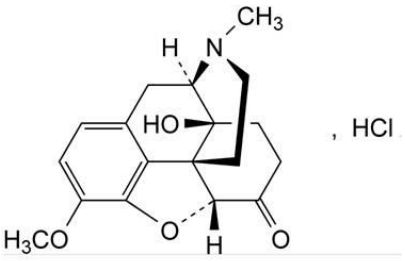
PRODUCT INFORMATION

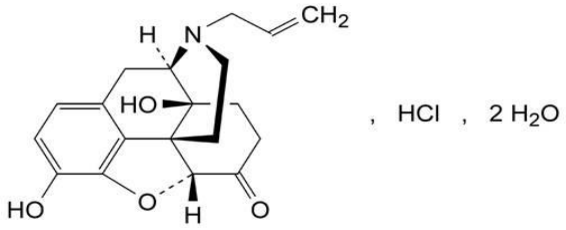
TARGIN® modified release tablets
2.5/1.25 mg, 5/2.5 mg, 10/5 mg, 15/7.5 mg, 20/10 mg, 30/15 mg, 40/20 mg, 60/30 mg, 80/40 mg

NAME OF THE MEDICINE
Oxycodone hydrochloride and naloxone hydrochloride anhydrous.

DESCRIPTION
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 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 hydrochloride is:



The inactive ingredients in the TARGIN modified release tablet core are lactose, ethylcellulose, stearyl alcohol, purified talc and magnesium stearate. TARGIN modified release tablets 2.5/1.25 mg, 5/2.5 mg and 15/7.5 mg also contain hydroxypropylcellulose. TARGIN modified release tablets 10/5 mg, 20/10 mg, 30/15 mg, 40/20 mg, 60/30 mg and 80/40 mg also contain povidone. The tablets are coated with polyvinyl alcohol, titanium dioxide, macrogol 3350 and purified talc. The tablet coat also contains brilliant blue FCF (5/2.5 mg), iron oxide red (2.5/1.25 mg, 15/7.5 mg, 20/10 mg, 30/15 mg, 60/30 mg), iron oxide yellow (2.5/1.25 mg,

15/7.5 mg, 30/15 mg, 40/20 mg, 80/40mg) and iron oxide black (15/7.5 mg, 30/15 mg, 60/30 mg, 80/40 mg).

PHARMACOLOGY

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).

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.

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%).

Pharmacokinetics

The pharmacokinetic characteristics of oxycodone from TARGIN modified release 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 5/2.5 mg, 10/5 mg, 15/7.5 mg, 20/10 mg, 30/15 mg, 40/20 mg, 60/30 mg and 80/40 mg modified release 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 modified release 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 modified release tablets were nominally increased compared with fasting state administration, but were not considered clinically relevant. TARGIN modified release 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 three 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 modified release tablets to patients with mild hepatic impairment. TARGIN modified release 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 modified release tablets to patients with renal impairment (refer to **PRECAUTIONS**).

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 modified release 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 modified release 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 modified release 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 modified release tablets compared with those taking oxycodone CR tablets. 278 patients were randomised to the double-blind phase (130 on TARGIN modified release 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 modified release tablets (-14.9; $p<0.0001$; CI -17.9 to -11.9). The actual observed difference of the means was -12.3 (TARGIN modified release tablets 40.94; oxycodone CR 53.27). Patients in the TARGIN modified release 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 modified release 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 1

	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			
▪ AUC_t	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 AUC_t values.		
Naloxone-3-glucuronide			
▪ AUC_{INF}	157% (89, 279)	128% (72, 227)	125% (71, 222)
▪ C_{max}	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 2

	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 doses up to 160/80 mg daily was assessed in a randomised, double-blind, 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 3

Number of Patients Receiving oxycodone ≥ 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 4

BFI observed values (FA population)					
Timepoint		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 response 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). Patients commencing treatment in this study had severe to very severe disease with median IRLS of 33 (Range 21 to 41).

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 5mg oxycodone hydrochloride/ 2.5mg naloxone hydrochloride twice daily, but up-titrated to higher dose levels (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 5

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 Min, Max	132 31.70 (4.37) 33.0 21, 39	144 31.55 (4.66) 33 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

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.

Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.

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; 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 monoamine oxidase inhibitors (MAOIs) and for 2 weeks after their cessation. History of opioid abuse for restless legs syndrome (RLS).

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 modified release tablets should be used with extreme caution in patients with sleep apnoea, 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.

Use in the elderly, debilitated patients and Special Risk Groups

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 modified release tablets and when TARGIN modified release tablets 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 modified release 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 modified release 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 modified release tablets is then indicated, the dosage should be adjusted to the new post-operative requirement.

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur, in particular at high doses. An oxycodone dose reduction or change in opioid may be required
TARGIN modified release 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 modified release 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 modified release tablets in this population is not recommended.

Long-term opioid treatment
In patients undergoing long-term opioid treatment, the switch to TARGIN modified release tablets can initially provoke withdrawal symptoms or diarrhoea. These patients require specific attention.

Restless Legs Syndrome
Sleep apnoea is more common in patients with restless legs 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 long-term treatment of RLS beyond 1 year (see section Dosage and Administration).

There is no clinical experience of concomitant dopaminergic agents with TARGIN modified release 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.

Withdrawal symptoms
TARGIN modified release tablets are not suitable for the treatment of symptoms of opioid withdrawal.

Use in chronic, non-malignant pain

Owing to the varied response observed to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose of opioid therapy and be titrated to an adequate level of analgesia, balanced against an acceptable frequency of adverse reactions.

The use of TARGIN modified release tablets for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative non-pharmacological and pharmacological methods of analgesia have been tried and have failed or are insufficient
- the pain is having a significant impact on the patient's quality of life
- there is no psychological contraindication, drug-seeking behaviour or past and current personal or family history of alcohol, prescription/illicit drug abuse or misuse.

Opioids, where clinically indicated, should only be prescribed as one component of a comprehensive multimodal management approach to chronic, non-malignant pain. Appropriate patient selection is the key to successful treatment of moderate to severe chronic 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 disorders). 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 modified release tablets or shorter acting opioid should be undertaken. Long-term administration of TARGIN modified release tablets should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid-naïve 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 modified release tablets should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential. Like other opioids, TARGIN modified release tablets can be diverted for non-medical use, into illicit channels of distribution.

Withdrawal symptoms may occur following abrupt discontinuation of all oxycodone therapy including TARGIN modified release 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 malignancy 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 modified release 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 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.

Clinical abuse potential studies

1. Study in Opioid-Dependent Subjects

The likeability of TARGIN® modified release 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 modified release 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 modified release is expected to reduce abuse via the IN and IV routes of administration. TARGIN modified release, 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 modified release tablets 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 modified release tablets must be swallowed whole with sufficient water 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 modified release tablets consist of a dual-polymer matrix, intended for oral use only. TARGIN modified release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take TARGIN modified release tablets. The empty tablet matrix may be visible in the stool. TARGIN modified release tablets may produce positive results in sports agency drug testing procedures.

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 modified release 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 modified release tablets, on a body surface area basis.

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 (Category C)

TARGIN modified release 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 modified release 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 modified release 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 modified release 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 modified release tablets on a body surface area basis. Because animal reproduction studies are not always predictive of human responses, this medicine should not be used during pregnancy.

Use in lactation
TARGIN modified release 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 modified release 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 modified release tablets, on a body surface area basis).

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

Paediatric use
TARGIN modified release tablets may be used in children from 12 years of age if clinically indicated, as both oxycodone and naloxone have been used in children.

Use in renal and hepatic impairment
TARGIN modified release tablets should be used with caution in patients with mild hepatic impairment and patients with renal impairment (CKD stages 2 to 5) (refer to Pharmacokinetics). Whilst the administration of TARGIN modified release 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 impairment (CKD stages 2 to 5) 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 modified release tablets are contraindicated in patients with moderate to severe hepatic impairment.

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.

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 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 11-fold the naloxone dose at the maximal recommended clinical dose of TARGIN modified release tablets, on a body surface area basis.

Driving and operating dangerous machinery
TARGIN modified release 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 modified release 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 (see section Interaction With Other Medicine).

