Midlands and Lancashire Commissioning Support Unit

New Medicine Recommendation

Tapentadol MR (Palexia® SR)

Tapentadol as a treatment option for intractable neuropathic pain in non-palliative care patients

Tapentadol MR is NOT recommended (RAG status 'Black') for use by the NHS in Lancashire in the following settings:

1. **As a treatment option for intractable neuropathic pain in non-palliative care patients.**
2. **As a treatment for nonspecific pain**

There is insufficient evidence to consistently demonstrate improved efficacy in the above settings when compared to opioid drugs and there is a lack of significant evidence to demonstrate efficacy in patients inadequately controlled on opioid drugs,.

Summary of supporting evidence:

- Tapentadol is a centrally active analgesic which acts as a μ-receptor agonist and a noradrenaline reuptake inhibitor. [1] Tapentadol exerts analgesic effects directly without a pharmacologically active metabolite. [2]
- The Scottish Medicines Consortium and All Wales Medicines Strategy Group approved tapentadol for use for patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated; [3] [4] The Canadian Agency for Drugs and Technologies in Health did not recommend the use of tapentadol across Canada. [5]
- One meta-analysis reported that the benefit-risk ratio for tapentadol was favourable when compared to step three opioids. For severe chronic pain tapentadol, in comparison to oxycodone:
    - Significantly reduced pain intensity (mean difference (MD) = -2.64, 95% CI -4.84 to -0.44; four RCTs).
    - No significant difference between tapentadol and oxycodone groups with respect to serious adverse effects was found.
    - Tapentadol was found to significantly reduce the risk of constipation, nausea and vomiting compared to oxycodone. [6] [7]
- For moderate to severe chronic pain, compared with oxycodone:
    - There was a significant difference in favour of tapentadol in pain intensity scores (MD = -2.45, 95% CI -4.04 to -0.86; seven RCTs).
    - The incidence of serious adverse effects was lower for tapentadol compared to oxycodone (relative risk (RR) = 0.53, 95% CI 0.28 to 1.00). [9] [10]
- Compared to placebo, tapentadol:
    - Significantly increased the risk of adverse effects, e.g. constipation and nausea, in both the severe and moderate to severe pain analyses. [10] [9]
- One withdrawal, placebo-controlled study in [8] patients with type I or II diabetes mellitus and chronic painful diabetic peripheral neuropathy demonstrated a mean change in pain intensity from baseline at the end of the 12 weeks maintenance period: 1.30 (placebo) and 0.28 for tapentadol MR (0 = "no pain" and 10 = "pain as bad as you can imagine"). [8]

- A second withdrawal, placebo-controlled study in patients with type I or II diabetes mellitus and chronic painful diabetic peripheral neuropathy with previous analgesic use showed a least-squares mean change in average pain intensity from the start of study to week 12 of tapentadol (0.0) and placebo (1.4). [9]
- A double blind study in patients with severe/very severe back pain comparing tapentadol 500mg daily and tapentadol/pregabalin. The change in pain level was -1.6 for tapentadol and -1.7 for tapentadol/pregabalin 300/300mg daily. Neuropathic pain change was 22.2 for tapentadol and 23.4 for tapentadol/pregabalin using the PainDETECT questionnaire. Using the mean NPSI total score, change from baseline was -16.4 for tapentadol and -16.7 for tapentadol/pregabalin. The pain figures helped lead to the conclusion that tapentadol MR 500mg is associated with comparable improvement in pain intensity compared to tapentadol MR 300mg plus pregabalin 300mg, with improved central nervous system (CNS) tolerability. [10]

