

TARGIN[®] Tablets

Oxycodone hydrochloride and naloxone hydrochloride dihydrate

Presentation

TARGIN[®] tablets are available as oblong, unscored film-coated tablets as follows:

- 5 mg anhydrous oxycodone hydrochloride/2.5 mg anhydrous naloxone hydrochloride (as the dihydrate) (light blue, marked "OXN" on one side and "5" on other)
- 10 mg anhydrous oxycodone hydrochloride/5 mg anhydrous naloxone hydrochloride (as the dihydrate) (white, marked "OXN" on one side and "10" on other)
- 20 mg anhydrous oxycodone hydrochloride/10 mg anhydrous naloxone hydrochloride (as the dihydrate) (pink, marked "OXN" on one side and "20" on other)
- 40 mg anhydrous oxycodone hydrochloride/20 mg anhydrous naloxone hydrochloride (as the dihydrate) (yellow, marked "OXN" on one side and "40" on other)

Uses

Actions

Oxycodone HCl is an opioid agonist with no antagonistic action. Its effects are similar to those of morphine.

The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Other Pharmacologic Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Naloxone also has an affinity for endogenous opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). However, in contrast, 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. 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 increases 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.

Pharmacokinetics

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[®] 5/2.5mg, 10/5mg, 20/10mg and 40/20mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) facilitating reliable dose titration and interchangeability between tablet strengths.

Absorption

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high bioavailability of up to 87% following oral administration. 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 to 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 and Elimination

Oxycodone has an elimination half-life of approximately 3 hours and is metabolised principally in the liver *via* the cytochrome P450 enzyme system, to noroxycodone, oxymorphone, noroxymorphone, 6 α 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, 6 β -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. In patients with moderate to severe hepatic impairment, TARGIN[®] tablets are contraindicated.

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 Special Risk Groups).

Indications

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

Dosage and 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.

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. 8am and 8pm). 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, elderly and children over 12 years:

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[®] 10/5 mg tablet at 12-hourly intervals, or one TARGIN[®] 5/2.5 mg tablet 12-hourly 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.

Increasing severity of pain may require an increased dosage of TARGIN[®] tablets using the 5/2.5 mg, or where appropriate, 10/5 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.

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: 10mg of oral oxycodone is equivalent to 20mg 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 TARGIN[®] tablets doses.

Due to the limited exposure of patients receiving daily doses beyond 80/40 mg, the maximum recommended daily dose of TARGIN[®] tablets is 80/40 mg (corresponding to 12-hourly administration of TARGIN[®] tablets 40/20mg). 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 with 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 upon 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 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 40/20 mg TARGIN[®] tablets are usually sufficient for the treatment of moderate to severe, chronic non-cancer pain, but higher doses of controlled release oxycodone may be required.

Children under 12 years:

Not recommended.

Contraindications

Hypersensitivity to opioids, naloxone and any of the excipients or any situation where opioids are contraindicated. Moderate to severe hepatic impairment, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, cor pulmonale, cardiac arrhythmias, uncontrolled bronchial asthma, severe chronic obstructive pulmonary disease, non-opioid induced paralytic ileus, pregnancy and 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.

Warnings and Precautions

Respiratory depression

Respiratory depression is the most important hazard of opioid preparations but occurs most frequently in overdose situations, in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia when even moderate doses may dangerously decrease respiration. TARGIN[®] tablets should be used with extreme caution in patients with a substantially decreased respiratory reserve or pre-existing respiratory depression and in patients with chronic obstructive pulmonary disease. Severe pain antagonises the respiratory depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest.

Special risk groups

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, 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 disorder 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.

Long-term opioid treatment

In patients undergoing long-term opioid treatment with higher doses of opioids, the switch to TARGIN[®] tablets can initially provoke withdrawal symptoms or diarrhoea. These patients require specific attention.

Withdrawal symptoms

TARGIN[®] tablets are not suitable for the treatment of withdrawal symptoms.

Use in chronic, non-cancer pain

The use of TARGIN[®] tablets for the treatment of chronic pain which is not due to cancer should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed;
- the pain is having a significant impact on the patient's quality of life;
- there is no psychological contraindication, drug seeking behaviour or history of prescription medicine, illicit drug or alcohol misuse.

