



Restless legs syndrome: Oxycodone/naloxone prolonged release

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in December 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In a 12-week randomised controlled trial (RCT) in people with severe restless legs syndrome (RLS), there was a moderate improvement in the score on the International RLS study group severity rating scale with oxycodone/naloxone prolonged release tablets compared with placebo. Adverse effects such as fatigue, constipation and nausea were very common. As with all opioids, there is a risk that people may develop opioid dependence. There are no published studies which compare oxycodone/naloxone with other possible treatments for restless legs syndrome and there is limited long-term

efficacy and safety data for its use in this indication.

Regulatory status: Oxycodone/naloxone prolonged release tablets (Targinact) were originally launched in the UK in 2009 for the treatment of severe pain which can be adequately managed only with opioid analgesics. The license extension for use in restless legs syndrome was granted in the UK in April 2015.

Effectiveness	Safety
<ul style="list-style-type: none">• There was a statistically significant reduction in the <u>International RLS study group severity rating scale sum score</u> with oxycodone/naloxone compared with placebo (treatment difference 8.15 [on a scale from 0 to 40]; 1 RCT; 12 weeks; n=306); described as a moderate effect in the European Medicines Agency (EMA) <u>referral assessment report</u>.• There were statistically significant improvements in sleep scores, pain scores, quality of life scores and daytime symptoms with oxycodone/naloxone compared with placebo; the clinical significance of these improvements is unclear.	<ul style="list-style-type: none">• People taking oxycodone/naloxone for restless legs syndrome should have their treatment evaluated at least every 3 months and it should only be continued if the benefit is considered to outweigh the risks.• The contraindications to the use of oxycodone/naloxone in the summary of product characteristics (<u>SPC</u>) are in-line with the usual contraindications of opioids as a drug class.• The <u>SPC</u> lists the following very common adverse effects (1 in 10 or more) when oxycodone/naloxone is used for the treatment of restless legs syndrome: headache, somnolence, vertigo, hot flushes, blood pressure alterations, constipation, nausea, flatulence, hyperhidrosis and fatigue.• The National Patient Safety Agency (NPSA) issued a rapid response report in July 2008 on <u>reducing dosing errors with opioid analgesics</u>.

Patient factors	Resource implications
<ul style="list-style-type: none"> Oxycodone is a strong opioid and about 1.5 times the potency of oral morphine. As with all opioids, there is a risk that people may develop opioid dependence. Oxycodone can impair cognitive function and affect a person's ability to drive safely. People taking oxycodone/naloxone must be informed that if their treatment causes somnolence they must not drive or take part in activities where impaired alertness may put themselves or others at risk. Loss of efficacy commonly occurs for all drugs in the treatment of restless legs syndrome. 	<ul style="list-style-type: none"> Costs for 28 days treatment with oxycodone/naloxone for restless legs syndrome ranges from £21.16 to £126.94 depending on the dose. Costs for 28 days treatment of pregabalin, gabapentin, clonazepam and codeine phosphate (all off-label use) depend on the drug choice and dosage used. For example, pregabalin capsules 75 mg twice daily cost £64.40 and codeine phosphate tablets 30 mg twice daily cost £2.80.

Introduction and current guidance

Restless legs syndrome is a neurological disorder characterised by an irresistible urge to move the limbs (usually the legs) accompanied by uncomfortable sensations. Symptoms are typically worse in the evenings, and are often associated with sleep disturbance. In most people with restless legs syndrome there is no apparent underlying cause. Frequency of symptoms vary considerably from less than once a month to daily, and severity of symptoms can vary from mildly annoying to disabling. For people with mild symptoms, explanation, reassurance and self-help measures may be sufficient. First line drug treatment options for people with frequent or daily symptoms include non-ergot dopamine agonists (for example, pramipexole, ropinirole or rotigotine) ([NICE Clinical Knowledge Summary](#)).

Full text of [introduction and current guidance](#).

Product overview

Oxycodone/naloxone prolonged release tablets (Targinact) are licensed for the second line

symptomatic treatment of adults with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy ([SPC: Targinact](#)). They are only licensed for use in adults who have had restless leg syndrome for at least 6 months and who have daily symptoms including daytime symptoms on at least 4 days a week. The SPC recommends that the usual starting dose for restless legs syndrome is oxycodone/naloxone 5 mg/2.5 mg at 12 hourly intervals and the maximum daily dose is oxycodone/naloxone 60 mg/30 mg (usually as 30 mg/15 mg at 12 hourly intervals). This is lower than the maximum daily dose for the pain indication. There is no clinical experience of using oxycodone/naloxone for longer than 12 months to treat restless legs syndrome; the SPC recommends that before continuing treatment beyond 12 months, a 'discharge regimen' should be considered, to establish if continued treatment with oxycodone/naloxone is indicated ([SPC: Targinact](#)).

Full text of [product overview](#).

