AWMSG Secretariat Assessment Report – Advice no. 1511
Tapentadol prolonged release (Palexia® SR▼) 50, 100, 150, 200 and 250 mg tablets

This assessment report is based on evidence submitted by Grünenthal Ltd on 2 June 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Tapentadol prolonged release (Palexia® SR▼) is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics[1].
Restrictions to submission	The company propose that tapentadol prolonged release (PR) be considered for patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated[2].
Dosing	Tapentadol PR is an oral formulation and should be taken twice daily, approximately every 12 hours. Dosing should commence at 50 mg in patients not taking opioid analgesics; higher doses may be required in patients currently receiving opioid medication. Titration in 50 mg increments every three days is considered appropriate for most patients, but each treatment should be individualised according to pain severity[1]. A total daily dose of tapentadol PR greater than 500 mg is not recommended. Tapentadol PR is not recommended for use in patients < 18 years[1]. To discontinue treatment it is advisable to taper the dose gradually to prevent withdrawal symptoms[1].
Marketing authorisation date	4 February 2011[1,2].

2.0 DECISION CONTEXT

2.1 Background

Chronic pain may be defined as pain that persists past the normal healing time of 3 months[3]. Chronic pain can severely affect quality of life, manifesting as physical and psychological disability with a high prevalence of comorbidities (e.g. anxiety, depression, sleeping difficulties, and hypertension)[4]. In an independent UK internet survey of 15,000 people produced by Consumer Health Sciences in 2008, 28.2% (4,231) of respondents suffered from pain, of which 23.9% (1,011) were experiencing severe pain associated mainly with back and joint problems[5]. A 2006 European survey also suggests that one in five Europeans suffer from chronic pain[6]. The applicant company estimates that 98,569

adults in Wales experience severe chronic pain, of which 6,269 would be eligible for tapentadol treatment[2].

Tapentadol is a centrally acting analgesic that combines two distinct mechanisms of action—noradrenaline reuptake inhibition (NRI) and mu-opioid receptor agonism—hence providing treatment for both neuropathic and nociceptive pain[7]. The dual mode of action results in an 'opioid sparing' effect, where the dose of tapentadol required to produce a given level of analgesia is lowered due to the contribution of the NRI component. The requirement of a lower dose of tapentadol reduces potential opioid-related side effects and treatment discontinuations. In addition, unlike some opioid analgesics, tapentadol has no serotonergic activity, and the associated side effects caused by increased serotonin (constipation, nausea, vomiting and diarrhoea) are therefore avoided. Tapentadol does not require metabolic activation and accordingly the relative contributions of the two mechanisms do not vary during metabolic transformation[7]. The information presented herein is related only to the prolonged release formulation of tapentadol.

2.2 Comparators

The Welsh Medicines Partnership (WMP) requested the following comparators:

- Morphine sulphate
- Oxycodone controlled release (CR) tablets (Oxycontin®)
- Fentanyl transdermal (TD) patch.

In line with their proposal that tapentadol PR be considered for patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated, the company presented oxycodone CR and fentanyl TD as comparators[2].

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE) clinical guidelines (CG88). Low back pain: early management of persistent non-specific low back pain. May 2009[8].
- The British Pain Society. Opioids in persistent pain: good practice. January 2010[9].
- The Pain Proposal. Improving the current and future management of chronic pain. A European consensus report. 2011[4].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence

The company submission includes several studies that evaluated the efficacy and safety of tapentadol PR: three phase III trials in patients with chronic osteoarthritis knee pain (KF11 and KF12)[2,10] or low back pain (KF23)[11], a phase III study in patients with chronic pain from diabetic peripheral neuropathy (DPN; KF36)[12], and a safety study (KF24) in patients with chronic knee osteoarthritis pain, hip osteoarthritis pain or low back pain[13]. A meta-analysis of trials KF11, KF12 and KF23 was also provided[14]. See Appendix 1 for a summary table of the trials included in the company submission.

3.1.1 Design of the clinical trials

KF11, KF12 and KF23 were randomised, double-blind, placebo- and oxycodone-controlled phase III studies[2,10,11]. Each study included a 3-week titration period where patients were initiated on 50 mg tapentadol PR twice daily, 10 mg oxycodone CR twice daily or placebo. After analgesic washout (3–7 days), patients were randomised 1:1:1 and doses were gradually adjusted to an optimal dose (100–250 mg tapentadol PR twice daily, 20–50 mg oxycodone CR twice daily) followed by a 12-week maintenance period, during which the only permitted additional analgesia was paracetamol (≤ 1,000 mg/day), as long as it was used for reasons other than study-related pain. KF36 consisted of an enrichment design where only subjects that experienced a reduction in pain intensity during the 3-week titration period were eligible for the 12-week maintenance period (randomised 1:1 to placebo or tapentadol PR)[12]. KF24 was a randomised, open-label, oxycodone CR-controlled safety study with a 1-week titration period and a 51-week maintenance period; patients were randomised 4:1 to receive controlled, adjustable twice-daily doses of tapentadol PR (100 to 250 mg) or oxycodone CR (20 to 50 mg)[13].