Opioids, where clinically indicated, are one component of, and should be integrated into, a comprehensive approach to chronic non-cancer pain. Appropriate patient selection is the key to successful treatment of moderate to severe pain with opioid analgesics.

An initial comprehensive assessment should be conducted using a biopsychosocial approach to identify a cause for the pain and the appropriateness of opioid therapy - and to identify psychosocial factors that may exacerbate pain or magnify overall distress (e.g.: depression, anxiety, post-traumatic stress disorder (PTSD), borderline personality disorder, marked family stressors, history of sexual abuse). In the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Factors that may put the patient at increased risk of opioid abuse/addiction include a

personal/family history of substance, prescription medication and alcohol abuse, and major psychosocial issues (e.g.: psychological/psychiatric disorder). The use of opioids to treat predominant emotional distress should be avoided.

Generally, opioid analgesics are not initiated prior to a full initial clinical assessment and before consideration of other treatment options such as physiotherapy/exercise/rehabilitation approaches, psychosocial interventions such as CBT (cognitive-behavioural therapy) self-management approaches, and involvement of a psychologist or psychiatrist to address psychological co-morbidities which may be impacting on pain coping, and trials of other non-opioid pharmacotherapeutic or interventional strategies.

Prior to long term prescription, a trial of TARGIN[®] tablets or shorter acting opioid should be undertaken. Long term administration of TARGIN[®] tablets should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid naive patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long term therapy.

One doctor only should be responsible for the prescription and monitoring of the patient's opioid use. Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. those published by the Australian Pain Society in the Medical Journal of Australia 1997;167:30-4).

Drug Dependence

As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of oxycodone. There is potential for abuse of the drug and for development of strong psychological dependence. TARGIN[®] tablets should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

Withdrawal symptoms may occur following abrupt discontinuation of all oxycodone therapy including TARGIN[®] tablets. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Oxycodone should be used with caution and under close supervision in patients with pain not due to cancer who have a prior history of prescription medicine, alcohol or other substance abuse. However, in such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

If abused parenterally or intranasally by individuals dependent on opioid agonists, such as heroin, morphine or methadone, TARGIN[®] tablets are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone, or to intensify already present withdrawal symptoms. Abuse by those drug addicts is strongly discouraged. Parenteral venous 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.

Formulation

TARGIN[®] tablets must be swallowed whole and must not be broken, chewed or crushed, as this can lead to the rapid release of the active ingredients and absorption of a potentially fatal dose of oxycodone.

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.

Renal and hepatic impairment

TARGIN[®] tablets should be used with caution in patients with mild hepatic impairment and patients with renal impairment (refer **Pharmacokinetics**). 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 or hepatic function. Therefore, initiation of dosing in patients with mild hepatic impairment or patients with renal failure (CL_{cr}<60mL/min) should be reduced to 1/3 to 1/2 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.

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being approximately 18% greater in elderly as compared to 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.

Elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are infirm or debilitated should be reduced to 1/3 to 1/2 of the usual doses.

Use in children

TARGIN[®] tablets may be used in children from 12 years of age if clinically indicated, as both oxycodone and naloxone have been used in children.

Driving and operating dangerous machinery

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.

Carcinogenicity

Long-term studies in animals to evaluate carcinogenic potential of oxycodone/naloxone in combination and oxycodone as a single entity have not been conducted. Naloxone was not carcinogenic in a 24-month dietary study in rats at doses up to 100 mg/kg/day,

which is about 20-fold the naloxone dose at the maximal recommended clinical dose of TARGIN[®] tablets, on a body surface area basis.

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.

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 the oxycodone dose at the maximal recommended clinical dose of TARGIN[®] tablets, on a body surface area basis. There were also no effects on the fertility in rats following oral administration of naloxone at doses up to 800 mg/kg/day, which is about 180-fold for the naloxone dose at the maximal recommended clinical dose of TARGIN[®] tablets, on a body surface area basis.

Use in Pregnancy

Australian Pregnancy Categorisation C: 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. In long-term administration during pregnancy, oxycodone may lead to withdrawal symptoms in the new-born 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 reproduction 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 the oxycodone dose at the maximum recommended clinical dose of TARGIN[®] tablets, on a body surface area basis) or to rabbits at doses of up to 112 mg/kg/day (more than 20-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 is more than 160-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 breast-feeding 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 0.7-fold 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 180-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 the breast milk. TARGIN[®] tablets should not be taken by breast-feeding mothers prior to the infant being weaned.

