LMMG New Medicine Recommendation

Tapentadol SR (Palexia® SR▼) for severe chronic pain in adults

LMMG Recommendation:

Black: Tapentadol SR (Palexia® SR▼) is **not** recommended for use in adult patients with severe chronic non-cancer pain

Summary of supporting evidence:

- The request to LMMG was for use of tapentadol SR as a third-line opioid in patients failing on or intolerant of oxycodone SR. There are no data relating to this proposed positioning for tapentadol SR in patients with severe pain who have failed on both morphine and oxycodone SR. There are no direct comparative data against transdermal fentanyl, which would potentially be displaced by the proposed use of tapentadol SR.
- Data to support the use of tapentadol SR in patients with severe pain who have failed on prior opioids are limited to subgroup analyses in a third of patients included in key trials. Prior opioid experience in this subgroup was mainly with tramadol and hydrocodone, rather than morphine or other strong opioids.
- A meta-analysis of three trials in patients with moderate to severe knee osteoarthritis and low back pain, with or without prior opioid treatment experience, indicates tapentadol SR was non-inferior to oxycodone SR, and was associated with fewer gastrointestinal adverse effects and improved patient health status compared with oxycodone SR, in these patients. However, the trials precluded use of breakthrough pain management and it is also unclear whether routine gastro-intestinal (GI) prophylaxis was used, which would be available in standard clinical practice. The extent to which the trial-based improved GI tolerability would be realised in routine practice is therefore unclear.
- There was a high degree of patient drop out from trials that created an imbalance in patient numbers analysed. The actual mean reductions in pain intensity over those achieved with placebo (-0.5 for tapentadol SR, and -0.3 for oxycodone SR) are statistically significant but the clinical significance of these is unclear for both tapentadol SR and oxycodone SR.
- Efficacy data appear limited to non-cancer pain; the licensed indication does not preclude use in cancer pain, but the SPC for tapentadol SR notes that only limited data are available for cancer pain and therefore, for the time being, there are not enough data to give any recommendations in this regard.
- At equivalent doses, the acquisition costs of tapentadol SR appear to be similar to oxycodone SR (current tariff price) and greater than transdermal fentanyl. It should be noted that oxycodone is off patent and its price may drop in the future.

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Reviewer:	**Warren Linley**
Version:	**LMMG Recommendation**
Clinical Reference Group (if appropriate)	**Rheumatology** **Pain clinic**

	Oncology **Palliative Care**
Date of formal consultation:	**08 August 2013**
Date of recommendation to member organisations by LMMG:	**12 September 2013**

Details of Review

Name of medicine (generic & brand name)**:** Tapentadol SR (Palexia SR®▼)[1]
Strength(s) and Form(s): Film-coated modified-release tablets[1] 50mg, 100mg, 150mg, 200mg and 250mg
Licensed indication(s): Management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics[1]
Reason for Review: Requested by Dr M Y Aglan (Chronic Pain Management). Also Dr De La Torre (Chronic Pain), Dr R Ley (Rheumatology), Dr M Hogg (Oncology), Dr M Kitching (Palliative Care, Dr Goorah (Care of the Elderly)
Proposed use (if different from or in addition to licensed indication above): As per licensed indication but limited to only those patients who are not responding to oxycodone. For initiation by consultants only, with continued prescribing in primary care.

Background and context

Chronic pain may be defined as pain that persists past the normal healing time of 3 months.[2] Chronic pain can severely affect quality of life, manifesting as physical and psychological disability with a high prevalence of comorbidities.

NICE clinical Guideline 88: Low back pain. Early management of persistent non-specific low back pain[3] suggests the following:

1.8.1 Advise the person to take regular paracetamol as the first medication option.
1.8.2 When paracetamol alone provides insufficient pain relief, offer:
- non-steroidal anti-inflammatory drugs (NSAIDs) **and/or**
- weak opioids

1.8.6 Consider offering strong opioids for short-term use to people in severe pain.
1.8.7 Consider referral for specialist assessment for people who may require prolonged use of strong opioids.

NICE clinical guideline 59: Osteoarthritis. This guideline covers the treatment, advice and support that people who have osteoarthritis[4] should be offered by their healthcare professional and when being referred to specialist care, and suggests the following for oral analgesia.

> 1.4.1 Oral analgesics
> 1.4.1.1 Healthcare professionals should consider offering paracetamol for pain relief in addition to core treatment; regular dosing may be required. Paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) should be considered ahead of oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids.
> 1.4.1.2 If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in elderly people.