Evidence review

- This evidence summary is based on a 12-week double-blind RCT which compared oxycodone/naloxone with placebo in 306 adults with restless legs syndrome that had not responded to previous treatment ([Trenkwalder et al. 2013](#)). This study also had a 40-week open label extension phase which included 197 participants, 157 of whom completed 40 weeks of treatment. During the double-blind RCT phase of the study the mean daily dose in the active treatment group was oxycodone/naloxone 22/11 mg. In the open-label phase the mean daily dose was oxycodone/naloxone 18/9 mg.
- For the primary outcome of change from baseline to week 12 in the [International restless legs syndrome \(RLS\) study group severity rating scale sum score](#) there was a statistically significant improvement with oxycodone/naloxone compared with placebo. This scale ranges from 0 (no symptoms) to 40 (very severe symptoms). In the oxycodone/naloxone group the mean score reduced from 31.7 at baseline to 15.1 at week 12; in the placebo group it reduced from 31.6 to 22.1. The estimated mean treatment difference between the 2 groups at week 12 was 8.15 (95% CI 5.46 to 10.85; $p < 0.0001$), described as a moderate effect in the European Medicines Agency (EMA) [referral assessment report](#) for oxycodone/naloxone prolonged-release tablets.

- There was an approximately 43 minute increase in time asleep in the oxycodone/naloxone group compared with the placebo group. At baseline, sleep quantity was 5.15 and 4.97 hours in the oxycodone/naloxone and placebo groups respectively. After 12 weeks treatment, this increased to 6.25 and 5.36 hours in the oxycodone/naloxone and placebo groups respectively ($p < 0.0001$). However, there was no statistically significant difference between the 2 groups at week 12 for feeling drowsy or sleepy during the day.
- There were statistically significant improvements in pain scores and daytime symptoms with oxycodone/naloxone compared with placebo. On a scale from 0 (no pain) to 10 (worst imaginable pain) there was a reduction in the oxycodone/naloxone and placebo groups respectively from 6.57 and 6.54 at baseline to 2.65 and 4.63 at 12 weeks ($p < 0.0001$ for comparison at 12 weeks). On a scale from 0 (not present) to 10 (very severe) for daytime symptoms at rest there was a reduction in the oxycodone/naloxone and placebo groups respectively from 6.70 and 6.69 to 2.50 and 4.44 ($p < 0.0001$ for comparison at 12 weeks).
- The EMA [referral assessment report](#) for oxycodone/naloxone prolonged release tablets states that a review of the safety data from the double-blind RCT phase and open-label extension phase of Trenkwalder et al. (2013) showed that the safety profile when used for restless legs syndrome was in-line with the known safety profile when used for pain. See the [SPC](#) for further information on contraindications, potential interactions and adverse effects of oxycodone/naloxone.
- Oxycodone/naloxone has only been compared with placebo. There are no published studies which compare it with other possible treatments for restless legs syndrome. Efficacy and safety data from a double-blind RCT are only available for relatively short-term use in restless legs syndrome (12 weeks). Trenkwalder et al. (2013) did include a 40-week open-label extension phase, however only 85 participants had active treatment for 52 weeks.

Full text of [evidence review](#).

Context

Oxycodone/naloxone should only be considered after failure of dopaminergic therapy. Other non-dopaminergic drug treatment options for restless legs syndrome include off-label use of pregabalin, gabapentin, clonazepam or weak opioids such as codeine. Apart from oxycodone/naloxone prolonged-release tablets, no other opioid preparations

are specifically licensed for the treatment of restless legs syndrome.

Full text of [context](#).

Estimated impact for the NHS

Oxycodone/naloxone is a potential second-line treatment option for people with severe to very severe restless legs syndrome. However, the risk of opioid dependence will need to be considered and people prescribed this treatment will need to be reviewed on a regular basis in-line with the [SPC](#) to assess if the benefits of treatment are continuing to outweigh the risks. Oxycodone is a strong opioid and about 1.5 times the potency of oral morphine ([British National Formulary \[BNF\]](#)). As recommended in the NPSA rapid response report on [reducing dosing errors with opioid analgesics](#), health professionals should check that the intended opioid dose is safe for the individual patient whenever opioids including oxycodone are prescribed, dispensed or administered.

Based on market research conducted in 2013 amongst neurologists, the manufacturer estimates that approximately 1133 patients with restless legs syndrome or 2.1% of those treated with first line dopamine agonists would be considered for treatment with oxycodone/naloxone (Personal communication: Napp Pharmaceuticals August 2015).

Full text of [estimated impact for the NHS](#).

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a neurological

disorder characterised by an irresistible urge to move the limbs (usually the legs) accompanied by uncomfortable sensations. Symptoms are typically worse in the evenings, and are often associated with sleep disturbance ([NICE Clinical Knowledge Summary \[CKS\]](#)).

In most people with restless legs syndrome there is no apparent underlying cause (idiopathic or primary restless legs syndrome). The 3 most common causes of secondary restless leg syndrome are pregnancy, iron deficiency or stage 5 chronic kidney disease. Restless legs syndrome may also be caused or exacerbated by certain drugs. This evidence summary discusses the evidence on the safety and efficacy of oxycodone/naloxone prolonged-release tablets ([Targinact](#)), which are licensed for the second-line treatment of severe to very severe idiopathic restless legs syndrome.

