Tapentadol sustained release (Palexia SR)
for chronic, severe disabling pain
(ta-PEN-ta-dol)

KEY POINTS

Tapentadol SR is an oral opioid analgesic with two actions
Tapentadol SR exerts its analgesic effect through mu-opioid receptor agonism and noradrenaline reuptake inhibition.

Tapentadol SR is PBS listed as an alternative to oxycodone and tramadol
Some studies have shown that tapentadol SR may have similar efficacy to that of oxycodone CR for the relief of chronic, moderate-to-severe disabling pain associated with osteoarthritis and low back pain. There are currently limited data regarding other chronic pain conditions. There are currently limited comparative data with other opioids, including tramadol.

Tapentadol SR is a schedule 8 (S8) drug
Prescribers should ensure they satisfy the State-based requirements for prescribing S8 drugs.

Tolerability and long-term safety uncertain
More research is required to assess long-term safety of tapentadol.

PBS listing
The listing for tapentadol SR is the same as for other schedule 8 opioid analgesics.

Restricted benefit
For the treatment of chronic, severe disabling pain not responding to non-narcotic analgesics.

Authorities for increased maximum quantities and/or repeats will be granted only for:

- chronic, severe disabling pain associated with proven malignant neoplasia; or
- chronic, severe disabling pain not responding to non-narcotic analgesics where the total duration of narcotic analgesic treatment is less than 12 months; or
- the first application for treatment beyond 12 months of chronic, severe disabling pain not responding to non-narcotic analgesics where the patient’s pain management has been reviewed through consultation by the patient with another medical practitioner, and the clinical need for continuing narcotic treatment has been confirmed.

Caution
The risk of drug dependence is high.

May be prescribed by nurse practitioners within collaborative arrangements
Authorised nurse practitioners may prescribe continuing therapy of this medicine after it has been initiated by a medical practitioner. See the PBS website for more information on nurse practitioner PBS prescribing.

What is it?
Tapentadol sustained release (SR) is a centrally acting opioid analgesic in tablet form taken twice daily. It acts primarily by binding to mu-opioid receptors as an agonist but also inhibits noradrenaline reuptake.

TGA indications and scheduling
Tapentadol SR is an S8 scheduled (controlled) drug indicated for the management of moderate to severe chronic pain unresponsive to non-opioid analgesics.
Who is it for?
Tapentadol SR may be an option for people with chronic, severe disabling pain for whom non-opioid analgesics provide insufficient pain relief, and for whom a trial of opioids as an alternative is indicated.

Malignancy
There are limited data regarding the use of tapentadol SR in patients with malignancy, and its safety and efficacy for these people is uncertain.

Potential for abuse
Tapentadol SR is a medicine with potential for abuse. Monitor patients regularly for signs of drug dependence or evidence of abuse. A number of screening tools are available to facilitate this assessment.

Where does it fit?
Tapentadol is an alternative to other opioid analgesics such as oxycodone and tramadol. Opioid analgesics do not provide clinically worthwhile pain relief for all users but may be considered for some people who are still experiencing severe disabling pain despite trialling other non-opioid options.

Be aware that the role of long-term use of opioid analgesics for people with chronic pain remains controversial and the evidence for efficacy overall is weak.

Safer opioid prescribing for chronic pain
Management of non-malignant chronic pain is complex, and analgesics should only be expected to provide some modification of pain.

Explore and consider trialling non-pharmacological options such as physiotherapy, cognitive behavioural therapy and other pain management programs before starting pharmacological treatment.

Guidelines for management of chronic pain advise that patients should try paracetamol, NSAIDs and adjuvant analgesics (such as anticonvulsants) in adequate doses before the addition of opioid analgesics is considered.

Before starting an opioid analgesic, guidelines recommend that health professionals fully counsel their patients about what can be realistically achieved, and that a pain free outcome may not be possible.

Before prescribing, assess patients for comorbid psychological conditions and any history of drug dependence. A number of screening tools are available to facilitate this assessment.

A contractual approach to opioid prescription is recommended. A short initial trial period, such as 1 month, is suggested when starting opioids. The goals of the trial should be set out and agreed by the patient and the health professional before starting.

Regular (weekly) follow-up is recommended as well as suggesting the patient keep a daily diary to monitor activities and pain-related impairment. Ensure the patient understands and agrees that if goals are not met at the end of the trial period, other alternatives will be explored.

Ongoing monitoring and assessment is necessary for any patient who remains on opioid therapy after the trial period, including ongoing assessment of efficacy, monitoring for side effects and evidence of dependence or diversion.

How does it compare?
A number of trials have been conducted comparing tapentadol SR with placebo and oxycodone CR for a variety of moderate-to-severe chronic non-cancer pain conditions.

Three pivotal trials, two published and one unpublished, were considered for the purposes of regulatory approval. These studies investigated the relative efficacy and safety of tapentadol SR and oxycodone for lower back pain and osteoarthritis of the knee.