The primary endpoint for KF11, KF12, KF23 and the meta-analysis was the change from baseline of the average daily pain intensity over the maintenance period[2,10,11,14]. For KF36, the primary endpoint was the change from baseline in average pain intensity over the last week of the maintenance period[12]. Using an 11-point numerical rating score (NRS, see Glossary), severe pain was defined as NRS ≥ 6 and moderate pain as NRS between 4–6[14].

Inclusion criteria for the above studies included:

- Age restrictions: ≥ 40 years (KF11, KF12)[2,10]; ≥ 18 years (KF23, KF36)[11,12].
- Baseline pain: NRS ≥ 5 after 3–7-day analgesic washout.
- At least three months on analgesic medication (non-opioids or opioids at doses equivalent to ≤ 160 mg oral morphine per day) and dissatisfied with treatment due to lack of efficacy or tolerability.

3.1.2 Results of the clinical trials

Baseline characteristics in the meta-analysis of the intent-to-treat (ITT) population (defined as all patients who took at least one dose of the study drug) were comparable across all groups i.e. tapentadol PR, oxycodone CR and placebo[14]. In the total ITT population (n = 2,968), 1880 (63.3%) subjects were females, 2010 (67.7%) suffered from knee osteoarthritis, 958 (32.3%) suffered from low back pain, and 2572 (86.6%) were suffering from severe pain.

Results from the meta-analysis indicate that both tapentadol PR (n = 975) and oxycodone CR (n = 996) significantly reduced mean pain intensity compared to placebo (n = 988; $p < 0.001$ in both cases), and tapentadol PR also caused a marginally significant reduction in mean pain intensity in comparison to oxycodone CR ($p = 0.037$)[14]. These results however, were not consistent throughout each individual trial: in KF11, the mean pain intensity in response to oxycodone CR was only marginally different to placebo ($p = 0.049$)[10], and neither tapentadol PR nor oxycodone CR were significantly different to placebo in KF12 ($p = 0.135$ and $p = 0.421$ respectively)[2]. Secondary analyses demonstrated that significantly more patients in the tapentadol PR group than in the placebo group experienced ≥ 50% improvement in pain intensity by the end of the study (30.1% [294/978] versus 23.5% [233/991]; $p < 0.001$), whereas no significant difference versus placebo was observed in the percentage of patients receiving oxycodone CR (20.8% [208/999]; $p = 0.153$). The PGIC score (see Glossary) in the meta-analysis

significantly favoured tapentadol PR over oxycodone CR ($p < 0.001$). Similarly, results of SF-36 and EQ-5D questionnaires (see Glossary) from the meta-analysis both indicate that tapentadol PR, in comparison to oxycodone CR, provides a more positive response[14]. Tapentadol PR was associated with significantly greater improvements compared to oxycodone CR in all individual SF-36 domain scores, except general health ($p \leq 0.048$ in all comparisons); this included mental and physical component summary indices. Moreover, the health status index score of the EQ-5D was significantly greater for tapentadol in comparison to oxycodone ($p < 0.001$)[14].

In KF36, DPN subjects treated with tapentadol PR (n = 196) maintained a stable NRS pain intensity reduction (mean NRS reduction of 3.2) during the maintenance period in comparison to placebo (n = 193; $p < 0.001$). Patient outcomes were also significantly superior in response to tapentadol PR[12]. In addition, a long-term safety (see Section 3.1.5) and efficacy trial (KF24) demonstrated that tapentadol PR and oxycodone CR reduced and controlled pain intensity endpoints to similar levels (mean NRS reduction of 3.2 and 3.1, respectively) over a one-year period[13].