The diagnosis of restless legs syndrome is based on symptoms, as there are no tests to confirm the diagnosis. The [International RLS Study Group](#) have [defined criteria](#) that must be present for a diagnosis to be made, including:

- An urge to move the legs usually, but not always, accompanied by or felt to be caused by uncomfortable and unpleasant sensations.
- Unpleasant sensations begin or worsen during periods of rest or inactivity such as sitting or lying down. They are partially or totally relieved by movement, such as walking or stretching at least as long as the activity continues.
- The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse during the evening or night than during the day.
- The occurrence of the above features is not solely accounted for as symptoms due to another medical or behavioural condition (for example, myalgia, venous stasis, leg oedema, leg cramps, positional discomfort, habitual foot tapping).

Frequency of symptoms vary considerably from less than once a month to daily and severity of symptoms can vary from mildly annoying to disabling.

Self-help treatments for people with idiopathic restless legs syndrome include good sleep hygiene, moderate exercise, stopping smoking and reducing caffeine and alcohol consumption. For people with mild symptoms, explanation, reassurance and self-help measures may be sufficient. First-line drug treatment options for people with frequent or daily symptoms include non-ergot dopamine agonists (for example, pramipexole, ropinirole or rotigotine); pregabalin (off-label use) and gabapentin (off-label use). Dopaminergic

treatment may be associated with impulse control disorders or with augmentation (worsening symptoms, in particular earlier onset in the day, increasing intensity, or spreading to the arms or trunk). CKS and specialists who commented on this evidence summary advise that weak opioids such as codeine (off-label use) may be an alternative option, particularly for people with painful symptoms of restless legs syndrome. However, there are limited published data on the use of opioids for this indication and potential risks include opioid dependence. The [International RLS study group 2013 best practice guidance for the long-term treatment of restless legs syndrome](#) also includes levodopa and clonazepam (although not as first-line treatment options). Use of these medicines would be off-label for the treatment of restless legs syndrome. Loss of efficacy commonly occurs for all drugs in the treatment of restless legs syndrome ([NICE Clinical Knowledge Summary](#)).

Product overview

Drug action

Oxycodone/naloxone prolonged-release tablets (Targinact) contain oxycodone (an opioid analgesic) and naloxone (an opioid antagonist). The opioid antagonist naloxone is added to counteract opioid induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut (summary of product characteristics [SPC]: [Targinact](#)).

Licensed therapeutic indication

Oxycodone/naloxone prolonged-release tablets (Targinact) were originally launched in the UK in 2009 for the treatment of severe pain which can be adequately managed only with opioid analgesics. The license extension for use in restless leg syndrome was granted in the UK in April 2015, following a [European Medicines Agency assessment report](#).

Oxycodone/naloxone prolonged-release tablets (Targinact) are licensed for the second line symptomatic treatment of adults with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy. They are only licensed for use in adults who have had restless leg syndrome for at least 6 months and who have daily symptoms including daytime symptoms on at least 4 days a week. The SPC defines dopaminergic treatment failure as an inadequate initial response; a response that has become inadequate with time; occurrence of augmentation or unacceptable tolerability despite adequate doses. It states that previous treatment with at least one dopaminergic product

should have lasted in general for 4 weeks ([SPC: Targinact](#)).

None of the other available oxycodone preparations are licensed for use in the treatment of restless legs syndrome. In addition, no other opioid preparations are licensed for use in the treatment of restless legs syndrome.

Course and cost

The SPC recommends that the usual starting dose when used for restless legs syndrome is oxycodone/naloxone 5 mg/2.5 mg at 12 hourly intervals. Titration on a weekly basis is recommended when higher doses are required. The mean daily dose in the pivotal study was approximately oxycodone/naloxone 20 mg/10 mg. The maximum daily dose for use in restless leg syndrome is oxycodone/naloxone 60 mg/30 mg (usually as 30 mg/15 mg at 12 hourly intervals). This is lower than the maximum daily dose when used for pain. The SPC states that symmetrical dosing (the same dose 12 hours apart) would be appropriate for the majority of people; however some people may benefit from asymmetric dosing tailored to the individual ([SPC: Targinact](#)).

People taking oxycodone/naloxone for restless legs syndrome should have their treatment evaluated at least every 3 months and it should only be continued if the benefit is considered to outweigh the risks. When treatment is discontinued it should be gradually tapered down over a period of approximately a week to reduce the risk of a withdrawal reaction. There is no clinical experience of using oxycodone/naloxone for longer than 12 months to treat restless legs syndrome; the SPC recommends that before continuing treatment beyond 12 months, a 'discharge regimen' should be considered, to establish if continued treatment with oxycodone/naloxone is indicated ([SPC: Targinact](#)).

