Oxycodone-with-naloxone controlled-release tablets (Targin) for chronic severe pain (OCK-see-CODE-own with na-LOCKS-own)

KEY POINTS

- Provides equivalent analgesia to that of oxycodone controlled-release (CR) tablets. Clinical data are largely from people with chronic musculoskeletal pain.

- The naloxone component reduces, but does not eliminate, opioid-induced constipation. In key trials, the prevalence of constipation with oxycodone-with-naloxone CR compared with oxycodone CR was about 25% lower among people with a history of constipation, and 7% lower in an unselected group.

- Long-term effect on constipation is uncertain. Average constipation symptoms at 52 weeks in uncontrolled extension trials were no worse than at 12 weeks. There are no trial data beyond 52 weeks.

- Can initially provoke withdrawal symptoms or diarrhoea in people who are opioid tolerant. However, in key trials the incidence of withdrawal symptoms was low and similar to that for oxycodone CR tablets.

- Contraindicated in moderate or severe hepatic impairment. Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min.

- No evidence regarding potential for problematic or illicit use. The naloxone component may deter injected or intranasal use, but this has not been tested.

PBS listing

Restricted benefit
Chronic, severe disabling pain not responding to non-opioid analgesics.

Authorities for increased maximum quantities will be available for patients meeting the criteria listed in the note in the Schedule of Pharmaceutical Benefits.1

Oxycodone is a Controlled Drug (Schedule 8) and so must be prescribed in accordance with State or Territory regulations (see www.tga.gov.au/industry/scheduling-st-contacts.htm).

May be prescribed by nurse practitioners (shared care model)
Authorised nurse practitioners may prescribe this medicine as part of a formal care plan with a medical practitioner. See the PBS website for more information on nurse practitioner PBS prescribing.
Oxycodone-with-naloxone controlled-release tablets (Targin)
NPS RADAR | DECEMBER 2011

What is it?
Oxycodone-with-naloxone controlled-release (CR) tablets (Targin) contain a combination of a strong opioid and an opioid antagonist in a controlled-release formulation. The tablets are bioequivalent to oxycodone CR (OxyContin) with regard to their oxycodone content and provide the same duration of action (i.e. approximately 12 hours). The available strengths are oxycodone/naloxone: 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg.*

Injected naloxone has long been used to reverse systemic opioid effects, whereas oral naloxone is unsuited for this purpose because it undergoes extensive first-pass metabolism and has low systemic bioavailability. The controlled-release tablets deliver a naloxone dose that blocks opioid receptors in the gut, but not elsewhere (e.g. central nervous system), and therefore reduces gastrointestinal effects with a minimal effect on analgesia.2

Who is it for?
Oxycodone-with-naloxone CR tablets are indicated for severe chronic cancer or non-cancer pain unresponsive to non-opioid analgesia.* The naloxone component reduces opioid-induced constipation.1,2 Oxycodone, as with all strong opioids, should be offered to people with chronic non-cancer pain only when:

- non-opioid methods of analgesia have been tried and failed
- pain has a significant effect on the patient’s quality of life
- there is no psychological contraindication, drug-seeking behaviour or history of drug or alcohol misuse
- prescribing is part of an agreed pain management plan that includes non-drug measures.2,3

See NPS Prescribing Practice Review 51 for information about developing a pain management plan.

Oxycodone-with-naloxone CR tablets are not indicated for acute pain.

Where does it fit?
An option for people with opioid-induced constipation
Oxycodone-with-naloxone CR tablets cause less constipation than conventional oxycodone CR tablets, but not all patients will benefit (see Less constipation than with oxycodone CR tablets). Switching from low-to-medium doses of oxycodone CR tablets to the fixed-dose combination tablets appears useful for people who suffer from constipation despite an adequate laxative regimen.

For palliative care patients experiencing opioid-induced constipation, adding methylnaltrexone (Relistor) to the existing opioid regimen is an option if laxatives fail (see the March 2010 NPS RADAR review ‘Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care’).

Among people without established opioid-induced constipation, a smaller proportion benefit (see Small benefit among people who do not already have opioid-induced constipation).