Details of Review

Name of medicine (generic & brand name)**:** Tapentadol MR various strengths (Palexia SR).
Strength(s) and form(s): Tapentadol MR tablets – strengths available = 50mg, 100mg, 150mg, 200mg and 250mg.
Dose and administration: severe chronic pain, initially 50 mg every 12 hours, adjusted according to response; max. 500 mg daily [11]
BNF therapeutic class / mode of action: 4.7.2 Opioid Analgesics. Tapentadol produces analgesia by two mechanisms: opioid-receptor agonist and inhibitor of noradrenaline reuptake**.** [11]
Licensed indication(s): PALEXIA SR is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. [2]
Proposed use (if different from, or in addition to, licensed indication above): Treatment option for intractable neuropathic pain in non-palliative and for neuropathic pain in palliative care patients
Course and cost: Annual cost of treatment if the patient receives tapentadol 50mg b.d. = £323.96; tapentadol 250mg b.d. (maximum dose) = £1619.15. [11]
Current standard of care/comparator therapies: Tricyclic antidepressants (amitriptyline), gabapentin, pregabalin and duloxetine.
Relevant NICE guidance: None.

Background and context

Epidemiological data suggest that 6 – 8% of the general population report chronic pain with neuropathic characteristics. Neuropathic back pain with radiating pain to the arm or leg and post-traumatic neuropathic pain (from accidental or surgical injury) are the most common causes. Approximately half of those that present will require medication and regular support for the management of neuropathic pain. [12] In Lancashire between 87,000 and 116,000 people could be living with neuropathic pain with between 43,000 and 87,000 potentially requiring medication for its management.

Neuropathic pain can be defined as: pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. The central and peripheral nervous systems are responsible for signalling pain and neuropathic pain is a consequence of damage, or pathological changes, within these systems. Therefore, neuropathic pain represents a varying set of symptoms rather than a single diagnosis. [12]

Painful symptoms arising in an area of altered sensation, e.g. numbness, are the hallmark of neuropathic pain. Symptoms can also include: spontaneous pain, abnormal responses to non-painful or painful stimuli, dysaesthesias, gnawing pain and abnormal thermal sensations. [12]

There is no standard diagnostic procedure for neuropathic pain. Diagnosis is based on clinical judgement. Screening methods are available, e.g. Leeds assessment of neuropathic symptoms and signs (LANSS), but are not a substitute for good clinical assessment. [12] The aim of clinical examination is to identify altered sensation in the painful area.

The Lancashire Medicines Management Group (LMMG) approved the pharmacological management of neuropathic pain guidelines in December 2015. The mainstay of pharmacological management in Lancashire is currently (sequentially): tricyclic antidepressants (amitriptyline), gabapentin and pregabalin. [13] Opioid analgesics also have a place in treating neuropathic pain.

Modified release morphine, oxycodone and tramadol are effective for the treatment of neuropathic pain. However, due to safety concerns such as tolerance, addiction, cognitive impairment these drugs are usually recommended as second or third-line treatments. Opioids could be considered first-line in some clinical situations such as intractable pain, episodic exacerbations of severe pain, acute neuropathic pain and neuropathic cancer pain. [12]

Tapentadol was first licensed for use in the UK in 2011. Tapentadol modified-release (MR) is licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. [2]

In May 2011, the Scottish Medicines Consortium (SMC) reviewed and approved tapentadol MR, restricting its use for patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated. The SMC considered the economic case for tapentadol use within NHS Scotland to be demonstrated. [3]

The Canadian Agency for Drugs and Technologies in Health (CEDAC) Reviewed tapentadol MR in September 2011. CEDAC did not recommend the use of tapentadol across Canada. The authors stated that there was insufficient evidence to determine the relative efficacy of tapentadol MR compared with oxycodone MR due the unequal withdrawal rate between treatment and active comparator groups across the three RCTs reviewed. Tapentadol is licensed for use in Canada for the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more. [5]

The All Wales Medicines Strategy Group (AWMSG) published an appraisal recommendation regarding the use of tapentadol within NHS wales in November 2011. [4] Like the SMC, AWMSG recommended the use of tapentadol MR as an option for the treatment of specific sub-populations within its licensed indicated: patients with severe chronic pain, in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated. AWMSG also

recommended that initial prescribing should be by a specialist (including GPwSI) and continued in primary care 'with appropriate communication and specialist input'. [4]