Oxycodone/naloxone prolonged-release tablets are available in 4 different strengths for the restless legs syndrome indication:

- oxycodone/naloxone 5 mg/2.5 mg, with a cost of £21.16 for 28 tablets
- oxycodone/naloxone 10 mg/5 mg, with a cost of £42.32 for 56 tablets
- oxycodone/naloxone 20 mg/10 mg, with a cost of £84.62 for 56 tablets
- oxycodone/naloxone 40 mg/20 mg, with a cost of £169.28 for 56 tablets

The maximum daily dose for this indication is oxycodone/naloxone 60 mg/30 mg. The SPC

states that symmetric administration is appropriate for the majority of people; the higher strength tablet (oxycodone/naloxone 40 mg/20 mg) may be used for those people who need an asymmetric dosing regimen.

Costs for 28 days treatment range from £21.16 at a dose of oxycodone/naloxone 5 mg/2.5 mg 12 hourly to £126.94 at a dose of oxycodone /naloxone 30 mg/15 mg 12 hourly (MIMS: November 2015).

Evidence review

This evidence summary discusses the [best available evidence](#) on the safety and efficacy of oxycodone/naloxone prolonged-release tablets (Targinact), which is a 12-week double-blind [randomised controlled trial](#) (RCT) comparing oxycodone/naloxone with placebo in people with restless legs syndrome ([Trenkwalder et al. 2013](#)). The pivotal study included a 40 week open label extension phase, which is only discussed briefly in the evidence summary due to the non-comparative design. Information from the published double-blind RCT phase and open-label extension phase studies have been supplemented and clarified using the European Medicines Agency (EMA) [referral assessment report](#) for oxycodone/naloxone prolonged-release tablets.

Trenkwalder et al. (2013)

- Design: 12-week double-[blind](#) placebo-controlled RCT, with a 40 week open-label extension phase. Conducted at 55 sites across 4 countries (Austria, Germany, Spain and Sweden). [Allocation was concealed](#).

- Population: The RCT included 306 adults (mean age 62 years; 66.5% women; mean duration of symptoms 10 years) with a diagnosis of primary restless legs syndrome not related to an underlying condition or medication (as assessed by a score of 11 or more on the restless legs syndrome diagnostic index). Participants had symptoms for at least 6 months, an International Restless Legs Syndrome (RLS) study group severity rating scale sum score of at least 15 (scale from 0 [no symptoms] to 40 [very severe symptoms]) and daytime onset of symptoms before 6pm on at least 4 days per week. Participants had received previous treatment for restless legs syndrome but this had either been ineffective or caused intolerable side-effects. At screening 221 participants were receiving dopaminergic treatment. Participants had not received regular opioid-containing medication prior to enrolment on the study. Other exclusion criteria included a history of sleep disturbances including sleep apnoea, acute clinical augmentation (according to Max Planck Institute diagnostic criteria), dementia, epilepsy, significant cardiovascular, renal, hepatic or psychiatric disease, a history of alcohol or drug abuse or people with respiratory disease or constipation. Stable non-opioid analgesics which were being taken for other indications could be continued during the study. The open-label extension phase included 197 participants recruited from the double-blind RCT phase, 157 of whom completed 40 weeks of treatment.
- Intervention and comparisons: At screening participants entered a washout phase where previous treatments for restless legs syndrome were tapered off. Participants had not received any drugs for restless legs syndrome for 7 days prior to randomisation. After the washout period participants were randomised 1:1 to either oxycodone/ naloxone prolonged-release tablets or matching placebo. Oxycodone/ naloxone was initiated at a dose of 5 mg/2.5 mg twice daily. During the first 6 weeks of the RCT this dose could be titrated as necessary in weekly increments to a maximum of oxycodone/naloxone 40 mg/20 mg twice daily. The achieved dose was then maintained for the second 6 weeks of the RCT. After the 12-week double-blind RCT phase of the study the dose was titrated down to oxycodone/naloxone 5 mg/ 2.5 mg twice daily (the starting dose for the open-label phase). During the open-label phase the dose could again be titrated up-to a maximum of oxycodone/ naloxone 40 mg/20 mg twice daily.

- **Outcomes:** The primary outcome was the mean change from baseline to week 12 for the International RLS study group severity rating scale sum score. This scale ranges from 0 (no symptoms) to 40 (very severe symptoms). The study was powered to detect a difference of 4 points between the 2 groups. Secondary outcomes included change in clinical global impression scores, pain scores, daytime symptoms, quality of life assessments, measures of sleep adequacy and quantity and incidence of augmentation. The efficacy outcomes for the RCT phase of the study were conducted on a modified intention to treat population (mITT, all participants randomised to treatment who received at least 1 dose of study drug during the double-blind phase and had at least 1 week of double-blind assessment for the primary outcome). Treatment groups were compared using a mixed-model repeated measure ANCOVA method. Safety outcomes were analysed descriptively in all participants who received study medication; outcomes included adverse events, changes in clinical laboratory parameters, vital signs and ECG readings.