3.1.3 Sub-group analysis: tapentadol PR in patients with severe chronic pain and failed morphine treatment

The company have submitted a sub-group analysis investigating the management of severe chronic pain in patients (NRS ≥ 6) from KF11, KF12 and KF23, where morphine sulphate failed to provide adequate pain control, or was not appropriate or not tolerated, in line with their proposal to restrict use to this patient population[2]. Importantly, the sub-group analysis was not powered sufficiently to evaluate statistical significance. The sub-group consisted of all patients failing on any opioid (mainly tramadol or hydrocodone), as the proportion of patients who failed morphine therapy was reportedly too small (numbers of patients not provided). The sub-group represented approximately 30% of the total population of the three studies combined. (889/2968); the sub-group differed from the total population in that 20% (466/889) more subjects suffered from lower back pain (950/2968). Tapentadol PR (n = 309), oxycodone CR (n = 283) and placebo (n = 297) all reduced the average pain intensity over the maintenance period (mean reduction in NRS -2.62, -2.97 and -2.18, respectively); the reduction in pain intensity was greater in response to oxycodone CR than tapentadol PR, but the difference was not statistically significant ($p = 0.082$). By the end of the study, a ≥ 50% improvement in average pain intensity was reported in 25.6% of subjects receiving tapentadol PR, 26.5% receiving oxycodone CR and 19.5% receiving placebo, but there was a significant difference between oxycodone CR and placebo ($p = 0.045$).

EQ-5D health status indices increased in both the tapentadol PR and oxycodone CR groups, with a greater increase in the tapentadol PR group (0.21 versus 0.18). However, results were collated from patients experiencing severe and moderate pain, as the former population was too small[2].

3.1.4 Effectiveness of tapentadol PR versus fentanyl TD in patients with chronic pain

In the absence of head-to-head trial data for tapentadol PR and fentanyl TD, the company presented an indirect comparison using four randomised controlled trials (versus morphine[15–17] or placebo[18]) and four open-label, non-comparative observational studies[19–22]. However, due to the heterogeneity between trials in study design, prior opioid exposure, treatment duration, population and dose, a meta-analysis could not be performed, and no efficacy or safety data was presented comparing fentanyl TD and tapentadol PR.

3.1.5 Comparative safety

The meta-analysis demonstrated that rates of discontinuation were similar in response to placebo and tapentadol PR (40.6% and 43.5%, respectively), but higher in response to oxycodone CR (61.7%)[14]. Adverse events (AEs) were the most common reason for discontinuation (39.4% for oxycodone CR and 18.3% for tapentadol PR). Gastrointestinal (GI) and central nervous system (CNS) disorders were the most frequent AEs, and led to a higher percentage of patients discontinuing treatment in the oxycodone CR group compared to the tapentadol PR group (GI: 24.7% versus 8.1%, CNS: 16.8% versus 6.8%, respectively). Common GI events (nausea, constipation, vomiting) were twice as prevalent in the oxycodone CR group. The incidence of pruritis was lower in the tapentadol PR group compared to the oxycodone CR group (5.2% versus 13.4%) The time to treatment discontinuation was significantly different between oxycodone CR and tapentadol PR (39 days versus 118 days, respectively, $p < 0.001$)[14]. Similarly, in the KF24 safety study, time to discontinuation in tapentadol PR-treated subjects took on average 268 days compared to 59 days in the oxycodone CR group[13]. The company also indicate that during KF24 the mean total daily dose of tapentadol PR was relatively stable (as were the mean pain intensity scores) suggesting that there were no signs of acquired tolerance in patients that completed the trial, and a low incidence (1.5%) of opioid-related withdrawal problems was reported after tapentadol PR discontinuation (0.9% in oxycodone CR group)[13].

In the sub-group analysis, discontinuation rates were similar (approximately 50%) in the tapentadol PR, oxycodone CR and placebo groups[2]. However, as observed in the total population, AEs were also the main reason for discontinuation and were more frequently reported in the oxycodone CR group in comparison to the tapentadol PR group (30.5% versus 18%, respectively). The most frequent AEs in both treatments arms were constipation (33.3% versus 12.5%), nausea (30.5% versus 18%), and vomiting (16.5% versus 8.4%)[2].

3.2 WMP critique

- In the meta-analysis, pain intensity was significantly reduced in the tapentadol PR group in comparison to the oxycodone CR group[14]. However, in the sub-group analysis, although not statistically significant, oxycodone CR improved pain relief to a greater extent than tapentadol PR. In light of these results, the company suggest that tapentadol PR and oxycodone CR have comparable efficacy[2].
- The sub-group analysis included patients failing on any opioid (mainly tramadol and hydrocodone) and is therefore not exclusive to morphine intolerance as stated in the restricted indication proposed by the company. The company acknowledge this in their submission, and state that professional opinion sought indicated that patients failing on other opioids could be a suitable surrogate for morphine[2]. Despite this assumption, the post-hoc sub-group analysis was not powered appropriately to evaluate statistical significance as the number of patients was too low.
- Despite the licence restriction to severe pain (pain score ≥ 6), the meta-analysis of the key phase III studies included patients experiencing both moderate and severe pain[14]. The EQ-5D scores generated from the sub-group analysis of patients who had failed morphine treatment also included patients with moderate and severe pain due to low numbers in the latter[2].