Laxatives may be required
As for oxycodone alone, advise people starting oxycodone-with-naloxone CR tablets to increase their fluid and fibre intake and exercise levels to reduce the risk of constipation. Recommend or prescribe regular laxatives as necessary (i.e. combined stool softener with stimulant laxative, such as docusate with senna [Coloxyl with Senna; Soflax], or an osmotic laxative, namely, sorbitol or lactulose).4,5

In trials, people taking oxycodone-with-naloxone CR tablets used laxatives only on demand, and 27–49% experienced some degree of constipation (see Less constipation than with oxycodone CR tablets).

Limited usefulness for people who need high doses of opioids
The maximum recommended daily dose of oxycodone-with-naloxone CR tablets is oxycodone 80 mg/naloxone 40 mg; higher doses have not been evaluated. People requiring a daily dose totalling more than oxycodone 80 mg can take additional oxycodone CR tablets 12 hourly, but a beneficial effect on constipation may be lessened.2

* The tablets are also indicated but not PBS listed for moderate pain unresponsive to non-opioid analgesia.

Refer to this review at www.nps.org.au for an assessment of oxycodone-with-naloxone CR tablets using a checklist of questions about fixed-dose combination preparations.
What is known about this drug

Oxycodone-with-naloxone controlled-release (CR) tablets provide equivalent analgesia to that of oxycodone CR tablets of the same oxycodone dose, with a similar adverse-effect profile.

Adding the naloxone component reduces, but does not eliminate, the prevalence of constipation. Compared with oxycodone CR, the number needed to treat (NNT) (for one person using opioids continuously to avoid constipation) was about 4 for people with existing opioid-induced constipation (after 4 weeks), and about 14 for people not selected for constipation symptoms (after 12 weeks).

Areas of uncertainty

Efficacy data regarding analgesia and constipation are from 12-week randomised controlled trials. Longer-term data (up to 52 weeks) are from uncontrolled trials. The tablets have not been compared with a regimen of oxycodone and prophylactic laxatives.

There are insufficient data from randomised controlled trials to characterise rare adverse events.

What does NPS say?

Switching to the fixed-dose combination tablets may benefit people who experience constipation while taking low to medium doses of oxycodone long term. Everyone taking regular opioids should increase their fluid and fibre intake and exercise levels to reduce the risk of opioid-induced constipation.

Among people without existing constipation, a small proportion will experience a benefit over oxycodone alone.

Evidence snapshot

Long-term efficacy data regarding effect on constipation are lacking

There are no comparative data to demonstrate that oxycodone-with-naloxone CR tablets continue to prevent constipation for longer than 12 weeks, the length of the three key randomised controlled trials. However, average patient-reported constipation symptoms did not worsen over 52 weeks in open-label uncontrolled extension trials.6

Naloxone may deter intranasal or injected use

Oxycodone-with-naloxone CR tablets contain a dose of naloxone that will antagonise the acute central nervous system effect of oxycodone if used intranasally or injected. In theory, this will reduce the pleasurable effects and provoke unpleasant withdrawal symptoms for people who are opioid tolerant. The tablets may therefore be less appealing for unsanctioned (problematic or illicit) administration, but there is currently no direct evidence to confirm this. The tablets do not deter unsanctioned oral use.

As with other oxycodone preparations, oxycodone-with-naloxone CR tablets are not recommended for treating opioid withdrawal, and should be prescribed with caution and under close supervision for people who are known or suspected to misuse prescription medicines, alcohol or other substances.2

How does it compare?

Similar analgesia to that of oxycodone CR tablets

A pooled analysis of two 12-week randomised controlled trials found that oxycodone-with-naloxone CR tablets provided analgesia that was no worse than that of conventional oxycodone CR tablets. Participants in the trials had chronic, non-cancer pain, mostly of musculoskeletal origin (e.g. osteoarthritis), and the average age was 58 years. The average difference in pain intensity score at 12 weeks was -0.01 (95% CI -0.15 to 0.13) on a pain scale from 0 to 10. There was no statistically significant difference in the amount of supplemental oxycodone used, and average daily oxycodone doses were similar in the two groups.7,8
Efficacy compared with prophylactic laxatives is not known

None of the clinical trials of oxycodone-with-naloxone CR tablets compared them with the combination of oxycodone or another strong opioid and a prophylactic laxative. Prophylactic laxative use is the standard of care when strong opioids are used regularly in chronic pain.4,9

Less constipation than with oxycodone CR tablets

In three comparative trials, oxycodone-with-naloxone CR tablets caused less constipation than oxycodone CR tablets, after 4 weeks and 12 weeks of therapy.10–12 Constipation was measured using the Bowel Function Index (BFI).* As a secondary outcome, all three trials reported the number of participants with fewer than three complete spontaneous bowel movements per week, a common definition for constipation (see Table 1). Using these results it is possible to estimate for each trial the proportion of patients who avoided constipation by using oxycodone-with-naloxone CR tablets rather than oxycodone CR tablets (responder data are not available for BFI).