Pharmacology and Pharmacokinetics

Tapentadol is a centrally active analgesic which acts as a μ-receptor agonist and a noradrenaline reuptake inhibitor. [1] Tapentadol exerts analgesic effects directly without a pharmacologically active metabolite. [2]

Tapentadol is extensively cleared by first-pass metabolism, oral bioavailability of Palexia SR being 32%. Maximum serum concentrations of tapentadol are observed at between 3 and 6 hours after administration of the MR preparation. Tapentadol has an apparent volume of distribution of 540 +/- 98Litres. Hence, distribution is extensive. Serum protein binding is low. [2]

Summary of evidence

Summary of efficacy data in proposed use:

There is one systematic review and four randomised controlled trials in the literature that relate to the use of tapentadol MR for the treatment of neuropathic pain either exclusively or considered alongside other pain components.

Meta-analyses and Systematic Reviews

Riemsma et al, 2011, published a systematic review of chronic pain treatment with strong opioids (step three World Health Organisation (WHO) pain ladder) and compared these treatments with tapentadol. [6] Relevant randomised controlled trials (RCTs) that involved the use of at least one step three opioid for the treatment of moderate and severe chronic pain. Chronic pain could be nociceptive or neuropathic, malignant or non-malignant. 'Severe' and 'moderate to severe' pain were analysed separately. Direct comparisons were made between tapentadol, oxycodone and placebo. Indirect comparisons between interventions were performed by network analysis. Enriched selection trials were excluded. The primary outcome measure was pain intensity. [6]

For severe chronic pain tapentadol, in comparison to oxycodone, significantly reduced pain intensity (mean difference (MD) = -2.64, 95% CI -4.84 to -0.44; four RCTs). No significant difference between tapentadol and oxycodone groups with respect to serious adverse effects was found. Tapentadol was found to significantly reduce the risk of constipation, nausea and vomiting compared to oxycodone. [6] [7]

For moderate to severe chronic pain, compared with oxycodone, there was a significant difference in favour of tapentadol in pain intensity scores (MD = -2.45, 95% CI -4.04 to -0.86; seven RCTs). The incidence of serious adverse effects was lower for tapentadol compared to oxycodone (relative risk (RR) = 0.53, 95% CI 0.28 to 1.00). [6] [7]

Compared to placebo, tapentadol significantly increased the risk of adverse effects, e.g. constipation and nausea, in both the severe and moderate to severe pain analyses. The authors concluded that the benefit-risk ratio for tapentadol was favourable when compared to step three opioids. [7] [6]

Randomised Controlled Trials

Vinik et al, 2014, reported a randomised, withdrawal, placebo-controlled study. [8] 459 adult patients with type I or II diabetes mellitus (DM) living with chronic painful diabetic peripheral neuropathy (DPN) for greater than six months were enrolled and received an open-label tapentadol titration regimen; 358 completed the titration phase. Patients received tapentadol MR 50mg twice a day for 3 days and were subsequently titrated over a three week period to their optimal dose, taking into account both the reduction in pain intensity and tolerability. Participants were then randomised to either a treatment or control group. The treatment group received the

optimum dose of tapentadol reached during the titration phase and the control group received placebo. The maintenance phase of the study was double-blinded and lasted 12 weeks. Breakthrough analgesia was permitted for participants of both groups up to a maximum of tapentadol MR 25mg b.d. in the first four days and once per day from day five onwards. [8]

The primary outcome measure was the mean change in average pain intensity from baseline to the end of the maintenance period. Average pain intensity over the last 12 h was recorded twice daily using an 11-point Numerical Rating Scale (0 = "no pain" and 10 = "pain as bad as you can imagine"). All patients that were randomised and received at least one dose of double-blind study medication were included in the final analysis. Mean pain intensity was 7.33 (standard deviation = 1.3) at the start and 4.16 (2.12) at week three of the open-label titration period; mean change = -3.22 (1.97). The mean change in pain intensity from baseline at the end of the 12 weeks maintenance period was: placebo, 1.30 (2.43); tapentadol MR, 0.28 (2.04). A positive figure indicates an increase in measured pain scores. The authors concluded that tapentadol MR 100mg to 250mg b.d. was effective and well tolerated for the management of moderate to severe chronic pain associated with DPN. [8]