- In the meta-analysis there was a higher discontinuation rate (mainly due to adverse events) in the oxycodone CR group compared to the tapentadol PR and placebo groups which may have resulted in an imbalance between groups.
- The studies did not allow for the use of breakthrough analgesia during the titration or maintenance periods; use of breakthrough medication would be normal clinical practice.
- Although the tapentadol Summary of Product Characteristics (SPC) does not preclude use in cancer pain, it is highlighted within the SPC that that there are limited data regarding the use of tapentadol in this patient group[1].
- One of the key studies included in the meta-analysis is KF12; however, this study has not been published and lacks peer-review.
- The fentanyl TD studies included in the indirect comparison demonstrated comparable efficacy between fentanyl and morphine, and reduced AEs in the former; however, no formal comparative analysis was undertaken to assess the relative efficacy or safety of tapentadol PR with fentanyl TD[2].
- A long-term safety study indicated that no tolerance was acquired, and low post-discontinuation withdrawal symptoms occurred in response to tapentadol PR over a one year study period. Nevertheless, despite tapentadol PR treatment lasting more than 4 times longer than oxycodone CR treatment (median durations of treatment 268 and 59 days, respectively), 46.2% of patients received tapentadol PR for a full year (35% in the oxycodone CR group)[13].
- Due to the lack of a single common pain biomarker, different patient outcome measures were used throughout the trials to evaluate efficacy endpoints. These measures included NRS, PGIC, BPI, SF-36, EQ-5D and others (see Glossary)[2].

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of tapentadol PR compared to oxycodone CR and fentanyl TD for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics[2]. The company has restricted its analyses to the use of tapentadol PR as a second-line treatment in patients who have had an inadequate response or intolerance to modified release morphine sulphate. Immediate release opioids are not considered and the efficacy data used throughout are derived in patients with non-cancer pain.

Two scenarios are considered. Scenario 1 includes both opioid-experienced and opioid-naïve patients with moderate or severe pain. Scenario 2 includes only opioid-experienced patients with severe pain, and is the most relevant to the licensed indication and company-proposed positioning of tapentadol PR[1]. Both scenarios assume three treatment sequences, starting from second-line tapentadol PR, oxycodone CR or fentanyl TD, and switching to the third- and fourth-line therapies in the case of discontinuation due to lack of efficacy or AEs. Transition probabilities for tapentadol PR and oxycodone CR were taken from a meta-analysis of three direct comparative studies in patients with musculoskeletal low back pain and osteoarthritis pain[14]. In the absence of a head-to-head comparison of tapentadol PR or oxycodone CR with fentanyl TD, the probabilities of transition among different health states were derived from a single non-comparative study in patients with

non-cancer pain[2]. The model assumes a four-week cycle and a one-year time horizon. See Appendix 2 for further details.

4.1.2. Results

Results of the base case analysis for scenario 2, which is the more relevant analysis for the decision context, are shown in Table 1. Tapentadol PR is estimated to be less costly and to generate more QALYs than both oxycodone CR and fentanyl TD. The key driver of the results is the probability of treatment discontinuation due to AEs, which is estimated to be lower with tapentadol PR treatment than with the comparators. In the model, this outweighs the greater probability of discontinuation due to lack of efficacy observed with tapentadol PR than with the comparators.

Table 1. Company-reported results of cost-utility analysis of tapentadol PR versus oxycodone CR and fentanyl TD in opioid-experienced patients with severe pain (Scenario 2)

Base case	Tapentadol PR	Oxycodone CR	Fentanyl TD
Drug costs (£)	1,270	1,249	1,414
Total cost (£)	3,703	3,754	3,879
Total QALYs	0.5658	0.5587	0.5591
Incremental cost per QALY gained (ICER)	Tapentadol PR dominated oxycodone CR and fentanyl TD*		
* Tapentadol PR was less costly and generated greater QALYs than the comparators			

One-way sensitivity analyses were conducted to address the uncertainties associated with costs (± 50%), utilities (± 20%) and transition probabilities between health states (± 20%). Different methods for extrapolating outcomes beyond week 16 were also explored. The ICERs were sensitive to variation in the probability of AEs for oxycodone CR and fentanyl TD, costs and utilities of treatment without AEs, utilities for fourth-line therapy and discontinuation due to AEs. However, in all of the sensitivity analyses presented, tapentadol PR remained less costly and generated greater overall QALYs than the comparators. The company's probabilistic sensitivity analysis indicates there is over 90% probability that tapentadol PR is cost-effective compared to fentanyl TD, and around 85% probability that tapentadol PR is cost-effective versus oxycodone CR at a threshold of £20,000 per QALY gained. However, the associated scatter plots indicate that in a substantial proportion of the 5,000 simulations, tapentadol PR was less costly and also generated fewer overall QALYs than the comparators.