Small benefit among people who do not already have opioid-induced constipation

One of the three key trials of oxycodone-with-naloxone CR tablets did not actively select participants with pre-existing opioid-induced constipation. In this trial, 80% of participants had no or mild constipation at randomisation (i.e. a BFI < 50), despite using an opioid analgesic for 2 or more weeks before enrolling in the study.12

In this population, there was a 7-percentage-point difference in constipation rates after 12 weeks of treatment between participants receiving oxycodone-with-naloxone CR tablets and participants receiving oxycodone CR tablets (see Table 1). People receiving oxycodone-with-naloxone CR tablets used laxatives on 7.9% of days, while people receiving oxycodone CR tablets used them on 10.4% of days (statistical significance of comparison not reported).7,12

There are few reliable data regarding the typical incidence of opioid-induced constipation, but the median rate of constipation was 30% in a meta-analysis of opioids for chronic non-cancer pain in older adults.13

No comparison with methylnaltrexone in palliative care population

Methylnaltrexone is an option for treating opioid-induced constipation in people receiving palliative care who have not responded to adequately titrated laxatives [see the NPS RADAR review ‘Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care’]. A reduction in constipation with oxycodone-with-naloxone CR tablets has been demonstrated with a mean daily oxycodone dose of up to about 70 mg7,10–12; patients with cancer pain or in palliative care may require higher oxycodone doses.

---

* The Bowel Function Index (BFI) is a patient-assessed score on a scale of 0 to 100 (0 = no symptoms). As well as frequency of bowel movements, the BFI incorporates other constipation-related symptoms such as straining and bloating. It was accepted by regulators as an outcome measure in oxycodone-with-naloxone trials but has not been used by other investigators.

Table 1.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Oxycodone-with-naloxone CR</th>
<th>Oxycodone CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with existing opioid-induced constipation (OIC)*</td>
<td>35% (50/144)</td>
<td>61% (83/137)</td>
</tr>
<tr>
<td>Patients not selected for existing OIC</td>
<td>49% (64/130)</td>
<td>74% (100/135)</td>
</tr>
<tr>
<td>Patients with existing OIC‡</td>
<td>27% (41/154)</td>
<td>34% (51/151)</td>
</tr>
</tbody>
</table>

* All trial participants had fewer than three complete spontaneous bowel movements per week at recruitment.
† After 4 weeks of double-blind therapy
‡ After 12 weeks of double-blind therapy. Bowel function variables were secondary outcomes in this study.
Safety issues

Oxycodone-with-naloxone CR tablets appear to have a similar safety profile to that of oxycodone CR tablets; however, there are insufficient data from randomised controlled trials to characterise rare adverse events.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the ‘Blue Card’ distributed three times a year with Australian Prescriber. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Diarrhoea may occur

In the three key trials, the incidence of diarrhoea was about 5% with either oxycodone-with-naloxone CR tablets or with oxycodone CR tablets. When switching from long-term higher-dose opioid treatment to oxycodone-with-naloxone CR tablets, people may initially experience diarrhoea.2

Contraindicated in moderate or severe hepatic impairment

People with hepatic impairment experience higher systemic exposure to naloxone, which can antagonise the central nervous system effects of oxycodone.2 This could result in reduced analgesia, and opioid withdrawal symptoms in people who are opioid tolerant.

