

Oxycodone/naloxone prolonged release (Targinact®) tablets

This is one of a number of bulletins providing further information on medicines contained in the DROP-List (Drugs to Review for Optimised Prescribing). This bulletin focuses on oxycodone/naloxone prolonged release (PR) (Targinact®) tablets and provides the rationale for therapy to be stopped or for patients to be switched to alternative agents and for new patients not to be started on Targinact® tablets. Further support materials, including the DROP-List, are available on the PrescQIPP website, available at: <http://www.prescqipp.info/resources/viewcategory/232-oxycodone-naloxone-prolonged-release-targinact-tablets>

Introduction

Nationally over £4.8 million is spent annually on oxycodone/naloxone PR (Targinact®) tablets (ePACT February 2014).

The DROP-List is an accumulation of medicines, originating from the East of England PCTs, which are regarded as low priority, poor value for money or medicines for which there are safer alternatives. Targinact® tablets is one of the items in the PrescQIPP DROP-List.

QIPP projects in this area are aimed at either reviewing the continued need for Targinact® and decreasing prescribed doses or switching to morphine sulfate or oxycodone with concomitant laxatives. This bulletin reviews the place in therapy of Targinact® and offers guidance and support material for organisations considering reviewing Targinact® prescribing as a QIPP project.

Recommendations

- Commence new patients requiring strong opioid therapy on morphine sulfate modified release (MR).
- Review all patients on Targinact® tablets for suitability for switching to morphine sulfate. Switch all suitable patients to an appropriate formulation of morphine sulfate with additional concomitant regular laxative therapy, for example a combination of stool-softening and stimulant laxatives (e.g. docusate plus senna or bisacodyl or co-danthramer in the terminally ill) or lactulose plus bisacodyl or senna in those not terminally ill. Please note it may not be appropriate to switch terminally ill patients.
- As with all switches, the dose should be tailored to the individual patient. Prescribers should be aware of the difference in potency of oxycodone compared to morphine.
- Patients unsuitable for a switch to morphine sulfate should be switched to an equivalent dose of oxycodone MR, prescribed as Longtec®, with additional concomitant regular laxative therapy.
- To avoid confusion between the modified release products and standard release products, all modified release opioids should be prescribed by brand.
- Prescribers should be aware of the abuse potential of all opioids and careful consideration should be given when prescribing opioids for non-cancer pain to patients with a history of substance misuse or where abuse is a concern.

National guidance

National Institute of Health and Care Excellence (NICE) clinical guideline 140 on the safe and appropriate prescribing of strong opioids for pain in palliative care of adults recommends morphine sulfate as the first line oral opioid of choice when initiating treatment and sustained release morphine sulfate as the strong oral opioid of choice for maintenance treatment. It also recommends that laxatives and/or antiemetic treatments are prescribed and optimised before considering changing oral opioid therapy. For patients experiencing drowsiness from therapy, NICE recommends either reducing the treatment dose if pain is controlled or switching the opioid if pain is not controlled.¹ There is no advice from NICE on the use of strong opioids for long term pain that is outside of palliative care.

The Scottish Intercollegiate Guidelines Network (SIGN) produced a guideline on the treatment of chronic pain in 2014 which states:²

“there is no clear evidence that any particular opioid including morphine is better than any other in terms of efficacy for pain relief”

The Scottish Medicines Consortium did not recommend the use of Targinact® tablets in NHS Scotland due to uncertain clinical benefit and an insufficiently robust economic analysis. Oxycodone prolonged release is restricted in NHS Scotland to use in patients in whom controlled release morphine sulfate is ineffective or not tolerated.³

The British Pain Society’s good practice guide for opioids for persistent pain states:

“There is evidence from clinical trials that opioids can be effective, in the short and medium term, in providing symptomatic improvement in a variety of non-cancer pain conditions. However, the safety and efficacy of opioids in the long term is uncertain as is the propensity for these drugs to cause problems of tolerance, dependence and addiction. The benefits of opioid treatment for the patient must be balanced against burdens of long term use as therapy for persistent pain may need to be continued for months or years. The position of opioid treatment must also be considered within a wider social context and issues such as diversion must be addressed.”⁴