Adverse Effects

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.

The following adverse reactions 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 $\geq 1\%$ of subjects by system organ class $\geq 10\%$ and preferred term in the double-blind phase of pivotal clinical study **OXN3001**:

Adverse Events in Study OXN3001:	TARGIN[®] tablet dose: Equivalent to OxyContin [®] tablets (N=162) (%)		Active Comparator: OxyContin [®] tablets 20-50 mg/day (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 $\geq 1\%$ of subjects by system organ class ($\geq 10\%$) and preferred term in the double-blind phase of pivotal clinical study **OXN3006**:

Adverse Events in Study OXN3006:	TARGIN [®] tablet 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 $\geq 2\%$ of subjects by system organ class ($\geq 10\%$) and preferred term in the double-blind phase of pivotal clinical study **OXN3401**:

Adverse Events in Study OXN3401:	TARGIN [®] tablet dose: Equivalent to OxyContin [®] tablets		Active Comparator: OxyContin [®] tablets 20-40 mg/day		Placebo (N=158) (%)
	(N=154)	(%)	(N=151)	(%)	
Ear & labyrinth disorders					
Vertigo	2	(1.3%)	5	(3.3%)	5 (3.2%)
Gastrointestinal disorders					
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)

Cardiac disorders

Uncommon palpitations (in the context of withdrawal symptoms)

Ear and labyrinth disorders

Common vertigo

Eye disorders

Uncommon visual disturbances

Gastrointestinal disorders

Common abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting

Uncommon eructation, flatulence

General disorders and application site conditions

Common asthenic conditions, chills

Uncommon chest pain, drug withdrawal syndrome, malaise, peripheral oedema

Hepatobiliary disorders

Common hepatic enzymes increased

Immune system disorders

Uncommon hypersensitivity

Injury, poisoning and procedural complications

Uncommon injuries from accidents

Metabolic and nutritional disorders

Common anorexia

Musculoskeletal and connective tissue disorders

Common muscle spasms, muscle twitching, myalgia

Nervous system disorders

Common dizziness, headache

Uncommon disturbance in attention, paraesthesia, somnolence, speech disorder, tremor

Rare convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), sedation, syncope

Psychiatric disorders

Uncommon anxiety, confusional state, depression, euphoria, hallucinations, insomnia, nervousness, restlessness, thinking abnormal

Rare nightmares

Renal and urinary disorders

Uncommon micturition urgency

Rare urinary retention

Reproduction system and breast disorders

Uncommon erectile dysfunction

Respiratory, thoracic and mediastinal disorders

Uncommon dyspnoea

Not known respiratory depression

Skin and subcutaneous tissue disorders

Common hyperhidrosis, pruritus, rash

Vascular disorders

Common decrease in blood pressure

Uncommon increase 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.

Cardiac disorders

Uncommon bradycardia, ST depression, supraventricular tachycardia

Ear and labyrinth disorders

Uncommon tinnitus

Eye disorders

Uncommon miosis

Gastrointestinal disorders

Common gastritis, hiccup

Uncommon colic, dental caries, dysphagia, gastrointestinal disorder, stomatitis

Not known ileus

General disorders and administration site conditions

Common drug withdrawal syndrome, fever

Uncommon facial flushing, lymphadenopathy, neck pain, oedema

Rare drug tolerance, thirst

Hepatobiliary disorders

Uncommon biliary spasm, cholestasis

Immune system disorders

Uncommon allergic reaction, anaphylactoid reaction
Very rare anaphylactic reaction

Metabolic and nutritional disorders

Uncommon hyponatraemia, increased appetite
Rare dehydration

Musculoskeletal and connective tissue disorders

Uncommon muscle contractions involuntary, muscular rigidity

Nervous system disorders

Common faintness
Uncommon amnesia, drowsiness, gait abnormal, hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, stupor, taste perversion

Psychiatric disorders

Common agitation, mood changes
Uncommon affect lability, disorientation, dysphoria, libido decreased
Not known drug dependence

Renal and urinary disorders

Common ureteric spasm, urinary abnormalities, urinary tract infection

Reproductive system and breast disorders

Rare amenorrhoea

Respiratory, thoracic and mediastinal disorders

Common bronchospasm, pharyngitis, voice alteration

Skin and subcutaneous tissue disorders

Uncommon exfoliative dermatitis
Rare dry skin
Very rare urticaria

Vascular disorders

Common orthostatic hypotension
Uncommon migraine, vasodilatation

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.