Tapentadol is an opioid analgesic combining two mechanisms of action: μ-opioid receptor agonism and noradrenaline re-uptake inhibition. Tapentadol sustained release (SR) is licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics[1].

LMMG has been requested to consider the use of Tapentadol SR by a consultant from the East Lancashire Health Economy, where it is reported that existing guidelines[5] for the management of severe pain with strong opioids recommend:

1st line: Morphine SR plus laxatives. If ineffective then

2nd line: Oxycodone SR (Oxycontin®) plus laxatives. If ineffective or not tolerated then

3rd line: Pain patch (Fentanyl).

The request to LMMG proposes that Tapentadol SR is used as the 3rd line agent following failure or intolerance on Oxycodone SR (i.e. before fentanyl patch). Initiation is to be by consultant only, with continued prescribing in primary care.

Evidence in Proposed Use

Summary of Efficacy Data in Proposed Use:

This evidence review draws largely on the comprehensive overview of efficacy , safety and cost effectiveness data included in the advice on tapentadol SR issued by the Scottish Medicines Consortium (SMC) in May 2011[6] and the assessment report of the All Wales Medicines Strategy Group (AWMSG) produced in October 2011[7], supplemented with published data.

Key efficacy data are derived from two trials in patients with osteoarthritis of the knee and one trial in patients with low back pain. All had common trial designs.

Trial designs: Randomised, double-blind, active and placebo-controlled, phase III studies. Initial three-week titration phase followed by a 12-week maintenance phase.

Patients: Adults aged 40 years or older with osteoarthritis of the knee, or 18 years and older with low back pain, who had moderate to severe pain requiring analgesics for three or more months (non-opioids or opioids at doses equivalent to 160mg or less oral morphine per day) but who were dissatisfied with their current analgesics. Around one-third of all patients had severe pain and were opioid treatment experienced.

Interventions and Comparators: Patients were randomised in a ratio of 1:1:1 to receive tapentadol SR, oxycodone MR or placebo, with stratification by study site. During a three week titration phase, patients were initiated on tapentadol SR 50mg twice daily, oxycodone MR 10mg twice daily or placebo, with the dose adjusted if required, to optimal dose (tapentadol SR 100 to 250mg twice daily; oxycodone MR 20 to 50mg twice daily) that was encouraged to be kept stable for the maintenance phase. No breakthrough pain relief was permitted in the maintenance phase.

Outcomes: A high proportion of patients failed to complete the 12 week maintenance phase across the three trials (62% on oxycodone SR, 44% on tapentadol SR and 41% on placebo). The primary endpoint was change from baseline in average pain intensity over the 12-week maintenance period, measured on a numeric rating scale with the last observation carried forward for missing data due to early discontinuation. The back pain study and one study in patients with knee osteoarthritis found a significant difference between both tapentadol SR and oxycodone SR against placebo. The second study in patients with knee osteoarthritis failed to find a significant difference between either tapentadol SR or oxycodone SR and placebo.

A pre-planned meta-analysis of the three studies was performed, firstly to test for superior gastrointestinal tolerability of tapentadol SR versus oxycodone SR and, if that was demonstrated, non-inferiority for efficacy. Tapentadol SR was non-inferior to oxycodone SR in terms of change from baseline in average pain intensity (change in pain intensity over 12 weeks: -2.2 for placebo vs. -2.7 for tapentadol SR, $p<0.001$; -2.5 for oxycodone MR, $p<0.001$)[8]. The meta-analysis also found that the secondary endpoint of proportion of patients achieving a $\geq$30% improvement from baseline in pain intensity was significantly greater for tapentadol SR versus placebo (41.3% vs. 34.8%; $p=0.003$; NNT=15), as was the proportion achieving a $\geq$50% improvement from baseline (30.1% vs. 23.5; $p<0.001$; NNT=15), but no significant difference versus placebo was observed in those who received oxycodone SR (20.8%; $p=0.153$). Despite these findings, treatment discontinuation due to lack of efficacy were marginally numerically more frequent for tapentadol SR than for oxycodone SR (6.2% vs. 3.4%). Although there were mixed results in the individual trials, the meta-analysis found tapentadol SR improved patients' own ratings of health status and health-related quality of life compared with both placebo and oxycodone SR[6,7,8].

The SMC and AWMSG reports also include brief details of a subgroup analysis in patients with severe pain and prior opioid experience (mainly tramadol, and also hydrocodone which is used mainly in the United States), representing around a third of the trial populations. Oxycodone SR was found to be significantly better than placebo at reducing the pain score from baseline over the whole maintenance period. For tapentadol SR, reductions in pain score from baseline were similar to those in the total meta-analysis population, but the statistical significance of the result compared with placebo was dependent on the methods used to account for treatment discontinuations. Responder rates at ≥30% and ≥50% level in the subgroup analysis were similar to those of the total meta-analysis population, but were not significant for tapentadol SR versus placebo. The only significant response was for oxycodone SR versus placebo for ≥50% improvement in pain intensity[6].