Schwartz et al, 2011, reported a double-blind, randomised-withdrawal, placebo-controlled phase III trial. [9] Participants were 18years or older with type I or II DM and had DPN for at least six months and had at least a three month history of analgesic use for this indication and dissatisfaction for with their current regimen. If the patient was already receiving opiates, an equivalent morphine dose ≤ 160mg was required for enrolment. The primary efficacy endpoint was the change in average pain intensity from baseline over the last week of the double-blind maintenance period. The endpoint measure was the 11-point numerical rating scale.

591 patients entered the open-label phase of the study and of those 588 received tapentadol MR. 395 were then randomised to receive double-blind treatment. The open-label phase lasted three weeks and all participants were titrated to their optimum dose of tapentadol MR. The maintenance phase lasted 12 weeks and was a double-blind withdrawal design; patients were randomised to receive either their optimum dose of tapentadol or placebo. Participants were further permitted to use tapentadol MR 25mg twice a day when required during the first four days of the maintenance phase across both groups. This was reduced to tapentadol MR 25mg once a day when required across both groups for the remainder of the study. All analgesic medication was withdrawn prior to titration and a washout period was observed. Patients were permitted to use a maximum daily dose (MDD) of 2gram paracetamol during the open-label phase of the study as rescue pain medication. [9]

193 participants received placebo and 196 received tapentadol MR during the maintenance phase of the study; 131 and 133 completed the study respectively. The least-squares mean change in average pain intensity from the start of the double-blind treatment to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol MR group. [9] The least-squares mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; $p < 0.001$). The study concluded that compared with placebo, tapentadol MR 100 – 250mg twice a day provided a clinically important improvement in pain relief and was well tolerated by patients with painful DPN. [9]

Baron et al, 2014, reported a randomised, double-blind, phase IIIb study of 489 with severe or very severe low back pain with a neuropathic component. [10] The primary efficacy endpoint was the change in average pain intensity from randomisation to the final evaluation visit (end of the comparative period). The primary efficacy measure was a three day average of pain intensity (11-point NRS-3).

The study consisted of a three week open-label titration period and an eight week double-blind comparative period concluding with a two week follow-up period. 445 received open-label medication during titration. Participants were titrated from tapentadol MR 50mg twice a day up to tapentadol MR 300mg. 313 were subsequently randomised to receive double-blind comparative treatment. 154 were randomised to receive tapentadol MR titrated to 500mg daily and 159

received tapentadol MR 300mg plus pregabalin 300mg daily. Participants were permitted to take paracetamol ≤ 1gram daily during the double-blind phase of the study for pain unrelated to low back pain. [10] Participants that achieved a satisfactory level of analgesia after the titration phase entered a parallel open-label continuation study. [14]

Results from the full analysis showed the mean change from randomisation to evaluation in pain intensity in the tapentadol MR and tapentadol MR and pregabalin group was: -1.6 (standard deviation = 2.47) and -1.7 (2.47; both $p < 0.0001$ for the change from randomisation) and the change from baseline was -4.1 (2.58) and -4.2 (2.66; both $p < 0.0001$) respectively. [10]

