MTRAC
Midlands Therapeutics Review and Advisory Committee

Considerations for Commissioners

Tapentadol PR *(Palexia SR®)*

For the treatment of severe chronic pain

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of tapentadol PR (prolonged release):

- The Scottish Medicines Consortium and the All-Wales Medicines Strategy Group recommend that tapentadol PR should be restricted to those patients with severe chronic pain in whom morphine sulphate modified release has failed to provide adequate pain control, or is not tolerated.
- It was the opinion of the MTRAC committee that ongoing management of chronic pain should be via a pain management clinic or service with access to a broad range of non-pharmacological therapies e.g. physiotherapy, cognitive behavioural therapy, occupational therapy.
- Within the context of use in a Pain Management service, tapentadol appears to be an effective treatment of similar efficacy to oxycodone.
- The British National Formulary (BNF) states that nausea, vomiting, and constipation are less likely to occur with tapentadol than with other strong opioid analgesics.[1]

Strength of the evidence for efficacy

The evidence for the efficacy of tapentadol PR came from five placebo-controlled RCTs, four of which showed a benefit over placebo in terms of improvement in pain intensity scores or prevention of deterioration in pain scores, and the fifth RCT that showed no benefit. A sixth trial, compared tapentadol PR with oxycodone/naloxone in people with low back pain with a neuropathic component, and found it to be superior for lowering pain intensity, and with significantly lower scores for neuropathic pain than oxycodone/naloxone treatment. A constipation symptom rating scale (PAC-SYM) also showed no change with tapentadol PR, but significantly lower scores for oxycodone/naloxone indicating deterioration.

MTRAC considered tapentadol PR at the request of local commissioners.

Description of technology

Tapentadol PR is a strong opioid analgesic with μ-agonistic opioid and additional noradrenaline reuptake inhibition properties[2]. It is licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

The recommended initial dose in opioid-naïve patients is 50 mg twice daily. For patients switching from another opioid, the initial dose of tapentadol PR will depend on previous treatment. In all patients, the dose should be titrated to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescriber[2]. To discontinue treatment, the dose should be tapered off gradually to prevent symptoms of withdrawal.

Tapentadol PR is a controlled substance according to Schedule 2 of the Misuse of Drugs Regulations 2001. Sections in the Summary of Product Characteristics regarding seizure risk and serotonergic syndrome have recently been amended following a European Medicines Agency examination of post-marketing safety data[3].

Background

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[4]. Chronic pain usually lasts longer than three months, and may have originated with an initial trauma/injury or infection, or may have an ongoing cause. Some people suffer chronic pain in the absence of any past injury or evidence of body damage. Chronic pain can interfere with quality of life, sleep and productivity[5].

Opioids are one of many analgesia options available for pain but must be used with care. Information on safer prescribing of analgesics is available from the British Medical Association and the Faculty of Pain Medicine has published the Opioids Aware campaign and resources.

West Midlands guidance is available in the form of a Decision-making support tool, and pain management pathway. A NICE clinical guideline on the assessment and management of chronic pain is expected in 2020.

Clinical evidence for efficacy and safety

MTRAC reviewed six randomised controlled trials (RCTs):

- three phase 3, double-blind trials *vs*. placebo for chronic osteoarthritis-related knee pain or low back pain, with oxycodone controlled release (CR) as an active control[7-9]; data from the three trials were also combined in a meta-analysis.[10]
- one phase 3 open-label trial *vs*. oxycodone/naloxone for severe chronic low back pain with a neuropathic component[11]
- two placebo-controlled trials *vs*. placebo for pain due to diabetic peripheral neuropathy (DPN)[12 13].
- A safety and tolerability study[14] evaluated people with osteoarthritis and chronic pain in the knee or hip, or low back pain over 52 weeks.

Following a washout period for current analgesia, dose titration took place over three weeks, before a

NICE accredited www.nice.org.uk/accreditation

NICE has accredited the process used by the Midlands Therapeutics Review and Advisory Committee to produce Commissioning support summaries. Accreditation is valid for 5 years from 7 March 2017. More information on accreditation can be viewed at www.evidence.nhs.uk

For full details of our accreditation visit: www.nice.org.uk/accreditation **Meeting date: January 2019**

maintenance period of 9 to 12 weeks in the efficacy trials, and 52 weeks in the safety study[14]. The trials involving patients with DPN used an enrichment design, in which only patients showing improvement on optimised tapentadol PR treatment (after titration) were then randomised to tapentadol PR or placebo during a double-blind phase[12 13].

The primary outcome in the trials was the change in average pain intensity from baseline to the end of the trial; one of the trials included an assessment of constipation symptoms as a co-primary outcome (PAC-SYM)[11]. Secondary outcomes included the clinician's and participant's global impressions of change (PGIC), and an assessment of improvement in quality of life (EQ-5D and SF-12).

Results

In the meta-analysis, tapentadol PR and oxycodone CR treatment both significantly reduced pain intensity scores more than placebo ($p < 0.001$), and indirectly, tapentadol PR was marginally more effective than oxycodone CR ($p = 0.037$)[10]. The results were inconsistent across the included trials: two trials showed greater improvements in pain intensity for both active treatments *vs*. placebo[7 9], but in one trial the difference for oxycodone CR *vs*. placebo was only marginally significant ($p = 0.049$)[7]; the third found no difference *vs*. placebo for either tapentadol PR or oxycodone CR[8].

