

## Resubmission

tapentadol, 50, 100, 150, 200 and 250mg prolonged-release tablets  
(Palexia® SR) SMC No. (654/10)

**Grünenthal Ltd**

06 May 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**tapentadol prolonged-release (Palexia® SR)** is accepted for restricted use within NHS Scotland.

**Indication under review:** the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

**SMC restriction:** patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated.

Results of a meta-analysis of three, 12-week studies suggest that tapentadol prolonged release has improved gastrointestinal tolerability and similar efficacy compared to another long-acting opioid included as an active control.

The manufacturer's submission related only to the use of tapentadol prolonged release in severe chronic pain. SMC has not yet received a submission for tapentadol immediate release tablets for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics. Tapentadol immediate release tablets are not recommended for use in NHS Scotland.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

## Indication

For the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

## Dosing Information

Tapentadol prolonged release should be taken twice daily, approximately every 12 hours.

For patients not currently taking an opioid analgesic, the recommended starting dose is tapentadol prolonged release 50mg twice daily. For patients currently taking an opioid analgesic, the recommended starting dose should take account of the nature of the previous medicinal product, the administration and mean daily dose and may require higher initial tapentadol prolonged release doses than for those not taking opioid analgesics. Titration should be in increments of 50mg twice daily every three days to achieve adequate pain control. Total daily doses greater than 500mg have not yet been studied and are not recommended.

## Product availability date

09 May 2011

## Summary of evidence on comparative efficacy

Tapentadol is an opioid analgesic combining two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol prolonged release, referred to as tapentadol SR), is licensed for severe chronic pain. The submitting company has requested that SMC consider tapentadol SR positioned as an alternative to oxycodone modified release or transdermal (TD) fentanyl patches in patients for whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated.

Efficacy in severe pain has been evaluated in three identically designed randomised, double-blind, active and placebo-controlled, phase III studies: two in patients with osteoarthritis of the knee and one in patients with low back pain. Eligible patients were aged  $\geq 40$  years (in the osteoarthritis studies) or  $\geq 18$  years (in the low back pain study) and had required analgesics for  $\geq 3$  months (non-opioids or opioids at doses equivalent to  $\leq 160$ mg oral morphine per day) but were dissatisfied with their current analgesics. They had average baseline pain intensity  $\geq 5$ , on an 11-point numerical rating scale (NRS), where 0="no pain" to 10="pain as bad as you can imagine" during the three days after screening and washout.

Eligible 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 the optimal dose (tapentadol SR 100 to 250mg twice daily; oxycodone MR 20 to 50mg twice daily).

Patients then entered the 12-week maintenance phase, during which they were encouraged to remain on a steady dose of study medication, although adjustments could be requested. The

only permitted additional analgesia was paracetamol ( $\leq 1000\text{mg/day}$ ) as long as it was used for reasons other than the study-related pain.

The primary endpoint was change from baseline in average pain intensity over the 12-week maintenance period, using last observation carried forward to account for missing data due to early discontinuation. A pre-planned meta-analysis was also performed, firstly to test for superior gastrointestinal tolerability of tapentadol SR versus oxycodone MR, then if that was demonstrated, non-inferiority in terms of efficacy of tapentadol SR versus oxycodone MR. A substantial proportion of patients failed to complete the 12-week maintenance phase. The discontinuation rate was highest in the oxycodone MR group, as demonstrated in the meta-analysis population in which 59% of placebo, 56% of tapentadol and 38% of oxycodone patients completed the maintenance phase. Key results for the primary efficacy endpoint are detailed in the table below. The second study in patients with osteoarthritis of the knee failed to find a significant difference between tapentadol SR and placebo. This study has not been published. The meta-analysis found that tapentadol SR was non-inferior to oxycodone MR.