Neuropathic pain components were evaluated using the PainDETECT questionnaire and the Neuropathic Pain Symptom Inventory (NPSI). The mean PainDETECT score at baseline derived from the full analysis set (last observations carried forward [LOCF]) as was 22.2 (standard deviation = 5.69) in the tapentadol MR group and 23.4 (5.94) in the tapentadol and pregabalin group. From randomisation to final evaluation PainDETECT scores (LOCF) reduced in the tapentadol MR group by -5.8 (8.66) and in the tapentadol MR and pregabalin group by -6.1 (7.42; both $p < 0.0001$). The mean NPSI total score (LOCF) at baseline was 62.2 (17.84) in the tapentadol MR group and 64.3 (19.00) in the tapentadol MR and pregabalin group. Changes from baseline to final evaluation (LOCF) were -32.8 (22.56) and -34.6 (23.71) and from randomisation to final evaluation (LOCF) -16.4 (18.83) and -16.7 (19.85; all $p < 0.0001$ for the change from baseline) respectively. The authors concluded that tapentadol MR 500mg is associated with comparable improvement in pain intensity compared to tapentadol MR 300mg plus pregabalin 300mg, with improved central nervous system (CNS) tolerability. [10]

Other efficacy data:

Comparison with Tramadol

There is one meta-analysis, one randomised trial and two descriptive studies that compare use of tapentadol with tramadol.

Mercier et al, 2014, published a meta-analysis indirectly comparing the efficacy and tolerability of tramadol and tapentadol in patients with chronic non-malignant pain. [15] The authors include phase II and III studies. The authors stated that tramadol 300mg once a day was slightly more in reducing pain than tapentadol 100 – 250mg twice a day. The authors went on to state that tapentadol was associated with slightly lower risks of constipation and nausea compared to tramadol. In conclusion, the authors stated that the benefit-risk profiles of tramadol 300mg once a day and tapentadol 100 – 250mg twice a day were approximately even. [15]

Iyer et al, 2015, published a randomised, active-control, single- experimenter-blinded study. [16] Sixty adult patients undergoing cardiac surgery were randomised to receive tapentadol 50mg oral or tramadol 100mg oral. The participants were given the drug after extubation. All patients received paracetamol 1gram four times a day concurrently. Pain scores were noted using a VAS before each drug dose, 3 hours later and on coughing. Results were taken for six doses (up to 48hours after extubation). The authors reported that patients receiving tapentadol had significantly better analgesia 3hours after drug administration (mean VAS score for tapentadol at 3hours = 2.68 [1.27; $p < 0.001$]) and on coughing (3.86 [1.81; $p = 0.001$]) than patients receiving tramadol (3.91 [1.01] and 4.93 [1.04] respectively) after the third dose. The authors also found that tapentadol produced less drowsiness and vomiting than tapentadol.

Kress et al, 2016, have published a post-hoc, sub-group analysis evaluating the efficacy and tolerability of tapentadol MR in patients that had previously been dissatisfied with tramadol. [17] The data was derived from a 2014 study by the same author that has already been discussed. [18]

129 patients had received tramadol prior to receiving tapentadol MR prior to randomisation in the study. Results for the 129 participants in this subgroup were compared against the results

collected for all 338 participants that received tapentadol MR during the titration phase. Responder rates were better for the tapentadol MR versus tramadol sub-group (69.8% [90/129]) versus overall tapentadol MR group (63.9% [214/335]). Tolerability profiles were comparable. [17] The authors of the study stated that patients that had received tramadol previously could switch directly to tapentadol MR with the majority experiencing improved efficacy. [17]

Summary of safety data:

The Summary of Product Characteristics (SPC) states that the ADRs experienced by participants in placebo versus Palexia SR (tapentadol MR) RCTs were predominantly of mild to moderate severity. ADRs that occur "very commonly" and "commonly" mostly relate to the gastrointestinal and central nervous systems. Adverse events occur with the following frequencies:

≥1/10 - dizziness, somnolence, headache, nausea, constipation;

≥1/100 to <1/10 - decreased appetite, anxiety, depressed mood, sleep disorder, nervousness, restlessness, disturbance in attention, tremor, involuntary muscle contractions, flushing, dyspnoea, vomiting, diarrhoea, dyspepsia, pruritus, hyperhidrosis, rash, asthenia, fatigue, feeling of body temperature change, mucosal dryness and oedema. [2]