Results of the base case analysis for scenario 1 are presented in Table 2B, Appendix 2. Results of the sensitivity analyses conducted around scenario 1 were consistent with those observed for scenario 2.

4.1.3 WMP critique

Strengths of the economic evidence include:

- The company conducted a range of sensitivity analyses to address several areas of uncertainty, including those arising from limited trial data.

Limitations of the economic evidence include:

- The efficacy data available to inform the comparison of tapentadol PR with oxycodone CR in the most relevant scenario (scenario 2) is based on a subgroup, representing around a third of patients enrolled in the three comparative trials. There are no trial data relating specifically to the use of tapentadol PR in patients who have had an inadequate response or intolerance to morphine sulphate.
- The comparative trial designs precluded the use of medication to treat breakthrough pain, such as might be used in practice. Discontinuation rates due to lack of efficacy observed in the trials contribute to the estimated QALY gains and may be influenced by the (lack of) use of additional breakthrough pain treatment.
- Discontinuations due to lack of efficacy were greater with tapentadol PR than with oxycodone CR.
- The efficacy data for fentanyl TD are based on a selected single-arm study. The comparison of tapentadol PR against fentanyl TD is an unadjusted/naive indirect comparison, which is subject to considerable uncertainty. This is compounded by the use of data from the comparison of tapentadol PR with oxycodone CR to adjust the fentanyl TD withdrawal rates in line with a four-week cycle.
- Deterministic sensitivity analyses indicate that the conclusion of dominance for tapentadol PR is robust within the range of the parameter values explored. However, the probabilistic sensitivity analyses indicate a good deal of uncertainty in the estimated effectiveness of tapentadol PR relative to the comparators.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of tapentadol PR compared to oxycodone CR and fentanyl TD for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company has provided a cost analysis relating to the use of second-line tapentadol PR in adult patients with chronic severe pain who have had an inadequate response or intolerance to modified release morphine sulphate.

Based on the results of a pain survey conducted in Europe (including the UK)[6], the company estimates there are currently 98,569 adults with severe chronic pain in Wales, of which 6,269 are eligible for treatment with strong opioids. Company market research data are reported to indicate that 30% of patients requiring strong opioids use slow release morphine[2]. Therefore, the estimated number of patients receiving alternative opioids is 4,388. Assuming that this number will remain constant over the next five years, and that the uptake of tapentadol PR will increase from 1% to 15% over the same time period, the number of patients anticipated to be prescribed tapentadol PR in Wales is expected to increase from 45 in the first year to 660 in the fifth year. It is assumed that patients would on average receive 235 days of treatment each year, and that, based on an equianalgesic ratio of 5:1 for tapentadol:oxycodone, there would be no net budget impact from the use of

tapentadol PR instead of oxycodone CR, as tapentadol PR is priced at parity with oxycodone CR. The company estimates that the use of tapentadol PR instead of fentanyl TD would result in a cost saving of £88 per patient per year[2]. The estimated number of patients treated with tapentadol PR and the associated costs over the five-year period are shown in Table 2.

Table 2. Company-reported costs associated with tapentadol PR treatment

	2011	2012	2013	2014	2015
Number of eligible patients	4,388	4,388	4,388	4,388	4,388
Uptake (%)	1	5	9	12	15
Number of treated patients	45	220	395	525	660
Tapentadol PR costs (£)	32,940	161,040	289,140	384,300	483,120

No sensitivity or scenario analyses have been provided in the company's submission.

5.1.2 WMP critique of the company's budget impact estimates

The company has presented a simple costing exercise rather than a budget impact analysis. The extent to which tapentadol PR may displace either oxycodone CR or fentanyl TD is not discussed, although in the case of oxycodone CR the acquisition costs are the same. As the company based their estimations on a telephone survey[20], the number of eligible patients appears subject to uncertainty.

5.2 Comparative unit costs

Example acquisition costs for non-morphine opioids used in the management of chronic pain are presented in Table 3.

Table 3. Examples of acquisition costs for non-morphine opioids used in the management of severe chronic pain.