**Table: Primary endpoint results for individual studies and the meta-analysis in the intention to treat (ITT) populations**

	Placebo	Tapentadol SR	Oxycodone MR
<b>Study A: Osteoarthritis of the knee</b>			
Change in mean (SD) pain intensity over 12 weeks	(n=337) -2.2 (2.4)	(n=344) -2.9 (2.3)	(n=342) -2.5 (2.3)
LSM difference versus placebo (95% CI)		-0.7 (-1.00 to -0.33) p<0.001	-0.3 (-0.67 to -0.0) p=0.049
<b>Study B: Osteoarthritis of the knee</b>			
Change in mean (SD) pain intensity over 12 weeks	(n=337) -2.2 (2.1)	(n=319) -2.5 (2.2)	(n=331) -2.1 (2.2)
LSM difference versus placebo (95% CI)		-0.2 (-0.55 to 0.07) p=0.135	0.1 (-0.18 to 0.44) p=0.421
<b>Study C: Low back pain</b>			
Change in mean (SD) pain intensity over 12 weeks	(n=319) -2.1 (2.2)	(n=318) -2.8 (2.5)	(n=328) -2.9 (2.4)
LSM difference versus placebo (95% CI)		-0.7 (-1.06 to -0.35) p<0.001	-0.8 (-1.16 to -0.46) p<0.001
<b>Meta-analysis</b>			
Change in mean (SD) pain intensity over 12 weeks	(n=988) -2.2	(n=975) -2.7	(n=996) -2.5
LSM difference versus placebo (95% CI)		-0.5 (-0.73 to -0.34) P<0.001	-0.3 (-0.52 to -0.14) p<0.001

SD=standard deviation; LSM=least square mean; CI=confidence interval

A key secondary endpoint in each study was responder rate defined as the proportion of patients achieving  $\geq 30\%$  and  $\geq 50\%$  improvement in pain intensity from baseline. Patients who discontinued study medication before week 12 were classified as non-responders.

In the individual studies, results were mixed, with one study finding a significant difference between tapentadol SR and placebo for the  $\geq 50\%$  improvement outcome, one study not finding any difference in responder rates, and the third study finding a significant difference in both thresholds for improvement. The meta-analysis found that both  $\geq 30\%$  and  $\geq 50\%$  improvements

were significant for tapentadol SR versus placebo ( $\geq 30\%$ : 41% versus 35% respectively;  $\geq 50\%$ : 30% versus 24% respectively).

The submission also presented results of an in-house subgroup analysis in patients with severe pain and prior opioid experience comprising 309 tapentadol SR, 283 oxycodone MR and 297 placebo patients. It noted that the method of imputation for missing data had an effect on the primary end point. For all methodologies, oxycodone MR was found to be significantly better than placebo at reducing the pain score from baseline over the whole maintenance period. In contrast, while reductions in pain score from baseline were similar to those in the total meta-analysis population, tapentadol SR was only significantly better than placebo using two of the five methods. Responder rates at each response level in the subgroup analysis were similar to those of the total meta-analysis population, but neither  $\geq 30\%$  and  $\geq 50\%$  improvements were significant for tapentadol SR versus placebo. The only significant response was for oxycodone MR versus placebo for  $\geq 50\%$  improvement in pain intensity. The analysis was not powered to detect differences between the subgroups.

The Patient Global Impression of Change (PGIC) assessed a patient's perceived change in overall health status on a 7-point scale where 1="very much improved" to 7="very much worse". It found significant improvements with tapentadol SR over placebo in each study and the meta-analysis, and with tapentadol SR over oxycodone MR in the meta-analysis. The EuroQol-5 Dimension (EQ-5D) assessed five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as an overall health status and found mixed results during each study. In the meta-analysis, there was significantly greater improvement in the overall health status score with tapentadol SR compared with placebo and oxycodone MR. There were mixed results in the Short Form-36 (SF-36) Health Survey in each study but in the meta-analysis there were significantly greater improvements in all individual domains of the SF-36, except general health, and in the physical and mental component summaries, with tapentadol SR compared with oxycodone MR.

Supportive data were also presented from: a placebo-controlled, phase III study in patients with painful diabetic peripheral neuropathy; an open-label, phase III, one year comparison with oxycodone MR in patients with moderate to severe chronic pain due to osteoarthritis of the hip or knee or low back pain; interim results (87 patients) of an open-label, uncontrolled, phase IIIb study assessing the effectiveness and tolerability of tapentadol SR, in conjunction with immediate release tapentadol for breakthrough pain, in patients switched from WHO stage three opioid analgesics that had been effective but poorly tolerated.