Summary of Safety Data:

The meta-analysis of the three key trials indicated that tapentadol SR had significantly better gastrointestinal tolerability than oxycodone SR (see Table 1). The total incidence of gastrointestinal adverse events was significantly lower with tapentadol SR than oxycontin SR (42.8% versus 65.6%; p<0.001; one more patient experienced a gastrointestinal adverse event for every four patients treated with oxycodone SR instead of tapentadol SR). The incidence of constipation was reported to be significantly lower with tapentadol SR than oxycodone SR, as were nausea and vomiting. Adverse events related to the nervous system were generally numerically but not statistically significantly lower in the tapentadol SR group than the oxycodone SR group. Discontinuations due to adverse events occurred in 18% of tapentadol SR, 39% of oxycodone SR and 6.6% of placebo recipients.

Table 1: Summary of meta-analysis for incidence (%) of adverse events (ADR)

ADR	Tapentadol SR (%)	Oxycodone SR (%)	NNH†
Constipation*	16.9	33.0	6
Nausea*	20.7	36.2	6
Vomiting*	8.2	21.0	8
Nausea & vomiting*	23.3	42.7	5
Dizziness	17	21	
Headache	15	13	
Somnolence	12	17	
Pruritus	5.2	13.4	

*p<0.001, otherwise not statistically significantly different
†Number needed to harm; number of patients needed to be treated with oxycodone SR instead of tapentadol SR for one more patient to experience the ADR

Summary of Evidence on Cost Effectiveness and Patient Outcomes:

SMC and AWMSG reports include details of cost utility analyses of tapentadol SR compared to oxycodone SR and fentanyl transdermal patches for the management of severe chronic pain in adults. The analyses were restricted to the use of tapentadol SR as a second-line treatment in patients who have had an inadequate response or intolerance to modified release morphine sulphate. Based on data from the meta-analysis of the three key trials, tapentadol SR was estimated to be both less costly and to generate more quality-adjusted life years (QALYs) than oxycodone SR in the whole trial population (patients with moderate to severe pain with or without prior opioid treatment experience) and in the more relevant subgroup of patients with severe pain and prior opioid treatment experience. The key driver of these results was the higher rate of discontinuations due to adverse events with oxycodone SR, which outweighed the higher rate of discontinuations due to lack of efficacy observed with tapentadol SR[7,8].

Tapentadol SR was also estimated to be less costly and more effective than fentanyl transdermal patches at equivalent analgesic doses; however, the analysis relied on an unadjusted/naive indirect comparison of trial data, which is subject to considerable uncertainty.

Key Points to Note from the Available Evidence:

- The request to LMMG was for use of tapentadol SR as a third-line opioid in patients failing on or intolerant of oxycodone SR. There are no data relating to this proposed positioning for tapentadol SR in patients with severe pain who have failed on both morphine and oxycodone SR. There are no direct comparative data against transdermal fentanyl, which would potentially be displaced by the proposed use of tapentadol SR.
- Data to support the use of tapentadol SR in patients with severe pain who have failed on prior opioids are limited to subgroup analyses in a third of patients included in key trials. Prior opioid experience in this subgroup was mainly with tramadol and hydrocodone, rather than morphine or other strong opioids.
- A meta-analysis of three trials in patients with moderate to severe knee osteoarthritis and low back pain, with or without prior opioid treatment experience, indicates tapentadol SR was non-inferior to oxycodone SR, and was associated with fewer gastrointestinal adverse effects and improved patient health status compared with oxycodone SR, in these patients. However, the trials precluded use of breakthrough pain management and it is also unclear whether routine gastro-intestinal (GI) prophylaxis was used, which would be available in standard clinical practice. The extent to which the trial-based improved GI tolerability would be realised in routine practice is therefore unclear.
- There was a high degree of patient drop out that created an imbalance in the patient numbers analysed. The actual mean reductions in pain intensity over those achieved with placebo (-0.5 for tapentadol SR, and -0.3 for oxycodone SR) are statistically significant but the clinical significance of these is unclear for both tapentadol SR and oxycodone SR.
- Cost effectiveness analyses indicate tapentadol SR is less costly and generates more QALYs than oxycodone SR. These results were driven by the higher rate of discontinuations due to adverse events observed with oxycodone SR in the trials.
- Efficacy data appear limited to non-cancer pain; the licensed indication does not preclude use in cancer pain, but the SPC for Tapentadol SR notes that only limited data are available for cancer pain and therefore, for the time being, there is not enough data to give any recommendations in this regard[1].