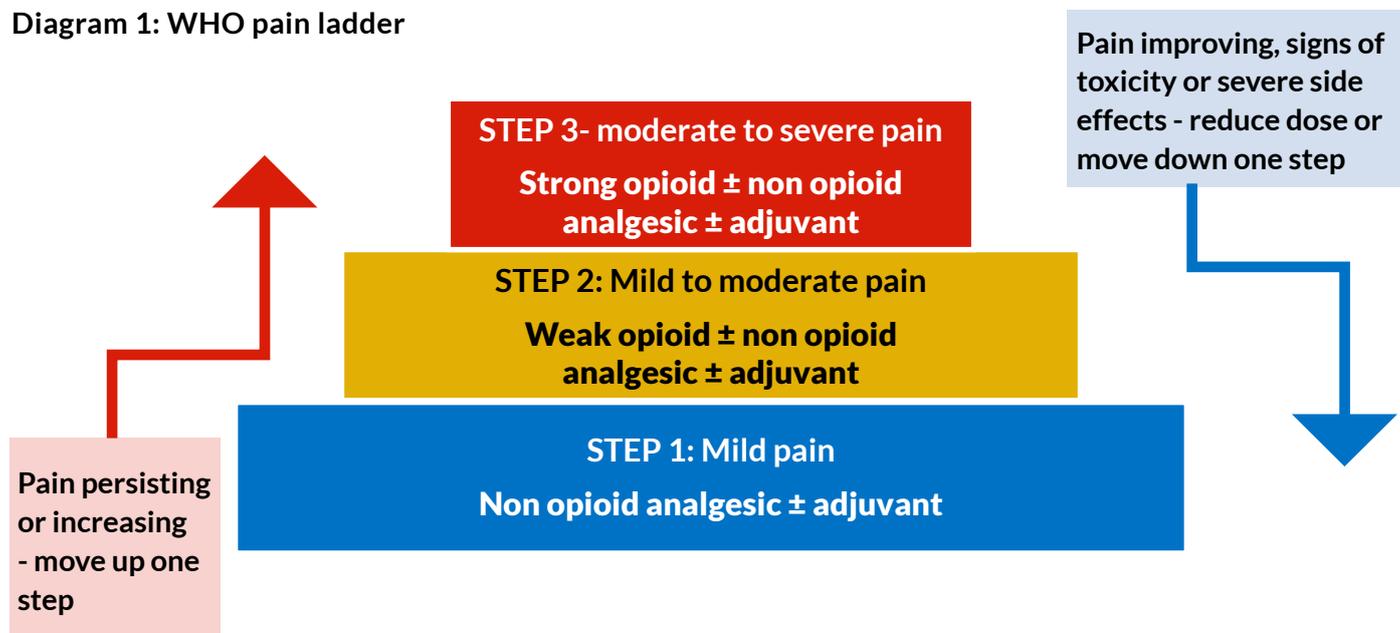
Clinical evidence

Strong opioids should only be initiated in patients after non opioid analgesics and mild opioid analgesics have been tried. This is particularly important in patients with non-cancer pain where careful consideration should be given before prescribing strong opioids.

A stepwise approach to pain management in line with the World Health Organisation (WHO) recommendations should be adopted as this minimises the risk of respiratory depression and other adverse effects in opioid naïve patients.

Diagram 1, on the following page, is an adaptation of WHO pain ladder. Although this was originally developed as a resource for cancer pain, it is regularly used in non-cancer pain.

Diagram 1: WHO pain ladder



When a strong opioid is considered an appropriate treatment, morphine sulfate is widely considered as the first line strong opioid of choice. Patients are normally initiated with treatment on the immediate release products (given as a 4-6 hourly dose) formulations. Once their pain is controlled and the dose stabilised, the opioid can be converted to a twice-a-day sustained release formulation.