If prescribing to people with renal impairment or mild hepatic impairment, titrate the dose cautiously and monitor carefully. As with conventional oxycodone CR tablets, renal or hepatic impairment may increase oxycodone plasma concentrations (see Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min). Do not prescribe in moderate or severe hepatic impairment.2

Low incidence of withdrawal symptoms in trials

People receiving long-term higher-dose opioid treatment can initially experience opioid withdrawal symptoms when switching to oxycodone-with-naloxone CR tablets.2 In key trials the incidence of withdrawal symptoms was low and similar for oxycodone-with-naloxone CR tablets and oxycodone CR tablets.7

Few data about rare adverse events

Naloxone has been used as a parenteral opioid antagonist for several decades, and appears to cause few adverse effects except for those associated with acute opioid withdrawal.4

There is less experience with long-term oral use of naloxone and insufficient data from randomised controlled trials to characterise rare adverse events with oxycodone-with-naloxone CR tablets. However, oxycodone-with-naloxone CR tablets were first registered in Germany in 2006, and the Australian TGA-approved product information lists adverse events from European postmarketing data.7

Reason for PBS listing

In July 2010, the Pharmaceutical Benefits Advisory Committee (PBAC) rejected a submission requesting the PBS listing of oxycodone-with-naloxone CR tablets because of uncertain cost-effectiveness. The PBAC observed that the benefits appeared modest, especially in the population of patients who were not constipated before starting oxycodone with naloxone.14

A subsequent submission in November 2010 amended the price and also addressed uncertainties identified by the PBAC, including efficacy in the non-constipated population, the use of prophylactic laxatives, and the likely average daily dose of oxycodone. The PBAC recommended listing on the basis that the revised cost-effectiveness estimates were acceptable, relative to oxycodone CR tablets without prophylactic laxatives.

The PBAC accepted that oxycodone-with-naloxone CR tablets are efficacious in both constipated and non-constipated patients. They considered that availability of the tablets would improve the management of opioid-induced constipation, and may reduce diversion. They noted data indicating that GPs co-prescribed laxatives at a low rate for people receiving opioids, but also noted that many people purchase over-the-counter laxatives.15
### Dosing issues

Initiate and dose oxycodone-with-naloxone CR tablets as for oxycodone CR tablets. People already receiving single-ingredient oral oxycodone preparations (immediate or controlled release) may switch to the combination tablets at the same total daily oxycodone dosage, equally divided into two 12-hourly doses.2

If switching from oral morphine, the Targin product information states that oxycodone 10 mg is equivalent to oral morphine 20 mg. Note that guidelines recommend starting with a lower dose than that calculated (e.g. 50% to 75% of the equianalgesic dose) then titrating to response. This is recommended to cater for differences in how people tolerate different opioids.2,4,9

The tablets are registered for use by children and adolescents from 12 years of age2, but oral opioids generally have a very limited role in treating chronic non-cancer pain in children.

**Maximum strength is oxycodone 40 mg/ naloxone 20 mg**

There is no tablet strength corresponding to existing oxycodone CR 80 mg tablets. The maximum recommended dose is one oxycodone 40 mg/naloxone 20 mg tablet 12 hourly, but supplementary oxycodone CR tablets can be added (see Limited usefulness for people who need high doses of opioids).2

#### Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min

For people with mild hepatic impairment or renal impairment and creatinine clearance < 60 mL/min, reduce the dose to one-third to one-half of the usual. Titrate cautiously with careful monitoring. The tablets are contraindicated in moderate or severe hepatic impairment.2

#### Advise people to take the tablets whole

Breaking, dissolving, chewing or crushing the tablets can lead to the rapid release of oxycodone and naloxone, and a potential overdose of oxycodone. The tablets are for oral use only.2

### Information for patients

Advising patients as follows.

- Swallow the tablets whole with a full glass of water; do not chew, crush, break or dissolve the tablets.
- Take every 12 hours, with or without food.
- Do not take any other pain reliever or opioid, sleeping tablets or muscle relaxants without speaking with a doctor or pharmacist.
- Avoid drinking alcohol.
- The tablets can cause constipation, diarrhoea, nausea, vomiting, dizziness, drowsiness, headache, itching and other side effects.
- Laxatives may still be required — follow the course recommended by your doctor.
- Note carefully which of your existing medicines are being replaced by the combination tablets and return the unneeded medicines to a pharmacy.

Discuss the Targin consumer medicine information (CMI) leaflet with the patient.

Advise patients to reduce the chance of constipation by drinking water regularly throughout the day, increasing their fibre intake and keeping as mobile as they can. Consider recommending or prescribing regular laxatives (e.g. combined stool softener with stimulant laxative, such as docusate with senna [Coloxyl with Senna; Soflax]).4,5

Patients switching from another opioid preparation may need to reduce their laxative intake.
REFERENCES


Date published: December 2011.

The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.