Productivity, Service Delivery and Implementation Considerations:

The proposal would introduce an additional step in the analgesia ladder. Tapentadol SR would be initiated by specialist, with continued prescribing in primary care, as may be the case with oxycodone SR.

Innovation, Need and Equity Considerations:

Tapentadol SR demonstrated an improved tolerability profile compared with oxycodone SR in clinical trials, but it is unclear if this will be observed in practice if routine GI prophylaxis is implemented as recommended. There are no anticipated need or equity considerations.

Recommended Place in Therapy

Black: Tapentadol SR (Palexia® SR▼) is **not** recommended for use in adult patients with severe chronic non-cancer pain

Financial and Service Implications

Comparative unit costs:

The currently used strong opioids on the pain ladder in ELHT are morphine SR and oxycodone SR. The equivalent doses for modified release oxycodone:morphine:tapentadol are approximately 1:2:5, respectively.[9] Table 2 summarises the comparative annual costs for the equivalent doses of each drug and also include Fentanyl as the inclusion of Tapentadol SR in the proposed position would in essence displace Fentanyl.

Table 2. Reimbursement costs of Tapentadol SR and potential comparators

Drug name	Comparison of equivalent doses	Cost for 28 days treatment	Annual maintenance cost per patient (ex VAT)
Tapentadol SR 100mg	100mg to 250mg bd	£49.82 to £124.55	£648 to £1,619
Morphine SR capsules	40mg to 100mg bd	£10.99 to £23.94	£143 to £311
Oxycodone MR* tabs	20mg to 50mg bd	£50.08 to £124.89	£651 to £1,624
Oxycodone MR** caps 20mg	20mg to 50mg bd	£45.71 to £114.28	£594 to £1,486
Fentanyl patches***	25 to 75 microgram/hr every 72hr	£35.98 to £93.98	£468 to £1,222
Costs based on MIMS list prices as of July 2013 using approximate equianalgesic doses *OxyContin (Drug Tariff price) **OxyNorm ***Durogesic D Trans			

Anticipated patient numbers and net budget impact:

The requesting clinician estimates that there would be 50-75 patients in ELHE likely to receive this medicine each year when used as proposed, i.e. third-line following oxycodone SR. Extrapolating these figures across Lancashire suggests use in 143 - 214 patients per year. It is not clear if these estimates would account for cumulative use.

ePACT data from the latest 3 months is summarised in Table 3, along with the current RAG status for tapentadol SR. Primary care prescribing costs for oxycodone SR and tapentadol SR across Lancashire are currently £1.8million per annum. Assuming one prescription per patient per month, these data would suggest there may be around 15 patients on tapentadol SR across Lancashire, with little prescribing in Blackpool, Chorley & South Ribble and Lancashire North CCGs. Using the same assumption, around 2,900 patients currently receive oxycodone SR each year; however it is not clear how many of these patients would use oxycodone SR for chronic non-cancer pain.

At equivalent doses, tapentadol SR would appear to be cost neutral to oxycodone SR (based on current list and drug tariff prices July 2013). It should be noted that oxycodone is off patent and its price may drop in the future.

Tapentadol SR is more costly than transdermal fentanyl, the use of which would be displaced / delayed by the requested use tapentadol SR following failure or intolerance to oxycodone SR.

Table 3: Prescribing data for the March – May 2013 from ePACT

CCG (with RAG status)	Tapentadol SR		Oxycodone SR	
	Total Items	Total Act Cost	Total Items	Total Act Cost
BLACKBURN WITH DARWEN CCG	14	£682.20	1,529	£58,140.54
BLACKPOOL CCG	1	£46.00	641	£37,474.58
CHORLEY AND SOUTH RIBBLE CCG	1	£23.01	935	£50,847.98
EAST LANCASHIRE CCG	4	£115.06	2,882	£146,929.64
FYLDE & WYRE CCG	4	£161.12	662	£38,908.71
GREATER PRESTON CCG	14	£765.60	1,040	£53,241.19
LANCASHIRE NORTH CCG	3	£57.54	551	£25,332.63
WEST LANCASHIRE CCG	5	£131.58	439	£29,382.44
TOTALS	***46***	***£1,982.11***	***8,679***	***£440,257.71***

Impact of Implementation:

It is essential that current guidelines on the use of opioids in the management of severe pain are followed to ensure appropriate treatment and limit the potential for redirection of strong opioids for illicit use.

References

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