Targinact® tablets are licensed for severe pain which can be adequately managed only with opioid analgesics.⁵ The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

Naloxone is also used intravenously to reverse the effects of acute opioid overdose.

Constipation is one of the most common adverse effects from opioids; unlike some other adverse effects, tolerance does not develop on long-term use. All patients prescribed regular long-term strong opioids should also be prescribed regular laxatives.⁶

The NICE Clinical Knowledge Summaries (CKS) service recommends that when introducing an opioid, a stimulant laxative (such as bisacodyl, senna or danthron-containing laxative for the terminally ill) and a softening laxative (such as docusate) should be prescribed at the time of first prescription.^{7,8} A laxative with both properties (for example, co-danthramer or co-danthrusate) is also an option in terminally ill patients. The patient should also be advised of the risks of constipation, and an adequate fluid and dietary intake (including fruit juice and fruit specifically) should be encouraged. For patients who are not terminally ill, lactulose plus bisacodyl or senna is the preferred option.⁸

There have been a number of studies which have assessed the efficacy and safety of oxycodone/naloxone PR tablets. There are three randomised-controlled trials which have compared oxycodone/naloxone PR tablets with oxycodone PR tablets in patients with moderate-to-severe non-cancer pain.^{9, 10, 11, 12, 13} Note that the product is only licensed for severe pain.

Two of the studies had a similar design;^{12, 13} all three lasted 12 weeks.¹¹⁻¹³ All studies found analgesia was similar between oxycodone/naloxone PR tablets and oxycodone PR tablets.

In two studies,^{12, 13} the primary outcome was patients' assessment of their symptoms of constipation as measured by the Bowel Function Index (BFI). In both studies, the BFI improved with oxycodone/naloxone PR tablets statistically significantly more than with oxycodone. In one study,¹¹ after four weeks 30% of patients receiving oxycodone/naloxone PR tablets required laxatives compared with 54% taking oxycodone. The studies have been criticised for either not reporting the laxative rescue protocol used or for the use of oral bisacodyl, a stimulant laxative, rather than the recommended regular prophylactic use of a stimulant laxative plus a faecal softener.

A further long-term observational non-blinded follow-up of the first two studies¹⁴ evaluated the effects of oxycodone/naloxone PR tablets for a further 52 weeks after the end of the initial study phase. Analgesia control and use of laxatives remained constant throughout the 12 months.

There are no published randomised controlled trials comparing oxycodone/naloxone PR tablets against oral morphine or other opioids, or against oral strong opioids given with a recommended laxative regimen of regular stool-softening and stimulant laxatives. One paper, published online, only compared oxycodone/naloxone PR tablets against oxycodone in patients with cancer pain.¹⁵ As in the previously discussed studies, this four week study used bisacodyl only as rescue therapy. Full results are not available but there was no significant difference between the groups in the percentage of patients taking rescue bisacodyl.

The Drug and Therapeutics Bulletin could see no reason why Targinact® tablets should be prescribed given the limitations of the trials, the lack of data to show that Targinact® reduces or eliminates the need for laxatives in the long term, and the cost differential against other opioids.⁹

The use of oxycodone first line over morphine sulfate as a strong opioid is rarely justified as there is a lack of evidence to suggest oxycodone has any clinical advantages over morphine sulfate² and the cost of oxycodone is significantly higher than morphine sulfate.

Oxycodone and morphine are both strong opioids with similar efficacy and side effect profiles.⁶ Studies have shown that oxycodone MR is as effective as morphine sulfate MR in relieving chronic cancer-related pain, with similar adverse effect profiles.^{16, 17, 18} These studies have all been small and of short duration. No studies have demonstrated benefits of oxycodone over morphine sulfate. **There is a lack of evidence from high quality comparative trials that other opioids have advantages over morphine in terms of either efficacy or side effects.**

It is difficult to determine a precise equivalent dose for oxycodone to morphine as reported equi-analgesic dose ratios vary widely. When converting from one opioid to another, regular assessment and reassessment of efficacy and adverse effects is essential because of the lack of evidence on equi-analgesic doses and inter-individual variation.