INTERACTIONS WITH OTHER MEDICINES
Alcohol
Dissolution studies with TARGIN modified release 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 modified release 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 modified release 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, anti-histamines, anti-emetics 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 with a history of or present alcohol, drug or medicines abuse.

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 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 (e.g. clarithromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir), and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

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 modified release tablets.

In vitro metabolic studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, TARGIN modified release 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 modified release 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 modified release tablets then the dose of each medicine may need to be reduced.

ADVERSE EFFECTS

Analgesia

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time. The naloxone in TARGIN modified release 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 modified release 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 modified release 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 6

Adverse Events in Study OXN3001:	**TARGIN® tablets 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 modified release 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 7

Adverse Events in Study OXN3006:	**TARGIN® tablets dose:** Equivalent to OxyContin® tablets (N=130)	(%)	**Active Comparator:** OxyContin® tablets 60-80 mg/day (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 modified release 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 8

Adverse Events in Study OXN3401:	**TARGIN® tablets dose:** Equivalent to OxyContin® tablets (N=154) (%)	**Active Comparator:** OxyContin® tablets 20-40 mg/day (N=151) (%)	Placebo (N=158) (%)
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 modified release 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% %
Not known (cannot be estimated from 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

Eye disorders
Uncommon visual impairment

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

General disorders and application site conditions
Common asthenic conditions, fatigue
Uncommon chest pain, chills, drug withdrawal syndrome, malaise, peripheral oedema, thirst

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

Psychiatric disorders

Common	insomnia
Uncommon	anxiety, confusional state, depression, nervousness, restlessness, abnormal thinking
Rare	drug dependence (see PRECAUTIONS, Drug dependence)
Not known	nightmares, euphoric mood, hallucinations

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

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, drug tolerance

Not known drug withdrawal syndrome neonatal

Hepatobiliary disorders
Uncommon biliary spasm
Not known cholestasis

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,
Not known aggression

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

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 modified release tablets in pain and not observed in RLS study population were added with the frequency of not known

TABLE 9

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

DOSAGE AND ADMINISTRATION

TARGIN modified release 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 modified release tablets 60/30 mg and 80/40 mg, should only be used in opioid-tolerant patients. In patients not previously exposed to opioids (opioid naïve), these tablet strengths may cause fatal respiratory depression.

Analgesia.

Adults, elderly and children from 12 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 10/5 mg 12-hourly. Two lower strengths (2.5/1.25 mg and 5/2.5 mg) are available to facilitate dose titration when initiating opioid therapy, and individual dose adjustment. One TARGIN modified release tablet 5/2.5 mg taken 12-hourly, or one TARGIN modified release tablet 2.5/1.25 mg taken 12-hourly are suitable for patients with mild hepatic impairment or for 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 transferring from other opioid formulations
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.

For patients who are receiving an alternative opioid, the "oral oxycodone equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. The total daily oral oxycodone dosage should then be equally divided into two 12-hourly TARGIN tablet doses.

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(mg/Day Prior Opioid x Factor = mg/Day Oral Oxycodone)

TABLE 10

	Oral Prior Opioid	**Parenteral Opioid**
Oxycodone	1	--
Codeine	0.15	--
Fentanyl TTS	SEE BELOW**	SEE BELOW**
Hydromorphone	4	20
Pethidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

** Conversion from transdermal fentanyl to TARGIN tablets: 18 hours following the removal of the transdermal fentanyl patch, TARGIN tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-hourly of TARGIN tablets, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely.

It is emphasised that this is a guide to the required dose of TARGIN modified release tablets only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose. 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 may require "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 160/80 mg (12-hourly TARGIN tablets 80/40 mg). 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 modified release tablets and a subsequent switch to another opioid, a worsening of bowel function can be expected.

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 may be required. TARGIN tablets should not be prescribed and taken by the patient for longer than absolutely necessary. If long-term 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 therapy.

Missed dose

If the patient forgets to take a scheduled dose of TARGIN® tablets, they should be instructed not to take their next dose unless it is more than 8 hours before their next regularly scheduled dose. If so, they should be instructed to take the missed dose and return to their original dosing schedule, every 12 hours. Patients should be advised not to take extra tablets or a double dose to make up for a missed dose.