Table 1 Summary of 12-week RCT phase of Trenkwalder et al. (2013)

	Oxycodone/ naloxone prolonged-release	placebo	Analysis
Randomised ^a	n=150	n=154	
Efficacy (modified ITT population^b)	n=132	n=144	
Primary outcome: mean change from baseline (SD) to week 12 (SD) for the International RLS study group severity rating scale sum score ^c	Baseline: 31.7 (4.4) Week 12: 15.1 (10.6)	Baseline: 31.6 (4.7) Week 12: 22.1 (12.2)	Estimated treatment difference at week 12: 8.15 (95% CI 5.46 to 10.85; $p < 0.0001$)
Selected secondary outcomes:			
Clinical global impression-1 score relating to severity of disease (SD) ^d	Baseline: 5.24 (0.88) Week 12: 2.99 (1.48)	Baseline: 5.29 (0.85) Week 12: 4.10 (1.71)	$p < 0.0001$ for comparison at 12 weeks

RLS-6 daytime symptoms at rest score (SD) ^e	Baseline: 6.70 (2.19) Week 12: 2.50 (2.69)	Baseline: 6.69 (2.51) Week 12: 4.44 (3.30)	p<0.0001 for comparison at 12 weeks
RLS-QOL summary question 12 score (SD) ^f	Baseline: 4.30 (0.93) Week 12: 2.91 (1.48)	Baseline: 4.27 (1.10) Week 12: 3.64 (1.67)	p<0.0001 for comparison at 12 weeks
NRS pain score (SD) ^g	Baseline: 6.57 (2.53) Week 12: 2.65 (2.61)	Baseline: 6.54 (2.78) Week 12: 4.63 (3.21)	p<0.0001 for comparison at 12 weeks
Sleep quantity (SD) ^h	Baseline: 5.15 (1.47) Week 12: 6.25 (1.33)	Baseline: 4.97 (1.53) Week 12: 5.36 (1.76)	p<0.0001 for comparison at 12 weeks
Drowsy or sleepy during the day (SD) ^{h,i}	Baseline: 3.05 (1.32) Week 12: 3.70 (1.35)	Baseline: 3.08 (1.32) Week 12: 3.49 (1.52)	p=0.7455 for comparison at 12 weeks
Safety^j	n=150	n=154	
Any adverse event	84% (126/150)	69% (106/154)	
Adverse events leading to withdrawal from the study	15% (22/150)	7% (10/154)	
Serious adverse events related to treatment ^k	3% (5/150)	0	
Fatigue	29% (44/150)	13% (20/154)	
Constipation	19% (29/150)	5% (7/154)	
Nausea	17% (26/150)	9% (14/154)	

Headache	13% (20/150)	7% (11/154)	
<p>Abbreviations: CI, <u>confidence interval</u>; ITT, <u>intention to treat</u>; NRS, numerical rating scale; QOL, quality of life; RLS, restless legs syndrome; SD, standard deviation.</p> <p>^a 306 participants were randomised to treatment. Two participants did not receive the study drug. It was not reported which group these 2 participants had been randomised to.</p> <p>^b Modified ITT population: all participants randomised to treatment who received at least 1 dose of study drug during the double-blind phase and had at least 1 week of double-blind assessment for the primary outcome.</p> <p>^c <u>International RLS study group severity rating scale sum score</u>: this scale includes 10 questions which assess symptoms associated with restless legs syndrome. Each question is rated on a scale from 0 (no symptoms) to 4 (very severe symptoms). Sum score ranges from 0 to 40. The overall score gives an indication of severity: mild 1–10; moderate 11–20; severe 21–30; very severe 31–40.</p> <p>^d <u>Clinical global impression score</u>: from 1 (not ill at all) to 7 (extremely ill).</p> <p>^e <u>RLS-6 daytime symptoms at rest score</u>: from 0 (not present) to 10 (very severe).</p> <p>^f RLS-QOL summary question 12 score: 'To what degree did your RLS symptoms impair your quality of life during the last 4 weeks?' scored from 1 (not at all) to 6 (extremely).</p> <p>^g <u>NRS pain score</u>: from 0 (no pain) to 10 (worst imaginable pain).</p> <p>^h Measures of sleep adequacy taken from the <u>Medical Outcomes study sleep scale</u>.</p> <p>ⁱ Drowsy or sleepy during the day: from 1 (all the time) to 6 (never).</p> <p>^j Safety population: all randomised participants who received study medication. No statistical analysis reported for safety outcomes.</p> <p>^k Serious adverse events related to treatment: vomiting, constipation (n=2), ileus, subileus, acute flank plank.</p>			

Clinical effectiveness

Oxycodone/naloxone prolonged-release has been compared with placebo in adults with restless legs syndrome in whom previous treatment had either been ineffective or not tolerated in a 12-week double-blind RCT ([Trenkwalder et al. 2013](#)). During the double-blind RCT phase of the study the mean daily dose in the active treatment group was oxycodone/naloxone 22/11 mg. In the open-label extension phase the mean daily dose was oxycodone/naloxone 18/9 mg.

