a relatively high naloxone exposure in renally impaired patients is not yet known. Caution should be exercised when administering ***Targin***® tablets to patients with renal impairment (refer to section 4.4- Special warnings and precautions for use).

5.3 PRECLINICAL SAFETY DATA
Genotoxicity
The results of *in vitro* and *in vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone showed mutagenic activity in a mouse lymphoma assay, but was inactive in bacterial gene mutation assays. It also induced chromosomal aberrations in human lymphocytes *in vitro,* but not in immature erythrocytes *in vivo* in mice. Similar to oxycodone, naloxone induced gene mutations and chromosomal aberrations in mouse lymphoma cell lines and human lymphocytes *in vitro*, respectively, but did not induce chromosomal aberrations in immature erythrocytes under *in vivo* conditions.

Carcinogenicity
Long-term studies in animals to evaluate the carcinogenic potential of oxycodone/naloxone in combination have not been conducted.

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6mg/kg/day (equivalent to 6.8 mg/day in men and 24.6 mg/day in women, based on estimated AUC values). The doses were limited by opioid-related pharmacological effects of oxycodone.

Naloxone was not carcinogenic in a 24-month dietary study in rats at doses up to 100 mg/kg/day, which is about 11-fold the naloxone dose at the maximal recommended clinical dose of ***Targin***® tablets, on a body surface area basis.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Refer to Section 2 – Qualitative and quantitative composition

6.2 INCOMPATIBILITIES
NA

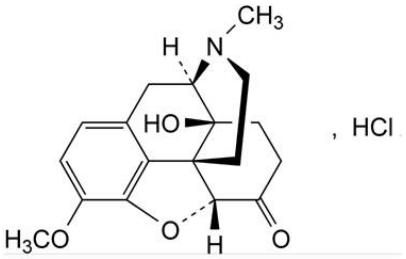
6.3 SHELF LIFE
Refer expiry date on outer packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30ºC.

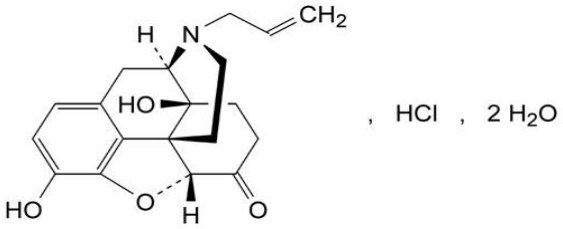
6.5 NATURE AND CONTENTS OF CONTAINER
Blister Pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
NA

6.7 PHYSIOCHEMICAL PROPERTIES
Oxycodone hydrochloride is a white, crystalline, odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether. The chemical name is 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (CAS No.: 124-90-3). The molecular formula is $C_{18}H_{21}NO_4$.HCl and molecular weight is 351.83. The pKa is 8.9 and the Partition Coefficient Log P is 0.7. The structural formula for oxycodone hydrochloride is:



Naloxone hydrochloride dihydrate is an off-white powder soluble in water. The chemical name is 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate (CAS No.: 51481-60-8). It is a synthetic congener of oxymorphone, with molecular formula $C_{19}H_{21}NO_4$.HCl.2(H_2O) and molecular weight 399.87. The pKa is 7.9 and the Partition Coefficient Log P is 1.5. The structural formula for naloxone dihydrate is:



7. MANUFACTURED BY:
Bard Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
Cambridgeshire CB4 0GW
United Kingdom

8. PRODUCT REGISTRATION HOLDER
DKSH MALAYSIA SDN BHD
B-11-01, The Ascent, Paradigm,
No. 1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya,
Selangor, Malaysia.

9. DATE OF REVISION
19 Jan 2026 (based on CCDS V15 & AUS PI- 10 Nov 2025)

®: TARGIN and OXYCONTIN are Registered Trademarks.