The summary of product characteristics (SPC) for OxyContin® states: Patients receiving oral morphine before OxyContin® therapy should have their daily dose based on the following ratio: 10mg of oral oxycodone is equivalent to 20mg of oral morphine. It must be emphasised that this is a guide to the dose of OxyContin® tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.¹⁹

However the BNF states 6.6mg of oral oxycodone is equivalent to 10mg of oral morphine.⁶

Safety of Targinact® tablets

In two of the randomised controlled trials, the overall incidence of adverse effects with oxycodone/naloxone PR tablets was similar to oxycodone and adverse effects were as expected with any strong opioid.^{11, 12} In one study, the overall incidence of adverse effects was higher with oxycodone/naloxone PR tablets than with oxycodone (63.1% vs 52.6%, p value not stated).¹³

Targinact® tablets are contra-indicated in patients with moderate or severe hepatic impairment.⁵ Plasma concentrations of both oxycodone, and particularly naloxone, are elevated in patients with hepatic impairment. The clinical significance of a raised naloxone plasma concentration is not clear but there is a theoretical risk that accumulation of unmetabolised naloxone could cause reversal of opioid analgesia.²⁰ In addition, Targinact® tablets should be used with caution in patients with mild hepatic impairment and in patients with renal impairment for the same reason.⁵

The maximum recommended dose of Targinact® tablets is 80mg oxycodone/40mg naloxone daily. For patients requiring higher doses of analgesia, administration of supplemental opioid therapy would be required. If supplemental opioids are given, the effect of naloxone on bowel function may be impaired.

The SPC notes that, after complete discontinuation of therapy with Targinact® tablets with a subsequent switch to another opioid, a worsening of the bowel function can be expected.⁵

Costs

There is a significant difference in cost between morphine sulfate MR products and Targinact® tablets. There is also a difference in cost between Targinact® tablets and oxycodone PR (prescribed as Longtec®). Table 1 below illustrates the cost differences between different brands of morphine sulfate MR and oxycodone MR. To aid comparison the oxycodone is placed at half the morphine sulfate dose, however it could also be 2/3 of the dose.