Summary of Post-marketing data

Post-marketing data are available from three Periodic Safety Update Reports (PSURs) for the period 31 March 2006 to 30 September 2007. Overall, 95 case reports were received from 5 countries, of which 66 were initial reports. A total of 205 adverse events were reported from the 95 cases, the majority being nervous system disorders (N=37), gastrointestinal disorders (N=32), psychiatric disorders (N=30), and general disorders

and administration site conditions (N=29). Of the 95 cases, 39 were rated as serious unlisted adverse events.

Interactions

Alcohol

Dissolution studies with TARGIN[®] tablets were conducted 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 with oxycodone may result in 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 (including antidepressants, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids, antihistamines, antiemetics and neuroleptic drugs, etc)

Concurrent use with oxycodone may enhance the CNS-depressant effect resulting in increased respiratory depression, hypotension, profound sedation or coma. 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 exhibiting signs of alcohol, drug or medicines abuse or a history of any of these.

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 metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly. Quinidine, a potent CYP2D6 inhibitor, has blocked the formation of oxymorphone, while the oxycodone concentration increased

marginally. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone. Ketoconazole, a CYP3A4 inhibitor, inhibited the formation of noroxycodone from oxycodone in human liver microsomes *in vitro*. 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.

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.

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 overdose are unlikely (treat symptomatically in a closely-supervised environment).

Symptoms of oxycodone overdose

Symptoms of oxycodone overdose include miosis (dilated if hypoxia is severe), cold and clammy skin, respiratory depression (reduced respiratory rate and/or tidal volume, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, bradycardia and hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more serious cases, and may lead to a fatal outcome.

The features of overdose may be delayed with a controlled release product such as TARGIN[®] tablets.

Treatment of oxycodone overdose

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 (eg 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 overdose or as a result of unusual sensitivity to oxycodone. 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. In this case, the infusion should be run at a rate consistent with the previously administered bolus doses and to the patient's response.

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 overdose may be less pronounced than expected, when pain and/or tolerance are manifest.

Please phone the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on managing overdose.

Pharmaceutical Precautions

Store below 25°C.

Shelf-life

3 years.

Medicine Classification

Controlled Drug B3.

Package Quantities

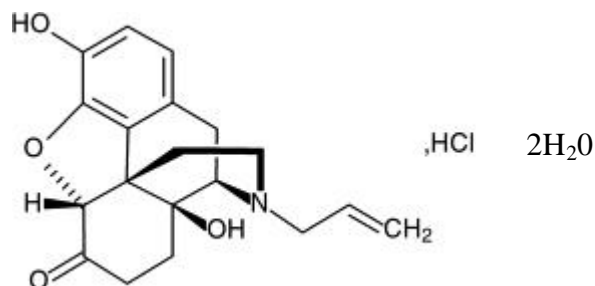
TARGIN[®] tablets are available in blister packs of 20 tablets, 28 tablets or 60 tablets (not currently marketed in NZ).

Further Information

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 4,5 α -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (CAS No: 124-90-3). The molecular formula is C₁₈H₂₁NO₄. 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-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate (CAS No: 51481-60-8). It is a synthetic congener of oxymorphone, with molecular formula C₁₉H₂₁NO₄. HCl.2(H₂O) and molecular weight 399.87. The pKa is 7.9 and the Partition Coefficient Log P is 1.5. The structural formula for naloxone hydrochloride dihydrate is:



The inactive ingredients in TARGIN[®] 5/2.5mg tablets are lactose, hydroxypropylcellulose, ethylcellulose, stearyl alcohol, talc and magnesium stearate. The inactive ingredients in TARGIN[®] 10/5mg, 20/10mg and 40/20mg tablets are lactose, povidone, ethylcellulose, stearyl alcohol, talc and magnesium stearate. All the tablets are coated with polyvinyl alcohol, titanium dioxide (E171), macrogol 3350 and talc. The tablet coat also contains brilliant blue CI42090 (5/2.5 mg tablets); iron oxide red CI77491 (20/10 mg tablets) and iron oxide yellow CI77492 (40/20 mg tablets).

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Date of Preparation

29 August 2011

(Aust PI 25/11/10)

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