Products	Example of daily doses*	Annual cost
Palexia® SR▼ (tapentadol PR) 50, 100, 150, 200 and 250 mg tablets	100 to 250 mg twice daily	£648 to £1619
Durogesic DTrans® (fentanyl) 12, 25, 50, 75 and 100 microgram/hr transdermal patch	25 to 75 microgram/hr patch once in 72 hours	£477 to £1241
OxyContin® (oxycodone) 5, 10, 15, 20, 30, 40, 60, 80, 120 mg prolonged release tablets	20 to 50 mg twice a day	£648 to £1621
Targinact®▼ (oxycodone/naloxone) 5/2.5, 10/5, 20/10 and 40/20 mg prolonged release tablets	20 to 50 mg (oxycodone) twice a day	£913 to £2282
*The dose is titrated until pain is controlled. In opioid-experienced patients the dose is adjusted according to previous analgesic dose. See individual Summaries of Product Characteristics for full dosing details. Costs are based on MIMS[23] list prices. This table does not imply therapeutic equivalence of drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that tapentadol PR is suitable for shared care within NHS Wales.

6.2 Ongoing studies

The company submission states that, as of 2 June 2011, there are two ongoing trials investigating:

- The safety and efficacy of tapentadol PR in tumour-related pain (KF15, n = 573).
- The effectiveness and tolerability of tapentadol sustained and immediate release on-demand, in subjects with severe chronic nociceptive, mixed or neuropathic low back pain taking strong analgesics but lack of tolerability (KF45, n = 180). An interim analysis demonstrated that after switching to tapentadol PR, NRS scores were comparable (maintained at approximately 4.2 over 12 weeks). At the time of the analysis only 87 patients had completed the study and a baseline NRS score ≤ 5 was required to be eligible for the study[24]. This study was completed in January 2011, but as of June 2011 no published results are available.

In addition, several reports are in progress for completed trials:

- The effectiveness and tolerability of tapentadol sustained- and immediate release on-demand in patients on weak or non-analgesic treatment (KF42, n = 180).
- The effectiveness and tolerability of tapentadol sustained- and immediate release on-demand, in subjects with severe chronic pain due to osteoarthritis of the knee taking strong analgesics but lack of tolerability (KF43, n = 180).
- The effectiveness and tolerability of tapentadol sustained- and immediate release on-demand, in subjects with uncontrolled severe chronic nociceptive, mixed or neuropathic low back pain taking weak or non-analgesic treatment (KF44, n = 180).
- Open-label assessment of cognitive and psychomotor performance in patients with chronic pain taking stable long-term tapentadol PR tablets (KF53, n = 30).

GLOSSARY

Nociceptive pain: a type of pain that is caused by physiological activation of specialised sensory nerves (nociceptors) by tissue-damaging stimuli[25].

Neuropathic pain: a type of pain that is caused by activity generated within the nociceptive system but without physiological stimulation of nociceptors[25].

Numerical rating scale (NRS): widely used and validated 11-point pain measurement scale, where 0 = no pain and 10 = worst pain imaginable.

Patient Global Impression of Change (PGIC): efficacy assessment based on a 7-point patient rating system from 'very much worse' to 'very much improved'.

Brief Pain Inventory (BPI): a short, self-administered 10-point test that assesses pain intensity and the degree which pain interferes with function.

Short Form-36 (SF-36): responsive and valid measure of health outcomes (vitality, physical functioning, bodily pain, general health, physical role, emotional role, social role, mental health) from a patient perspective.

EuroQol-5 Dimension (EQ-5D): validated self-reported single index value adaptable for clinical and economic evaluation of healthcare.

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Appendix 1. Additional clinical information