For the primary outcome of change from baseline to week 12 in the International RLS study group severity rating scale sum score there was a statistically significant improvement with oxycodone/naloxone compared with placebo (see table 1 above). In the oxycodone/naloxone group the mean score reduced from 31.7 at baseline to 15.1 at week 12, in the placebo group the mean score reduced from 31.6 at baseline to 22.1 at week 12. The estimated mean treatment difference between the 2 groups at week 12 was 8.15 (95% CI 5.46 to 10.85; $p < 0.0001$). After 12 weeks treatment statistically significantly more people in the oxycodone/naloxone group had at least a 50% improvement in the International RLS study severity rating scale sum score compared with the placebo group (57% [75/132] compared with 31% [45/144]; $p < 0.0001$).

The EMA referral assessment report for oxycodone/naloxone prolonged-release tablets describes this as a moderate treatment effect, noting that the treatment difference on the International RLS study group severity rating scale sum score seen with oxycodone/naloxone was in line with that shown in placebo-controlled studies of dopamine agonists as first-line treatments. However, this is not based on a direct comparison and the patient populations in these studies are likely to have been different (see evidence strengths and limitations).

Trenkwalder et al. (2013) included a variety of patient-orientated secondary outcomes assessing outcomes such as daytime symptoms, pain, sleep and quality of life (QOL). There were statistically significant improvements at week 12 in the oxycodone/naloxone group compared with the placebo group for clinical global impression score, RLS-6 daytime symptoms at rest score, RLS-QOL summary question 12 score, some medical outcomes study sleep subscale scores and the NRS pain score (see table 1 for details). However, the clinical significance of these improvements is unclear. There was a statistically significant increase in sleep quantity in the oxycodone/naloxone group compared with the placebo group. At baseline, sleep quantity was 5.15 and 4.97 hours in the oxycodone/naloxone and placebo groups respectively. After 12 weeks treatment, this increased to 6.25 and 5.36 hours in the oxycodone/naloxone and placebo groups respectively ($p < 0.0001$). This equates to approximately a 43 minute increase in sleep in the oxycodone/naloxone group compared with the placebo group. There was no statistically significant difference between the 2 groups at week 12 for feeling drowsy or sleepy during the day (see table 1 for details).

Trenkwalder et al. (2013) also included an open-label 40 week extension phase. The open-label extension phase included 197 participants, 157 of whom completed 40 weeks of treatment. At the start of the open-label phase the mean International RLS study group

severity rating scale sum score was 15.4, at the end of the open-label phase it was 9.7.

Participants were assessed for augmentation throughout the study (according to [Max Planck Institute diagnostic criteria](#)). During both phases of the study, 63 people who reported worsening symptoms were assessed for augmentation; however no augmentation was observed.

Safety and tolerability

An [EMA referral assessment](#) was conducted for oxycodone/naloxone prolonged release tablets, as there was a disagreement between member states regarding the license extension, with one European country of the opinion that the benefit-risk balance for the restless legs syndrome indication was negative, with particular concerns regarding tolerance and drug misuse.

The [EMA referral assessment report](#) for oxycodone/naloxone prolonged release tablets states that safety data from the double-blind RCT and open-label extension phases of [Trenkwalder et al. \(2013\)](#) show that when oxycodone/naloxone prolonged-release is used for restless legs syndrome the safety profile is comparable to the known safety profile when used for pain.

According to the EMA referral assessment report, the frequency of adverse events and related adverse events were mostly comparable for both the double-blind RCT and open-label extension phases of [Trenkwalder et al. \(2013\)](#).

During the double-blind RCT phase of [Trenkwalder et al. \(2013\)](#) adverse events were reported by 84% (126/150) of participants in the oxycodone/naloxone group and 69% (106/154) of participants in the placebo group. Fatigue, constipation and nausea were the most commonly reported adverse events (see table 1 for details). Adverse events that caused withdrawal from the study occurred in 15% (22/150) of participants in the oxycodone/naloxone group compared with 7% (10/154) in the placebo group. Serious adverse events related to treatment were reported in 3% (5/150) of participants in the oxycodone/naloxone group (vomiting, constipation [n=2], ileus, subileus and acute flank pain) and no participants in the placebo group. No statistical analysis was presented for the safety outcome data.

During the 40-week open label extension phase of the study, 76% (150/197) of participants reported adverse events, 9% (18/197) had adverse events that caused

withdrawal from the study and 2% (3/197) had serious treatment-related adverse events. Constipation was the most frequent adverse event during the open-label phase being reported by 15% (30/197) of participants. Nausea was reported in 10% (20/197) and fatigue was reported in 10% (19/197) of participants.

Four weeks after the end of the open-label phase of the study 176 participants were reassessed for symptoms of physical and psychological dependence (no details were provided on how this assessment was carried out). [Trenkwalder et al. \(2013\)](#) reported drug withdrawal symptoms in 1 participant after 12 weeks and 2 participants after 1 year of treatment. The EMA referral assessment report states that 10 people (out of the 176 reassessed) reported signs of physical dependence. However the referral assessment report comments that the study protocol did not stipulate dose tapering and in the majority of these 10 people no dose tapering had been conducted.