Restless legs syndrome

TARGIN tablets are indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be severe and 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. There is no clinical experience in administration of TARGIN modified release tablets with dopaminergic medication for the treatment of RLS. The combination was not assessed in the clinical trial OXN3502 in RLS patients.

Treatment should be under the supervision of a clinician with experience in the management of RLS.

At least every three months during therapy patients should be clinically evaluated and treatment should only be continued if TARGIN tablets are considered effective and the benefit is considered to outweigh adverse effects and potential harms in individual patients.

Prior to continuation of RLS treatment beyond 1 year a discharge regimen by gradually reducing the dose over a period of approximately one week should be considered to establish if continued treatment with TARGIN tablets is indicated.

When opioid treatment is no longer needed, the dose should be gradually reduced over a period of approximately one week, as recommended to minimise symptoms of withdrawal. (see PRECAUTIONS section).

Adults and elderly
The usual starting dose for an opioid naïve patient is 5mg/2.5mg of oxycodone hydrochloride/naloxone hydrochloride 12 hourly. Titration on a weekly basis is recommended in case higher doses are required.

Analgesia / Restless legs syndrome

Moderate to severe pain in the majority of patients is well managed by the symmetric administration (identical morning and evening doses) of TARGIN modified release 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

Use in children
Not recommended for use in children below 12 years of age.

Patients with impaired hepatic function
Caution must be exercised when administering TARGIN tablets to patients with mild hepatic and renal impairment (see PRECAUTIONS section for use in renal and hepatic impairment).
In patients with moderate and severe hepatic impairment TARGIN tablets is contraindicated (see Contraindications section).

OVERDOSAGE
Depending upon the history of the patient, an overdose of TARGIN modified release 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. 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 modified release 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 for advice on managing overdose.

PRESENTATION AND STORAGE CONDITIONS

TARGIN® modified release tablets are available* as round or capsule shaped, unscored film-coated modified release tablets in blister pack sizes of 20, 28 and 60 modified release tablets as follows:

2.5/1.25 contains oxycodone hydrochloride 2.5 mg/naloxone hydrochloride anhydrous 1.25 mg round, light yellow tablets with no markings;
5/2.5 contains oxycodone hydrochloride 5 mg/naloxone hydrochloride anhydrous 2.5 mg capsule shaped, blue tablets, marked "OXN" on one side and "5" on the other;
10/5 contains oxycodone hydrochloride 10 mg/naloxone hydrochloride anhydrous 5 mg capsule shaped, white tablets, marked "OXN" on one side and "10" on the other;
15/7.5 contains oxycodone hydrochloride 15 mg/naloxone hydrochloride anhydrous 7.5 mg capsule shaped, grey tablets, marked "OXN" on one side and "15" on the other;
20/10 contains oxycodone hydrochloride 20 mg/naloxone hydrochloride anhydrous 10 mg capsule shaped, pink tablets, marked "OXN" on one side and "20" on the other;
30/15 contains oxycodone hydrochloride 30 mg/naloxone hydrochloride anhydrous 15 mg capsule shaped, brown tablets, marked "OXN" on one side and "30" on the other;
40/20 contains oxycodone hydrochloride 40 mg/ naloxone hydrochloride anhydrous 20 mg capsule shaped, yellow tablets, marked "OXN" on one side and "40" on the other;
60/30 contains oxycodone hydrochloride 60 mg/ naloxone hydrochloride anhydrous 30 mg capsule shaped, red tablets, marked with "OXN" on one side and "60" on the other;
80/40 contains oxycodone hydrochloride 80 mg/ naloxone hydrochloride anhydrous 40 mg capsule shaped, brown tablets, marked with "OXN" on one side and "80" on the other.

*Not all strengths and pack sizes are currently marketed in Australia

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
88 Phillip Street SYDNEY NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

POISON SCHEDULE OF THE MEDICINE

S8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)
12 May 2010

DATE OF MOST RECENT AMENDMENT
8 December 2016

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