Table 1. Characteristics of the tapentadol PR clinical trials

Reference	Study type	Study drugs	Population	Treatment dosing	Baseline characteristics † (mean ± SD)	Primary endpoint	Secondary endpoints	Discontinued treatment
KF11	Randomised, double-blind phase III	Tapentadol PR (n = 337) Oxycodone CR (n = 344) Placebo (n =342)	Moderate to severe knee OA pain.	3 weeks flexible dose titration. 12 weeks controlled dose adjustment maintenance.	Age (years): 58.3 ± 9.85 Baseline pain (NRS): 7.3 ± 1.31	Change from baseline of the average pain intensity over the maintenance period	Responder rates based on 30% and 50% improvement in average pain intensity Time to treatment discontinuation PGIC, EQ-5D, SF-36, BPI (in KF23 and KF36). Refer to glossary for definitions	Tapentadol PR: 42.7% Oxycodone CR: 64.6% Placebo: 38.6%
KF12	Randomised, double-blind phase III[§]	Tapentadol PR (n = 319) Oxycodone CR (n = 331) Placebo (n = 337)	Moderate to severe knee OA pain.		Age (years): 62.1 ± 9.26 Baseline pain (NRS): 7.3 ± 1.1			Tapentadol PR: 41.7% Oxycodone CR: 63.4% Placebo: 34.4%
KF23	Randomised, double-blind phase III	Tapentadol PR (n =315) Oxycodone CR (n = 326) Placebo (n = 317)	Moderate to severe CLBP		Age (years): 49.9 ± 13.83 Baseline pain (NRS): 7.5 ± 1.29			Tapentadol PR: 47.8% Oxycodone CR: 59.5% Placebo: 52.4%
KF36	Randomised-withdrawal, double-blind phase III	Tapentadol PR (n = 196) Placebo (n = 193)*	Moderate to severe CP from diabetic peripheral neuropathy		Age (years): 60.2 ± 10.62 Baseline pain (NRS): 7.3 ± 1.41	Change from baseline of the average pain intensity over the last week of the maintenance period		Tapentadol PR: 30.1% Placebo: 30.6%*
KF24	Randomised, open-label phase III safety study	Tapentadol PR (n = 876) Oxycodone CR (n = 219)	Moderate to severe knee + hip OA pain, + CLBP	1 week flexible dose titration. 1 year controlled dose adjustment maintenance	Age (years): 57 ± 12.38 Baseline pain (NRS): 7.6 ± 1.55	No primary endpoint defined as it was a safety study	PGIC	Tapentadol PR: 53.8% Oxycodone CR: 65%
Lange and colleagues	Meta-analysis of KF11, KF12 and KF23	Tapentadol PR (n = 975) Oxycodone CR (n = 996) Placebo (n = 988)	Moderate to severe knee OA pain + CLBP	As described above for KF11, KF12 and KF13	Age (years): 56.8 ± 12.21 Baseline pain (NRS): 7.4 ± 1.24	All mentioned above	All mentioned above	Tapentadol PR: 43.4% Oxycodone CR: 61.6% Placebo: 40.5%

OA: osteoarthritis, CLBP: Chronic low back pain, NRS: numerical rating score, CR: controlled release, PR: prolonged release.
* Refers to the double-blind treatment period.
† Subjects had at least a ≥ 3-month history of analgesic use and were dissatisfied with current treatment.
§ This study has not been published.

Appendix 2. Additional health economic analysis information

Table 2A. Health economic analysis detail

	Base Case Model	Appropriate?
Comparator(s)	Oxycodone CR and fentanyl TD patch.	Yes, these comparators were requested by WMP. Comparison against morphine sulphate was also requested by WMP, but the company has restricted its analysis to the use of tapentadol PR as a second-line agent in patients in whom morphine sulphate is not tolerated or provides inadequate relief.
Population	Two scenarios are considered: • Adults with chronic pain, which can be adequately managed only with opioid analgesics. Both opioid-experienced and opioid-naive patients and a minority of patients with moderate rather than severe pain are included in this scenario. • Adults with severe chronic pain with prior experience of opioids (assumed to be morphine sulphate for the purposes of analysis).	Scenario 2 would appear the most informative for the company-proposed use of tapentadol PR. Scenario 1 includes patients with moderate pain, which are outside the licensed indication. All efficacy data employed within the model relate to the treatment of non-cancer type pain (e.g. osteoarthritis or low back pain).
Analysis type	Cost-utility analysis of tapentadol PR versus oxycodone CR or fentanyl TD, based on a Markov state transition model. Four states are modelled using four-week cycles: discontinuation due to AEs, discontinuation due to lack of efficacy, continuing treatment with mild/moderate AEs or continuing treatment without AEs. Subsequent lines of therapy include buprenorphine and oxycodone/naloxone.	Yes, cost-utility analysis is the preferred type of analysis and the Markov model would seem appropriate.
Perspective	Considers direct medical costs only, from the perspective of NHS Wales.	Yes.
Time horizon	The base case analysis assumes a one-year time horizon.	Yes, the time horizon is sufficient to capture all costs and benefits associated with the treatment of patients with severe chronic pain.
Discount rate	Discounting is not applied.	Appropriate, since the considered time horizon does not exceed one year.

Table 2A. Continued.