## Summary of evidence on comparative safety

The meta-analysis indicated that tapentadol SR had better gastrointestinal tolerability than oxycodone MR. The incidence of constipation was reported to be significantly lower with tapentadol SR than oxycodone MR (17% versus 33%), as were other gastrointestinal adverse events of nausea (21% versus 36% respectively), vomiting (8.2% versus 21% respectively) and nausea and vomiting (23% versus 43% respectively). The total incidence of gastrointestinal adverse events was significantly lower with tapentadol SR than oxycodone MR (43% versus 66%). Adverse events related to the nervous system were generally numerically lower in the tapentadol SR group than the oxycodone MR group: dizziness (17% versus 21% respectively), headache (15% versus 13% respectively) and somnolence (12% versus 17% respectively). The incidence of pruritus was also lower (5.2% versus 13%).

Discontinuations due to adverse events occurred in 18% (179/978) of tapentadol SR patients, 39% (394/999) of oxycodone MR patients and 6.6% (65/991) of placebo patients.

## Summary of clinical effectiveness issues

Tapentadol combines the following two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. Three individual phase III registration studies, two in osteoarthritis of the knee and one in low back pain, compared tapentadol SR with placebo. In one of the studies, in patients with osteoarthritis of the knee, both tapentadol SR and the active comparator failed to demonstrate a significant improvement in pain intensity compared with placebo. A meta-analysis of these phase III studies allowed comparison with the active control, oxycodone MR, to which tapentadol SR was shown to have improved gastrointestinal tolerability and non-inferior efficacy. However, there were substantial drop-outs and a higher discontinuation rate, mainly due to adverse events, in the oxycodone MR group than in the tapentadol SR and placebo groups which may have resulted in an imbalance between the groups. The lower discontinuation rate in patients treated with tapentadol SR appears to reflect the improved tolerability of this medicine compared to oxycodone MR, which may be an advantage in some patients.

The company has proposed that tapentadol SR should be considered as an alternative to oxycodone MR or TD fentanyl patch in patients where morphine sulphate modified release has failed to provide adequate pain control or is not tolerated. The evidence to support this positioning is limited. The inclusion criteria of the phase III studies required only that eligible patients were dissatisfied with their current analgesic (opioid or non-opioid) and only 34% of the meta-analysis population had received opioids within the previous 3 months. The studies also included a minority of patients with moderate pain, while the marketing authorisation for tapentadol SR stipulates use in severe pain, and there is no direct comparative data for TD fentanyl patches.

An in-house subgroup analysis compared improvement in pain intensity scores and responder rates for tapentadol SR with oxycodone MR in patients with severe pain who had previously received opioids (30% of the overall population), which more closely resembles the positioning relevant to this submission. There are uncertainties around this analysis; of note, the treatment effect of tapentadol SR with respect to reduction in pain scores compared to placebo was sensitive to the method used to impute missing data. The sub-group analysis was insufficiently powered to detect any differences between the groups.

The design of the studies did not allow for the use of breakthrough doses of the relevant drug during periods of dose titration, or indeed, maintenance therapy. Very limited doses of paracetamol (1g daily) were allowed only during the titration phase. Use of breakthrough medication would be normal practice.

There is no direct comparative data with any other opioid. An indirect comparison with TD fentanyl patches was presented within the submission to support the economic analysis. This was undertaken using naïve methodology by extracting outcome data from a single, uncontrolled, transdermal fentanyl study, reducing the validity of the result of the comparison.

## Summary of comparative health economic evidence

The manufacturer submitted two cost-utility analyses comparing tapentadol SR with oxycodone MR and with TD fentanyl for the management of severe chronic pain in patients in whom morphine sulphate MR has failed to provide adequate pain control or is not tolerated. One analysis focused on the whole trial population of patients with moderate to severe chronic pain (where only 34% of patients had prior opioid experience) and the other was based on a subgroup of patients with severe chronic pain and prior opioid experience. A Markov model was used to model the costs and benefits of treatments over a one year time horizon.