The seven RCTs and one descriptive study reviewed mainly reported ADRs that are listed in the SPC for Palexia SR. [10] [19] [18] [20] [9] [8] [21] [22] Significant ADRs that occurred in tapentadol MR treatment groups additional to those listed in the SPC were: delirium (prevalence in study population = 6% [10/168]), chest pain, fall, vertigo, abdominal and flank pain (all: 3.2% [5/154]), nasopharyngitis (5.4% [9/166]), abdominal obstruction, hypoglycaemia, euphoric mood, and visual disturbance [all: 0.11% [1/894]) . [10] [19] [18] [20] [9] [8] [22]

10 patients across three studies reported experiencing chest pain whilst receiving tapentadol MR. [9] [8] [10] One patient death that was related to myocardial ischaemia was also reported. [8] This was not thought to be related to use of tapentadol MR by investigators.

The SPC states that trials performed with Palexia SR with patient exposure up to one year have shown little evidence of withdrawal symptoms upon abrupt discontinuation and symptoms were generally classified as mild when they occurred. [2] Two RCTs also described the occurrence of mild withdrawal symptoms upon discontinuation of tapentadol. [8] [9] The SPC recommends that physicians should remain vigilant.

Abuse Potential

Cepeda et al, 2014, conducted a retrospective cohort study comparing the risks of 'opioid shopping' behaviour and opioid abuse between tapentadol IR and oxycodone IR. [23] 'Opioid shopping' is defined as obtaining opioid prescriptions from multiple prescribers. From a total group of 277,401 participants initiated on opioids, 39,524 patients were prescribed tapentadol and 237,877 were prescribed oxycodone. In the patients prescribed tapentadol or oxycodone, 0.6% demonstrated shopping behaviour in and 0.75% were considered to be abusing their opioid. A higher proportion of patients in the oxycodone group deminstrated shopping behaviour and abuse than in the tapentadol group (shopping: adjusted odds ratio [95% confidence interval], 0.45 [0.36 – 0.55]; abuse: 0.44 [0.37 – 0.54]). The authors state that opioid shopping behaviour and abuse were associated and concluded that among patients who commenced on tapentadol the risk of developing these behaviours is lower than those who initiated on oxycodone. [23]

Strengths and limitations of the evidence:

Limitations

1. Some studies had enriched enrolment of participants. [8] [17]
2. The Selection of responders to study medication from titration phases and subsequent

enrolment to maintenance phases limits statistical comparison of test groups. [18]
3. One RCT which concluded that tapentadol had a better gastrointestinal tolerability than oxycodone set the maximum study dose of tapentadol lower than the licensed dose (200mg twice a day versus 250mg twice a day). [19]
4. The ITT populations not used for final analyses in all RCTs
5. Additional rescue doses of analgesia, including tapentadol MR, were not considered in efficacy or safety assessments in all studies. [9]
6. Possible increase in placebo groups ADR figures could skew safety results.
7. All studies discussed, including systematic reviews, were conducted or sponsored by the manufacturers of tapentadol MR in their respective countries.

Strengths

1. Availability of one systematic review and seven RCTs.

Summary of evidence on cost effectiveness:

A review of cost-effectiveness was conducted by the SMC in 2011. [3]

Subgroup analysis of patients with severe pain and prior opioid use the manufacturer estimated that tapentadol MR would give a quality adjusted life year (QALY) gain of 0.0045 per patient compared to oxycodone and a QALY gain of 0.00379 per patient compared to transdermal fentanyl. A key driver behind these results was the favourable AE outcomes for tapentadol SR as the relative probabilities of discontinuation associated with lack of efficacy were less favourable for tapentadol SR [3]

Compared to oxycodone MR, tapentadol MR use would produce a potential annual saving for the NHS of between **£3.12** and **£1506.04** ***per patient*****.** Compared to oxycodone MR, tapentadol MR would be the preferred treatment on grounds of cost.