The [SPC](#) lists the following very common adverse effects (1 in 10 or more) when oxycodone/naloxone is used for the treatment of restless legs syndrome: headache, somnolence, vertigo, hot flushes, blood pressure alterations, constipation, nausea, flatulence, hyperhidrosis and fatigue. Oxycodone can impair cognitive function and affect a person's ability to drive safely. People taking oxycodone/naloxone must be informed that if their treatment causes somnolence they must not drive or take part in activities where impaired alertness may put themselves or others at risk ([SPC: Targinact](#)).

The contraindications to the use of oxycodone/naloxone are in-line with those of opioids as a drug-class. As stated in the SPC for people taking high doses of regular opioids, switching to oxycodone/naloxone could provoke withdrawal symptoms. Caution is advised in treating people with sleep apnoea syndrome in addition to restless legs syndrome, due to the additive risk of respiratory depression. People with sleep apnoea syndrome were excluded from clinical trials ([SPC: Targinact](#)).

As with all opioids, the SPC notes that there is a risk that people may develop opioid dependence. For the indication of restless legs syndrome, oxycodone/naloxone is contraindicated in people with a history of opioid abuse. The SPC recommends that treatment should be reviewed every 3 months to evaluate whether the benefits of treatment continue to outweigh the risks. There is no clinical experience of using oxycodone/naloxone for longer than 12 months to treat restless legs syndrome; the SPC recommends that before continuing treatment beyond 12 months, a 'discharge regimen' should be considered, to establish if continued treatment with oxycodone/naloxone is indicated ([SPC: Targinact](#)).

See the [SPC](#) for further information on contraindications, potential interactions and adverse effects of oxycodone/naloxone prolonged release.

The National Patient Safety Agency (NPSA) issued a rapid response report in July 2008 on [reducing dosing errors with opioid analgesics](#) in response to reports of 5 deaths and over 4000 dose-related patient safety incidents concerning opioid medicines. It reminds health professionals of their responsibility to check that the intended opioid dose is safe for the individual patient and applies when opioids including oxycodone are prescribed, dispensed or administered.

Evidence strengths and limitations

Oxycodone/naloxone prolonged-release has only been compared in 1 RCT, without an active control arm. Efficacy information from double-blind RCT data is only available for relatively short-term use (12 weeks). [Trenkwalder et al. \(2013\)](#) included an open-label 40-week extension phase, 101 people in the treatment arm of the double-blind RCT phase entered the open-label extension phase with 16 of these participants dropping out before completion, so 52-week safety data is only available for a small number of participants. In addition, participants and investigators in the extension-phase of the study were not blinded to treatment and therefore these results are subject to potential selection and attrition bias. The EMA [referral assessment report](#) for oxycodone/naloxone states that the investigators did put in place measures to mitigate for the methodological limitations of the extension phase and the Committee for Medicinal Products for Human Use ([CHMP](#)) considered that reasonable justifications were made by the manufacturer for maintenance of effect up to 52 weeks of treatment.

The EMA referral assessment report states that a review of the safety data from [Trenkwalder et al. \(2013\)](#) showed that the safety profile when used for restless legs syndrome was in-line with the known safety profile when used for pain. Oxycodone/naloxone prolonged release tablets have been available in the UK since 2009 for the treatment of severe pain which can be adequately managed only with opioid analgesics.

Oxycodone/naloxone has been compared with placebo. There are no published studies which compare oxycodone/naloxone with other possible treatments for restless legs syndrome. The EMA referral assessment report comments that the treatment difference on the International RLS study group severity rating scale sum score seen with oxycodone/naloxone was in-line with that shown in placebo-controlled studies of dopamine agonists as first-line treatments. However, this is not based on a direct comparison and the patient

populations in the 2 studies are likely to have been different with respect to disease severity and previous treatments used. Oxycodone/naloxone is licensed as a second-line treatment for people with severe to very severe idiopathic restless legs syndrome and the study population in Trenkwalder et al. (2013) reflected this. Studies of dopamine agonists as first-line agents are likely to have included people with less severe symptoms.

The primary outcome of the study was change from baseline in the International RLS study group severity rating scale sum score, which is a validated scale for assessing restless legs syndrome symptoms. A number of patient-orientated secondary outcomes were also assessed. It is unclear if validation of all the scales used for the secondary outcomes have been published; the RLS-QOL scale used has been published as an abstract only, for example. Allocation to the double-blind RCT phase of the study was concealed. The use of the analysis of covariance (ANCOVA) method of analysis adjusted for variables including baseline International RLS study group severity rating scale sum score.

Participants with sleep disorders including sleep apnoea syndrome were excluded from the study. This is highlighted in the SPC. People with clinically significant cardiovascular, renal, hepatic, psychiatric illness or dementia were also excluded from the study. Therefore the study provides no data on the use of oxycodone/naloxone to treat restless legs syndrome in people with these concomitant disorders.