Clinical data relating to the efficacy of tapentadol SR and oxycodone MR were taken from the pooled analysis of the lower back pain and osteoarthritis tapentadol MR studies with relevant subgroup data used for the analysis of patients with prior opioid use. Four 4- weekly cycles of probabilities of discontinuation due to adverse events (AEs), lack of efficacy, continuing treatment with mild/moderate AEs or continuing treatment without AEs were applied by treatment arm up to 15 weeks, and then the average probabilities across both treatment arms in cycle 4 applied for the duration of the model analysis. Subsequent lines of therapy included buprenorphine and oxycodone/naloxone, with efficacy for these taken from selected trials. For the comparison with TD fentanyl, a naïve indirect comparison of an open label study for fentanyl with the tapentadol pooled data was performed. As 4- week cycle data were not available for TD fentanyl, assumptions were made regarding the outcome probabilities for each cycle of the 15 week period for tapentadol versus TD fentanyl utilising the pooled tapentadol versus oxycodone data. The extrapolation method to one year was the same as for the comparison versus oxycodone. The cost of TD fentanyl was based on an equianalgesic dose ratio (EDR) of 100mg morphine to 1mg fentanyl.

EQ-5D data collected in the pooled tapentadol versus oxycodone trials were used to estimate utility values relating to the sub-group with severe pain of 0.633, 0.535, 0.432 and 0.321 respectively for treatment continuation, treatment continuation with AEs, treatment discontinuation due to AEs and treatment discontinuation due to lack of efficacy health states respectively. Slightly higher utilities were estimated for the whole patient trial population. Resource use estimates relating to pain specialist consultations, primary care visits and co-medications were selected from a retrospective database of Scottish centres where patients experiencing adverse events were estimated to incur additional resource.

Based on the more relevant subgroup analysis of patients with severe pain and prior opioid use, using the pooled data the manufacturer estimated tapentadol SR would produce a saving of £77 and quality adjusted life year (QALY) gain of 0.0045 per patient compared to oxycodone, and a saving of £201 and QALY gain of 0.00379 compared to TD fentanyl and therefore be the preferred treatment on cost-effectiveness grounds. Larger cost savings and QALY gains were estimated in the analysis using the whole pooled patient population. 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.

The main weaknesses with the analysis were:

- The analysis based on the subgroup is the more relevant given the licence and proposed positioning, but there are weaknesses with the quality of the data used. The use of

discontinuation data for defining lack of efficacy rather than pain score improvement may have clinical relevance but was limited by small patient numbers and lack of statistical testing.

- While the manufacturer indicated that the principal comparator was oxycodone, the comparison versus TD fentanyl was based on a naive indirect comparison and other assumptions based on data from the tapentadol versus oxycodone comparison. As such the results from this analysis are less robust.
- There is uncertainty over the appropriate EDR for TD fentanyl. The base case value used may be too low hence inflating the cost of TD fentanyl however the manufacturer provided some sensitivity analysis to provide reassurance on this aspect.

Extensive one way sensitivity and scenario analysis demonstrated that savings and QALY gains persisted for both comparisons, therefore despite weaknesses in the clinical evidence and other assumptions, the economic case for tapentadol SR is considered demonstrated.

## Summary of patient and public involvement

A Patient Interest Group submission was received from:

- Pain Concern

## Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network. (SIGN) No.106. November 2008. The control of pain in adults with cancer. This guideline recommends that the oral route should be used for administration of opioids, if practical and feasible. Oral morphine is recommended as first line therapy to treat severe pain in patients with cancer. Patients in whom pain is not controlled despite optimisation of dose and when opioid-related side effects preclude further upward titration, should be switched to a different opioid.

Quality Improvement Scotland. Best Practice Statement: The management of pain in patients with cancer. November 2009. This offers guidance to health professionals on the best practice in this area, aiming to provide a consistent approach to practice to enable seamless provision of care to be delivered between the hospital and the community.

Quality Improvement Scotland. Best Practice Statement: Management of chronic pain in adults. February 2006. This is aimed at general nursing and allied health professionals and does not cover Specialist Pain Services although it is acknowledged that they are a key element in the patient pathway for those with chronic pain.