Compared to transdermal fentanyl patches, tapentadol MR use would produce a potential annual **cost pressure to the NHS of between £166.08** and **£686.76** per patient**.** Use of tapentadol MR in preference to transdermal fentanyl patched would not be recommended on the basis of cost as QALY gains are low.

Prescribing and risk management issues:

1. Tapentadol is a schedule 2 controlled drug. Prescription writing and safe custody of controlled drug requirements must be adhered to by prescribers and those involved in dispensing and supply.
2. Tapentadol is an opioid analgesic and liable to abuse. There is some evidence to suggest that tapentadol is less likely to be abused than oxycodone. [23]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Tapentadol MR tablets	**100 – 250mg TWICE daily**	**100mg x 56 = £49.82; 250mg x 56 £124.55**	**£647.66 – £1619.15**

Oxycodone MR tablets	20 – 50mg TWICE daily	10mg x 56 = £25.04 20mg x 56 = £50.08; 40mg x 56 = £100.19	£651.04 – £1627.99
Transdermal fentanyl patches	25 – 50microgram/hour every 72hours	25microgram/hr patch x 5 = £17.99; 50microgram/hr patch x 5 = £33.66	£431.76 – £807.84
Morphine sulphate MR capsules	30 – 100mg TWICE daily	30mg x 60 = £8.30; 100mg x 60 = £21.80	£99.60 – £261.60
Tramadol MR tablets	100-200mg TWICE daily	100mgx60= £6.94 200mg x 60 = £14.19	£83.28- £170.28
Costs based on BNF list prices 28/04/2016 [11] This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

No manufacturer discounts are currently available.

It is not anticipated that additional secondary care appointment will be required upon initiation on tapentadol.

Productivity, service delivery, implementation:

It is not anticipated that additional secondary care appointment will be required upon initiation of tapentadol MR. Those commenced on tapentadol MR are expected to already be under the care of a specialist pain consultant.

Anticipated patient numbers and net budget impact:

Using figures from the SMC review of tapentadol MR an factoring in the population of Lancashire, uptake figures across Lancashire would be expected to be 22.4 patients in year1, rising to 335 in year 5. [3]
The net cost pressure to the NHS would be **£16,271** in **year 1** rising to **£20.479** in **year 5.** As the acquisition costs of tapentadol MR and oxycodone MR are similar, a neutral net drug budget impact was estimated for this displacement. The displacement of TD fentanyl was estimated to result in net savings of £196 in year 1 rising to £2.95K in year 5

Innovation, need, equity:

1. Tapentadol MR has been licensed for use in the UK since 2011. [2]
2. There is evidence to suggest that tapentadol MR has better gastrointestinal tolerability than comparators, such as oxycodone MR. [18] Better gastrointestinal tolerability would be beneficial for patients requiring long-term use of opioids.
3. Comparator studies did not reflect standard practice and populations where active-controls were co-prescribed alongside laxatives were not evaluated.

References

[1] Bundesinstitut fur Arzneimittel und Medizinprodukte, “Public Assessment Report - Palexia Retard and Yantil Retard (Tapentadol),” Federal Institue for Drugs and Medical Devices (Germany), Bonn, 2012.

[2] Grunenthal Ltd, “Electronic Medicines Compendium (EMC) - Palexia SR prolonged release tablets,” July 2014. [Online]. Available: http://www.medicines.org.uk/emc/medicine/28373 . [Accessed 11 April 2016].

[3] Scottish Medicines Consortium, “Resubmission - tapentadol, 50, 100, 150, 200 and 250mg prolonged-release tablets (Palexia SR) SMC No. (654/10),” NHS Scotland, Glasgow, 2011.

[4] All Wales Medicines Strategy Group, “Final Appraisal Recommendation - Tapentadol prolonged release (Palexia SR),” NHS Wales, Penarth, 2011.

[5] Canadian Agency for Drugs and and Technologies in Health, “CEDAC Final Recommendation - TAPENTADOL (Nucynta CR - Janssen inc.),” Canadian Agency for Drugs and and Technologies in Health, Ottawa, 2011.