Participants in Trenkwalder et al. (2013) had an established diagnosis of primary restless legs syndrome, had received previous treatment for restless legs syndrome (for an average of 5 years) with very severe symptoms at baseline (mean International RLS study group severity rating scale sum score approximately 32). The results of this study provide no evidence on the use of oxycodone/naloxone as a first-line treatment for restless legs syndrome, for use in people with less severe symptoms, or for use in those with symptoms secondary to medication or an underlying condition. This is in-line with the licensed indication, second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.

Context

Alternative treatments

Oxycodone/naloxone prolonged release (Targinact) is licensed for the second line symptomatic treatment of adults with severe to very severe idiopathic restless legs

syndrome after failure of dopaminergic therapy. Other non-dopaminergic drug treatment options for restless legs syndrome include pregabalin, gabapentin, clonazepam or weak opioids such as codeine. The use of all these alternative treatments in people with restless legs syndrome is off-label.

Costs of alternative treatments

Drug	Example doses	Estimated cost for 28 days treatment (excluding VAT) ^c
Oxycodone/naloxone prolonged release	One 10 mg/5 mg prolonged-release tablet every 12 hours ^a	£42.32 ^c
Clonazepam (off-label use)	One to four 500 microgram tablets at night ^b	£2.03 to £8.13 ^d
Codeine phosphate (off-label use)	One 30 mg tablet 1 to 4 times a day ^b	£1.40 to £5.60 ^d
	One 60 mg tablet 1 to 4 times a day ^b	£2.52 to £10.08 ^d
Gabapentin (off-label use)	One 300 mg capsule 3 times a day ^b	£3.19 ^d
	One 600 mg tablet 3 times a day ^b	£9.12 ^d
Pregabalin (off-label use)	One 75 mg capsule twice a day ^b	£64.40 ^d
	One 150 mg capsule twice a day ^b	£64.40 ^d

^a Mean daily dose used in the pivotal study.

^b Doses shown are example doses and do not represent the full range that can be used and do not imply therapeutic equivalence. For prescribing information please refer to the relevant [summary of product characteristics](#).

^c Prices based on [MIMS](#) November 2015.

^d Prices based on [Drug Tariff](#) November 2015.

Estimated impact for the NHS

Likely place in therapy

Oxycodone/naloxone prolonged-release is licensed for the second line symptomatic treatment of adults with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy ([SPC: Targinact](#)). It is only licensed for use in adults who have had restless leg syndrome for at least 6 months and who have daily symptoms including daytime symptoms on at least 4 days a week. It should only be considered after failure of previous dopaminergic treatment.

Oxycodone/naloxone prolonged-release has been compared with placebo in a 12-week double-blind RCT. There are no published studies which compare the efficacy or safety of oxycodone/naloxone with other possible treatments for restless legs syndrome. Other non-dopaminergic drug treatment options for people with restless legs syndrome include off-label use of pregabalin, gabapentin, clonazepam, or weak opioids such as codeine. Apart from oxycodone/naloxone prolonged-release tablets, no other opioid preparations are specifically licensed for the treatment of restless legs syndrome.

Oxycodone is a strong opioid and about 1.5 times the potency of oral morphine ([British National Formulary \[BNF\]](#)). As with all opioids there is a risk that people may develop opioid dependence. The SPC recommends that treatment should be reviewed every 3 months to evaluate whether the benefits of treatment continue to outweigh the risks. There is no clinical experience of using oxycodone/naloxone for longer than 12 months to treat restless legs syndrome; the SPC recommends that before continuing treatment beyond 12 months, a 'discharge regimen' should be considered, to establish if continued treatment with oxycodone/naloxone is indicated ([SPC: Targinact](#)).

Loss of efficacy commonly occurs for all drugs in the treatment of restless legs syndrome, this will need to be considered alongside the risk of opioid dependence in people prescribed oxycodone/naloxone for this indication. They will need to be reviewed on a regular basis in-line with the SPC to assess if the benefits of treatment are continuing to outweigh the risks. Oxycodone can impair cognitive function and can affect a person's ability to drive safely, these risks should be discussed when this treatment is being considered.

Estimated usage

Based on market research conducted in 2013 amongst neurologists, the manufacturer estimates that approximately 1133 patients with restless legs syndrome or 2.1% of those treated with first line dopamine agonists would be considered for treatment with oxycodone/naloxone (Personal communication: Napp Pharmaceuticals August 2015).

Relevance to NICE guidance programmes

Oxycodone/naloxone for the indication of restless legs syndrome is not appropriate for referral for a NICE technology appraisal and it is not currently planned into any work programme.

There is no published NICE guidance on the treatment of restless legs syndrome.

References

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Hilary Tyne has had 1 night accommodation costs and 50% reimbursement for train fare costs for attendance at an educational meeting paid for by Lundbeck Teva

Dr Sundus Alusi and Dr Timothy Malone had no relevant interests to declare

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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