British Pain Society. Opioids for persistent pain. January 2010. This offers guidance to health professionals who manage patients with persistent pain, to help their understanding of the role of opioids in pain management.

## Additional information: comparators

Comparators include other opioid analgesics used for severe pain. Oral morphine is generally considered first line with other agents used in those who fail to respond to or cannot tolerate morphine e.g. oxycodone, transdermal fentanyl and transdermal buprenorphine (transdermal buprenorphine has been not recommended by SMC).

## Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
<b>Tapentadol MR tablets</b>	<b>100 to 250mg twice daily</b>	<b>648 to 1,619*</b>
Oxycodone MR tablets	20 to 50mg twice daily	648 to 1,619
Transdermal fentanyl	25 to 50micrograms/hour every 72 hours	616 to 1,150
Transdermal buprenorphine (Transtec®)	35 to 52.5micrograms/hour every 96 hours	358 to 536
Morphine sulphate MR capsules	40 to 100mg twice daily	168 to 311

Doses are for general comparison and do not imply therapeutic equivalence. The doses are not exact comparisons but are as close an approximation as possible when applying different conversion factors and with the limited dose flexibility of the patches. Morphine 80mg is equivalent to oxycodone 40mg; transdermal fentanyl "25" is equivalent to 90mg of morphine/day and transdermal buprenorphine "35" is approximately equivalent to 30 to 60mg morphine/day.

Costs from eVadis on 04 March 2011 except \* taken from company submission

## Additional information: budget impact

The manufacturer estimated that 80 patients who are receiving oxycodone or TD fentanyl would be treated with tapentadol MR in year 1 rising to 1,193 patients in year 5 (2% of oxycodone market share in year 1 and 28% in year 5, and 10% of TD fentanyl market share annually). This resulted in a gross drug budget impact of £58k in year one rising to £873k in year five. As the acquisition costs of tapentadol MR and oxycodone MR are the same, a neutral net drug budget impact was estimated for this displacement. The displacement of TD fentanyl was estimated to result in net savings of £700 in year 1 rising to £10.5K in year 5.

## References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Afilalo M, Etropolski MS, Kuperwasser B et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee. Clin Drug Investig 2010; 30:489-505

Etropolski MS, Shapiro DY, Okatomo A et al. Efficacy and tolerability of tapentadol extended release for diabetic peripheral neuropathic pain: results of a randomised-withdrawal, double-blind, placebo-controlled, phase III study. Poster presented at the 2009 annual meeting of the American Academy of Neurology (ANN), April 25 – May 2 2009, Seattle, Washington.

Grunenthal Ltd. Clinical study report KF5503/11. A randomised double-blind, placebo- and active-control, parallel arm, phase 3 study with controlled adjustment of dose to evaluate the efficacy and safety of tapentadol extended release (ER) in subjects with moderate to severe chronic pain due to osteoarthritis of the knee. 22 January 2009

Grunenthal Ltd. Clinical study report KF5503/12. A randomised double-blind, placebo- and active-control, parallel arm, phase 3 study with controlled adjustment of dose to evaluate the efficacy and safety of tapentadol extended release (ER) in subjects with moderate to severe chronic pain due to osteoarthritis of the knee. 27 February 2009

Buynak R, Shapiro DY, Okatomo A et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomised, double-blind, placebo- and active-controlled phase III study. Expert Opin Pharmacother 2010

Lange B, Kuperwasser B, Okatoto A et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. Adv Ther 2010; 27:

Grunenthal Ltd. Summary of clinical efficacy. 31 March 2009.

Grunenthal Ltd. Report CG5503-MA-01. Pooled subgroup analysis of the effect of tapentadol PR in subjects pre-treated with opioids having severe pain at baseline in trials KF5503/11, KF5503/12, and KF5503/23. 24 January 2011

Steigerwald I, Hans G, Schafer M et al. Equipotency of tapentadol and World Health Organisation (WHO) Step III opioids for the management of severe, chronic low back pain – interim results from an open-label, phase 3b study (Abstract) 20 January 2011.

Wild JE, Grond S, Kuperwasser B et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Practice 2010

This assessment is based on data submitted by the applicant company up to and including **15 April 2011**.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are

commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*