[6] Riemsma et al, “Systematic review of tapentadol in chronic severe pain,” *Current Medical Research and Opinion,* vol. 27, no. 10, pp. 1907-1930, 2011.

[7] University of York: Centre for Reviews and Dissemination, “Database of Abstracts of Reviews and Effects: Systematic review of tapentadol in chronic severe pain,” NHS National Institute for Health Research, York, 2016.

[8] Vinik et al, “A randomised withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy,” *Diabetes care,* vol. 37, no. 8, pp. 2302-2309, 2014.

[9] Schwartz et al. , “Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomised-withdrawal, placebo-controlled trial.,” *Current Medical Research and Opinion,* vol. 27, no. 1, pp. 151-162, 2011.

[10] Baron et al, “Effectiveness and safety of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin for the management of severe, chronic low back pain with a neuropathic component: a randomised, double-blind, phase 3b study,” *Pain Practice ,* vol. 15, no. 5, pp. 455-470, 2014.

[11] Royal Pharmaceutical Society, British National Formulary, vol. 70, London: Pharmaceutical Press, 2016.

[12] Freynhagen et al, “Diagnosis and managaement of neuropathic pain,” *British Medical Journal,* vol. 339, no. 3002, 2009.

[13] Lancashire Medicines Management Group, “The Pharmacological Management of Neuropathic Pain in Adults,” NHS Midlands and Lancashire CSU, Preston, 2015.

[14] Baron et al, “Effectiveness and tolerability of a moderate dose of tapentadol prolonged release for managing severe, chronic low back pain with a neuropathic component: an open-label continuation arm of a randomised phase 3b study,” *Pain Practice,* vol. 15, no. 5, pp. 471-486, 2015.

[15] Mercier et al, “A model-based meta-analysis to compare efficacy and tolerability of tramadol and tapentadol for the treatment of chronic non-malignant pain,” *Pain Ther,* vol. 3, pp. 31 - 44, 2014.

[16] Iyer et al, “Comparison of tapentadol with tramadol for analgesia after cardiac surgery,” *Annals of Cardiac Anaesthesia,* vol. 18, no. 3, pp. 352 - 360, 2015.

[17] Kress et al, “Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain,” *European Journal of Pain,* vol. [Published ahead of print], April 2016.

[18] Kress et al, “Tapentadol prolonged release for managing moderate to severe, chronic malignant tumour related pain.,” *Pain Physician,* vol. 17, pp. 329 - 343, 2014.

[19] Imanaka et al, “Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumour pain,” *Current Medical Research and Opinion,* vol. 29, no. 10, pp. 1399-1409, 2013.

[20] Schikowski et al, “Tapentadol prolonged release for severe chronic cancer-related pain: effectiveness, tolerability and influence on quality of life of patients,” *Journal of Pain Research,* vol. 8, pp. 1-8, 2014.

[21] Afilalo, “Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chromic pain related to osteoarthritis of the knee: A randomised, double-blind, pbo-and active-controlled phase III stud,” *Clinical Drug Investigations,* vol. 30, no. 8, pp. 489-505, 2010.

[22] Wild et al, “Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain,” *Pain Practice,* vol. 10, no. 5, pp. 416-427, 2010.

[23] Cepeda et al, “Comparison of the risks of shopping behaviour and opioid abuse between tapentadol and oxycodone and association of shopping behaviour and opioid abuse,” *The Clinical Journal of Pain,* vol. 30, no. 12, pp. 1051-1056, 2014.

[24] Guillen Astete et al, “Comparison of tapentadol versus conventional treatment with tramadol and/or NSAIDs in the management of mechanical low back pain with a neuropathic component,” *Annals of Rheumatic Diseases,* vol. 74, p. 1218, 2015.

[25] Munoz et al, “Pain treatment with tapentadol in departments of radiation oncology,” *Palliative Medicine,* vol. 28, no. 6, pp. 847 - 848, 2014.

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