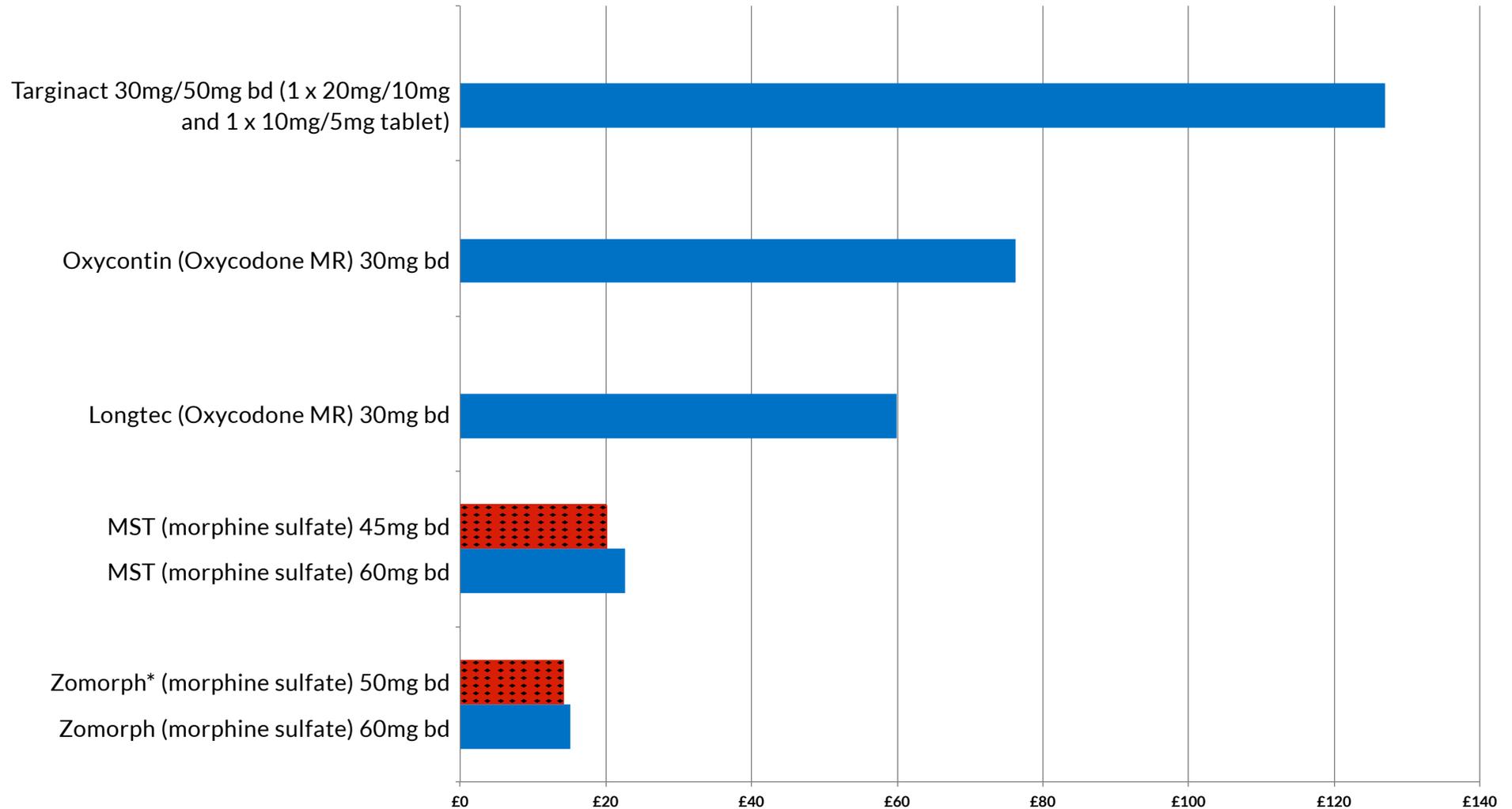
Table 1 - Cost comparisons of Targinact® tablets against morphine sulfate MR and oxycodone MR products at approximately equivalent doses^{21,22}

Cost for 28 days as a twice daily dose				Cost for 28 days as a twice daily dose			Cost for 28 days as a twice daily dose	
Morphine sulfate				Oxycodone			Oxycodone/naloxone	
	Generic/MST	Zomorph®	Filnarine SR®		Oxycontin®	Longtec®		Targinact®
5mg	£3.07							
10mg	£4.83	£3.24	£3.08	5mg	£25.04	£20.00	5mg/2.5mg	£42.32
15mg	£8.49							
				10mg	£25.04	£19.99	10mg/5mg	£42.32
30mg	£11.64	£7.75	£7.36	15mg	£38.12			
				20mg	£50.08	£39.98	20mg/10mg	£84.62
60mg	£22.70	£15.12	£14.36	30mg	£76.23			
				40mg	£100.19	£79.98	40mg/20mg	£169.28
				60mg	£152.49			

Chart 1 illustrates the cost differences between Targinact® tablets at a dose of 30mg oxycodone/15mg naloxone twice a day, oxycodone MR 30mg twice a day and different brands of morphine sulfate MR.

Morphine sulfate has been shown at a dose range of 45mg/50mg (red, spotted bar) - 60mg (blue, plain bar) twice daily, to illustrate the differing recommended dose conversion ratios: 30mg twice daily oxycodone is equivalent to 45mg morphine twice daily using the BNF conversion or 60mg morphine twice daily, using the Oxycontin® SPC conversion. There would also be the additional costs of laxatives (if not already prescribed), however these would be offset by the savings made.