	Base Case Model	Appropriate?
Efficacy	Efficacy data for comparison of tapentadol PR with oxycodone CR were derived from a meta-analysis of three phase III studies KF11, KF12 and KF23[14]. These data included the proportions of patients remaining in treatment and withdrawn due to AEs and lack of efficacy. Due to a lack of head-to-head comparative data for tapentadol PR or oxycodone CR against fentanyl TD, efficacy estimates for fentanyl TD were derived from a published non-comparative study[20] identified from a systematic review of the literature.	The efficacy data derived for the scenario 2 population (i.e. the most relevant population for this analysis) are based on a sub-group of the relevant trial populations; only around a third of the patients enrolled in the three trials had prior experience with opioids, and none of the trials were powered to detect a difference between tapentadol PR or oxycodone CR in this sub-group. The three comparative trials did not permit use of medication to treat breakthrough pain, such as might have been used in practice, which would possibly influence withdrawal rates. The comparison of tapentadol PR against fentanyl TD is an unadjusted/naive indirect comparison, which is subject to considerable uncertainty. This is compounded by the use of data from the comparison of tapentadol PR with oxycodone CR to adjust the fentanyl TD withdrawal rates in line with a four-week cycle. The average of the tapentadol PR and comparator treatment-specific probabilities of moving between the four health states between weeks 13 and 16 were assumed to apply for the rest of the year. It is therefore assumed that there is no difference in efficacy (or withdrawal rates) between tapentadol PR and the comparators beyond 16 weeks of treatment. The probabilities of patients switching to the different subsequent lines of therapy appear to be based on expert opinion in relation to switching rates for oxycodone, which would seem a source of uncertainty.
Adverse effects	Common AEs including nausea, diarrhoea, constipation, vomiting and headaches. Patients with severe AEs were withdrawn from treatment, while patients with mild and moderate AEs continued their treatments.	Appropriate. The probability of discontinuation of treatment due to AEs in the economic model is based on the proportion of patients who were withdrawn from clinical studies due to severe AEs. The probability of continuing treatment with adverse reactions in the economic model is based on clinical data for patients who had AEs, which did not lead to treatment discontinuation.
Utility values	Utility estimates for tapentadol PR and oxycodone CR treatments were derived from EQ-5D data collected in phase III studies in the relevant populations. The mean average utility value for each of the four modelled health states are assumed for all opioids considered in the model.	Utility values are health state dependent and are assumed to be independent of the opioid product characteristics (e.g. there is no consideration of differences related to oral formulations versus TD formulations). Due to a lack of quality of life data for patients treated with fentanyl TD, there is uncertainty about the utility values assumed for health states reached using fentanyl TD treatment. Variations in utility values for fentanyl TD had a significant impact on ICERs, as demonstrated by the deterministic sensitivity analyses.

Table 2A. Continued.

	Base Case Model	Appropriate?
Resource use and costs	Doses of tapentadol PR and oxycodone CR were derived from a meta-analysis of the phase III studies[14]. Corresponding doses of fentanyl TD were calculated using equianalgesic dose ratios. Drug acquisition costs were estimated for average doses. The frequency and types of consultations and pharmaceutical prescribing for patients receiving strong opioid analgesia was reportedly derived from a retrospective cohort study of patients treated in UK general practices participating in The Health Information Network (THIN). Published unit costs were applied to these other items of resource use based on 2007 prices, which are inflated to 2009/10.	Appropriate sources of resource use appear to be considered. With respect to costs, consultations and prescriptions, more recent unit costs are available.
Uncertainty and scenario analyses	One-way deterministic analysis was conducted to identify the impact of model parameters (costs, utilities and transition probabilities between health states) on the ICERs. Probabilistic sensitivity analysis was conducted to estimate the probability that tapentadol PR is a cost effective treatment strategy versus oxycodone CR or fentanyl TD at £20,000 per QALY gained.	A wide range of sensitivity and scenario analyses have been conducted. Probabilistic sensitivity analysis is reported to indicate probabilities of tapentadol PR being cost effective at threshold of £20,000 per QALY gained in excess of 80%; however these probabilities should be interpreted with caution as visual inspection of the scatter plots indicates that a substantial proportion of the 5,000 simulations fell within the south-west quadrant of the cost-effectiveness plane, where tapentadol PR is both less expensive and less effective than the comparators.
Model Provided?	Yes.	Yes.

TD: transdermal, CR: controlled release, PR: prolonged release, ICER: Incremental cost per QALY gained, AE: adverse event.

Table 2B. Company-reported results of cost-utility analysis of tapentadol PR versus oxycodone CR and fentanyl TD in opioid-naïve or experienced patients with moderate or severe pain (Scenario 1)

Base case	Tapentadol PR	Oxycodone CR	Fentanyl TD
Drug costs (£)	1,128.50	1,101.29	1,227.89
Total cost (£)	3,542.50	3,656.22	3,705.27
Total QALYs	0.6371	0.6237	0.6259
ICER	Tapentadol PR dominated oxycodone CR and fentanyl TD*		
* Tapentadol PR was less costly and more effective than the comparators.			