In a sub-group of patients not achieving adequate pain control with morphine sulphate, tramadol or hydrocodone; tapentadol PR, oxycodone CR or placebo reduced the average pain intensity over the maintenance period (mean reduction in 0 to 10 point numerical rating scale of -2.62, -2.97 and -2.18, respectively). Pain intensity reduction was greater with oxycodone CR than tapentadol PR, but the difference was not statistically significant ($p = 0.082$).

Compared with oxycodone/naloxone PR, tapentadol PR treatment was superior for the improvement in pain intensity scores and, showed significantly greater improvement in neuropathic pain symptoms[11]. Constipation symptoms worsened with oxycodone/naloxone PR treatment but not with tapentadol PR.[11]

For the relief of chronic pain due to DPN, there was an initial improvement in the condition of all patients during the tapentadol PR dose titration phase. Both trials showed greater deterioration in pain scores with placebo than with tapentadol PR during the double-blind phase ($p < 0.001$)[12 13].

The 52-week safety trial showed lower pain intensity scores with both tapentadol PR and oxycodone CR treatment, that were maintained over the trial duration[14].

Secondary outcomes: The PGIC score was significantly better for tapentadol PR *vs*. placebo and oxycodone ($p < 0.001$). Similarly, results of SF-36 and EQ-5D questionnaires from the meta-analysis showed a more positive response for tapentadol PR than oxycodone CR.

Adverse events

Adverse events were the most common reason for treatment discontinuation with tapentadol PR or oxycodone CR, whilst lack of efficacy was the most common reason in the placebo group[10]. Oxycodone treatment led to significantly earlier discontinuation than placebo- or tapentadol PR-treatment ($p<0.001$ for both comparisons); the median time to discontinuation was 39 days with oxycodone CR and 118 days with tapentadol PR.

The reports of treatment-emergent adverse events (TEAEs) were similar across the trials and included nausea, dizziness, constipation, headache, somnolence, fatigue, vomiting, dry mouth, hyperhidrosis, pruritus, and diarrhoea. The overall incidence of gastrointestinal disorders in the meta-analysis (constipation, nausea and vomiting) was significantly lower in the tapentadol PR group (42.8%) compared with the oxycodone CR group (65.6%; $p < 0.001$). There were also numerically lower incidences of nervous system disorders and pruritus in the tapentadol PR group *vs.* oxycodone CR.

A recent Drug Safety update warned of an increased risk of seizures and reports of serotonin syndrome when tapentadol PR was co-administered with other medicines i.e. antidepressants and antipsychotics[3].

Considerations for cost impact

Estimates of the number of potential recipients for tapentadol PR are based on chronic pain survey data.[6] Assuming that 11,400 patients with chronic pain in the West Midlands may be eligible for treatment with strong opioids, and 30% of those are able to tolerate morphine sulfate SR, then 7,991 West Midlands patients may need an alternative treatment option.

Current cost of selected strong opioids for 28 days (excluding VAT):

Fentanyl (Matrifen®) 12-25mcg/hr	£13.90 to £19.88
Morphine Sulfate (Zomorph®) 20–120mg	£ 3.24 to £ 15.12
Oxycodone CR (Oxycontin®) 10-60 mg	£12.52 to £76.24
Oxycodone SR (Abtard®) 10-60 mg	£ 6.26 to £38.12
Oxycodone SR (Oxeltra®) 10–60 mg	£ 3.13 to £19.06
Oxycodone/Naloxone (Targinact®) 10/5 - 40mg/20mg	£21.16 to £84.62
Tapentadol (Palexia SR®) 50-300mg	£12.46 to £74.73

References

1. Analgesics: BNF; 2019; accessed 01 2019.
2. Grunethal Ltd. Palexia SR prolonged release tablets 2019.
3. Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines. *Drug Safety Update* 2019; 12(6).
4. IASP Terminology 2017.
5. Rosenblum A et al. *Exp Clin Psychopharmacol* 2008; 16(5).
6. Breivik H et al. *European journal of pain* 2006;10(4):287-333.
7. Afilalo M et al. *Clinical drug investigation* 2010; 30(8):489-505.
8. Serrie A et al *Current medical research and opinion* 2017;33(8):1423-32.
9. Buynak R et al. *Expert opinion on pharmacotherapy* 2010; 11(11):1787-1804.
10. Lange B et al.. *Advances in therapy* 2010; 27:381-399.
11. Baron R et al. *Pain practice* 2016;16(5):580-99 and 600-619.
12. Schwartz S et al. *Current medical research and opinion* 2011; 27(1):151-162.
13. Vinik AI et al. *Diabetes care* 2014;37(8):2302-9.
14. Wild JE et al. *Pain practice* 2010; 10(5):416-427.

Launch date: February 2011 *Manufacturer: Grunenthal Ltd*

Keele University Centre for Medicines Optimisation
School of Pharmacy, Keele University, Keele, Staffordshire ST5 5BG Tel: 01782 733831 Email: mtrac@keele.ac.uk Web: www.mtrac.co.uk