PHARMACY PROFILE: Oxycodone/naloxone controlled release tablets (Targin®)

Key Messages

- **Targin®** is a modified release product. Patients should be advised not to break, dissolve, chew or crush the tablets (as this may lead to rapid release of oxycodone and naloxone with potential for toxicity).
- Palliative care nurses play an important role in educating patients and their families about prevention of constipation.
- Given the multiple causes of constipation in palliative care patients, this product does not eliminate the need for lifestyle approaches and, in many patients, additional laxatives.
- All patients receiving Targin® should be advised about safe disposal to minimise the risk of abuse/misuse/accidental exposure.

Oxycodone/naloxone modified release (MR) tablets are indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in the fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid induced constipation. [1] Oxycodone/naloxone MR tablets are subsidised on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit for patients with chronic, severe disabling pain unresponsive to non-narcotic analgesics. Targin® is available in four different strengths in Australia: 5 mg oxycodone/2.5 mg naloxone; 10 mg oxycodone/5 mg naloxone; 20 mg oxycodone/10 mg naloxone; 40 mg oxycodone/20 mg naloxone. The oxycodone/naloxone MR tablets are a fixed dose tablet containing a 2:1 ratio of oxycodone and naloxone. This ratio was determined to provide the greatest efficacy and tolerability in dose finding studies. [2]

Naloxone has been used in an injectable form to reverse systemic opioid effects for a long time. Oral naloxone is unsuitable for this because it undergoes extensive first-pass metabolism and has low systemic bioavailability. When taken orally the naloxone specifically blocks opioid receptors in the gut, but not elsewhere, and therefore reduces the gastrointestinal effects (particularly constipation) of the opioid but has minimal effect on its analgesic effects. [3]

Oxycodone/naloxone MR tablets may have a role in patients who experience constipation while taking low to medium doses of oxycodone long term, particularly if optimised regular laxatives for opioid-induced constipation are inadequate. [4] Constipation may still occur, and all patients still need advice on measures to reduce the risk of opioid-induced constipation, including lifestyle approaches. Laxatives may be needed in addition to manage constipation in these patients.

Considerations for use in palliative care

- The maximum recommended daily dose of Targin® is oxycodone 80 mg/naloxone 40 mg (in two divided doses or 40/20 twice daily). [1] Higher doses have not been adequately studied. In patients needing a daily dose of more than 80 mg oxycodone, additional oxycodone controlled release (CR) tablets could be taken, but the beneficial effect on constipation may be lessened. As patients with cancer pain or in palliative care often require higher oxycodone doses, the benefit on constipation with Targin® may be less.
• An isolated published case report described a cancer patient who was receiving increasing doses of oxycodone/naloxone (up to 240 mg oxycodone with 120 mg naloxone) with an unexpected decline in analgesia. In this patient, when treatment was changed to 240 mg oxycodone CR (ie. without naloxone) adequate analgesia was regained. This suggests that it is possible that at large doses absorption of naloxone is increased enough to have a central antagonist effect on analgesia. [5]

Tips for palliative care nurses
• As Targin® is a MR product, patients should be advised not to break, dissolve, chew or crush the tablets (as this may lead to rapid release of oxycodone and naloxone with potential for toxicity).
• When patients are switched to oxycodone/naloxone MR tablets, a reduction in pre-existing laxatives is advisable.
• Patients should be advised that while constipation may be reduced with this product, it will often still occur. Education about lifestyle strategies is important, as is education about use of laxatives where necessary.

Evidence of efficacy
• Most Targin® trials have been in chronic non-cancer pain. In these trials the naloxone component reduced the prevalence of opioid-induced constipation by approximately 25% among people with a history of constipation and 7% in an unselected group. [3]
• One small randomised controlled trial evaluated the safety and efficacy of oxycodone/naloxone MR tablets in patients with moderate/severe chronic cancer pain. In this study oxycodone was used in doses up to 120 mg/day. The oxycodone/naloxone MR was as effective in terms of analgesia compared to oxycodone CR alone and associated with significantly improved bowel function and reduced symptoms of constipation. [6]
• Longer term effects on constipation are unknown. Trials have not extended beyond one year.
• Comparative studies between oxycodone/naloxone MR tablets and oxycodone CR with regular laxatives are lacking, and would be useful.

Safety
• Oxycodone/naloxone MR tablets need to be considered in the same way as other Schedule 8 opioids with respect to storage, accountability and disposal, as this product still has the potential for misuse.
• Oxycodone/naloxone MR tablets appear to have a similar safety profile to that of oxycodone CR tablets; however, there is insufficient data from randomised controlled trials to characterise rare adverse effects. There is a risk of initial diarrhoea, particularly when switching from long-term higher dose opioid therapy to oxycodone/naloxone MR tablets. [3]
• The most commonly reported adverse events associated with oxycodone/naloxone MR tablets in clinical trials were usually GI-related (e.g. constipation, nausea, vomiting, diarrhea, abdominal pain). [7]
• Oxycodone/naloxone MR tablets are contraindicated for people with moderate to severe hepatic impairment. The dose needs to be reduced (to one-third to one-half of the usual dose) in patients with mild hepatic impairment and in patients with a creatinine clearance < 60 mL/min. [3]
References

- MIMS Australia. MIMS Online [Internet]. 2016. [cited 2016 Feb 16].

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Useful resources

- Contact your local pharmacist or hospital drug information service.
- National Prescriber Service Website – NPS Medicinewise is an excellent resource for consumers and health professionals.