Chart 1: Cost of morphine sulfate modified release, oxycodone modified release and Targinact®



Zomorph not available in 5mg tablet therefore not exact 1.5 dose conversion

28 day costs of laxatives²²

This list is not exhaustive.

Bisacodyl 10mg at night	£2.12
Lactulose 15ml twice daily	£4.74
Senna 15mg at night	£10.92
Co-danthramer 37.5/500 capsules two at night	£14.51

Switching options and savings available

There are several potential switch/review options for Targinact® products (although clinicians may choose other options according to the clinical need of the patient). These include:

1. For patients that have not previously tried morphine sulfate, switching all Targinact® prescriptions to morphine sulfate controlled release 12 hourly tablets or capsules (Zomorph® capsules or Filnarine SR® are the least costly products, MST Continus® is the most commonly prescribed tablet) could save approximately £6,900 per year per 100,000 patients. **Total savings are approximately £3.9 million nationally.**

Switch doses will need to be agreed locally between GPs, medicines management teams and pain specialists. It is advisable to use a lower dose ratio, as used in the BNF, for the switch (morphine sulfate MR at 1.5 times the oxycodone dose) and add morphine sulfate oral solution for breakthrough pain if needed. The dose of morphine sulfate can then be titrated up after review

Additional costs of laxatives or anti emetics (if needed and not already prescribed) would be minimal and have been taken into account with these savings.

2. For patients where morphine sulfate would not be suitable, a switch where appropriate to an equivalent or appropriate dose of Longtec® (branded oxycodone MR), with concomitant laxatives could save approximately £1,700 per year per 100,000 patients. **Total savings are approximately £977,000 nationally.**
3. If at review the prescribing of an opioid analgesic is no longer appropriate, then therapy should be tapered down and discontinued. Non-opioid analgesia may be appropriate in some patients. A reduction of 30% of Targinact® prescribing could save approximately £2,600 per year per 100,000 patients. **Total savings are approximately £1.5 million nationally.**

The savings above illustrate the maximum savings available, in reality the total amount would not be achieved as different options would be suitable for different patients. The data pack attached shows prescribing data at CCG level and annual savings available for each CCG for the above switches. The data pack can be downloaded by subscribers here:

<http://www.prescqipp.info/resources/viewcategory/232-oxycodone-naloxone-prolonged-release-targinact-tablets>

Savings have been calculated using a rough approximation of morphine sulfate MR being approximately 80% cheaper than oxycodone MR on average across all doses and formulations, and Longtec® being approximately 20% cheaper than Oxycontin®/generically prescribed oxycodone MR on average across all doses.

Summary

- Targinact® tablets are licensed for severe pain which can be adequately managed only with opioid analgesics. The naloxone component in Targinact® tablets is intended to counteract opioid-induced constipation.
- Trials conducted with Targinact® in patients with moderate to severe non-cancer pain have shown no difference in pain control against oxycodone. Targinact® tablets reduced but did not eliminate the need for laxatives. However, the trials did not use regular stool-softening and stimulant laxatives, as is standard practice.
- There are no published trials comparing oxycodone/naloxone PR tablets against other oral strong opioids given with regular stool-softening and stimulant laxatives, the recommended laxative regimen.
- The Scottish Medicines Consortium have not approved its use in NHS Scotland, noting that the clinical benefit in patients receiving regular laxative therapy is uncertain and the economic case for use was not proven.
- Switching treatment to morphine sulfate can lead to significant savings. If morphine sulfate is unsuitable for the patient then switching treatment to Longtec® a branded oxycodone MR product will also provide savings. Additional laxatives should be prescribed.
- Patients on long term opioid therapy for non-cancer pain should be reviewed regularly to assess whether there is a continued need for treatment.

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Additional PrescQIPP resources



Briefing



Data pack



Patient letters

Available for download here:

<http://www.prescqipp.info/resources/viewcategory/232-oxycodone-naloxone-prolonged-release-targinact-tablets>

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