All three pivotal trials were phase III, randomised, double-blind, active and placebo-controlled, parallel group, multicentre trials. In all three trials patients were randomised to receive placebo, oxycodone CR or tapentadol SR.

The primary endpoints for all three studies were:
- change from baseline of average pain intensity (numerical rating scale) over a 12-week maintenance period
- change from baseline of average pain intensity (numerical rating scale) in the last week (week 12) of the maintenance period.
EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?
Tapentadol SR is a centrally acting opioid analgesic that binds to the mu-opioid receptor. In addition it inhibits noradrenaline reuptake. Trials have shown that tapentadol SR may have analgesic effects equivalent to those of oxycodone CR for certain chronic pain conditions.

AREAS OF UNCERTAINTY
While some trials have shown that tapentadol SR may be equally effective as oxycodone CR in relieving chronic non-cancer pain, the three pivotal trials provided mixed results, with only two achieving their primary efficacy endpoints of a significant change in baseline pain intensity compared with placebo.

While analysis of phase II/III trials indicated that tapentadol SR was associated with numerically fewer adverse events than oxycodone CR, whether this is clinically relevant is unclear. Safety was not the primary endpoint of the trials, and the long-term safety profile is currently unknown. Based on current evidence it should be assumed that tapentadol is associated with the same risks as oxycodone, and patients should be managed accordingly.

To date, the pain conditions for which the efficacy and safety of tapentadol SR have been mainly assessed in randomised controlled clinical trials are osteoarthritis and low back pain. The efficacy of tapentadol in the treatment of chronic, severe disabling pain due to other conditions is unclear.

WHAT DOES NPS SAY?
Tapentadol is PBS listed as an alternative to other opioids such as oxycodone for chronic, severe disabling pain not responding to non-opioid analgesics.

However, the clinical trials produced mixed results and were limited by a high study drop-out rate. This may have introduced a potential source of bias even though this was corrected for statistically.

Due to limited long-term safety and efficacy data it is currently not possible to suggest which patients may gain the most benefit from tapentadol SR.

It is important to follow opioid-prescribing guidelines when considering tapentadol SR treatment for people with chronic pain. Trial non-pharmacological and non-opioid treatments for chronic pain before considering opioid analgesia.

Prescribers should ensure they satisfy the State-based requirements for prescribing S8 drugs.

Prescribers should develop a pain management plan with the patient and monitor for efficacy, adverse effects and aberrant drug-related behaviours. Consider referral to a pain medicine specialist for review.

ADDITIONAL INFORMATION
See the online version of this article at www.npsradar.org.au/tapentadol for an assessment of the evidence quality using the ‘GRADE’ criteria

Pivotal trials show mixed efficacy results
Two of the three pivotal trials reached their primary efficacy endpoints by demonstrating superiority of tapentadol SR over placebo in the change from baseline of average pain intensity at week 12, and the average change in pain intensity over the whole 12-week maintenance period.8,9

This average change in baseline pain intensity was <1 point on the 12-point numerical rating scale for both trials.8,9 The unpublished study (KF5503/12) involving 986 patients failed to meet the primary efficacy endpoints for both the tapentadol SR and oxycodone CR arms.
The results from the three pivotal trials were re-analysed in a pooled analysis. In this analysis, tapentadol treatment did result in a statistically significant reduction in average pain intensity compared with placebo and was non-inferior to oxycodone.\(^1\)

**Safety in the pivotal trials: possible improved overall tolerability**

In all three pivotal trials the types of adverse events experienced by patients taking tapentadol SR were consistent with those associated with opioid analgesics.\(^1,2,8,9\)

Adverse effect frequency was not the primary endpoint of the trials, but there was a decreased frequency and lower intensity of adverse events, and a lower rate of treatment discontinuations due to adverse events, in people taking tapentadol SR compared with those taking oxycodone.

**Fewer discontinuations due to adverse events**

The discontinuation rates for the trials were high. In the trials with published results the total discontinuation rates were above 50%.\(^8,9\)

Main reasons for discontinuation were lack of efficacy in the placebo arms and adverse events in the tapentadol SR and oxycodone CR arms.

In both published trials oxycodone CR had a higher rate of discontinuation due to adverse events than tapentadol SR (32.3% vs 16.7%\(^9\) and 43.0% vs 19.2%\(^8\), respectively).

Analysis of pooled data from the three trials demonstrated that patients in the oxycodone group discontinued earlier than those in the tapentadol SR and placebo groups. Median time to discontinuation was 39 days for oxycodone, 118 days for tapentadol SR and 124 days for placebo (p < 0.001).\(^10\)

**Comparison with tramadol**

While clinical trials have focussed on comparing the safety and efficacy of tapentadol SR to that of oxycodone CR, the dual action of tapentadol SR suggests it may be an alternative to tramadol.

Both tramadol and tapentadol have mu-opioid agonist activity in addition to effects on noradrenaline reuptake.\(^1,11,12\) There has been one phase II trial in which tapentadol SR was compared with tramadol.

However, this trial was of short duration (4 weeks) and neither tramadol nor tapentadol SR demonstrated analgesic effects greater than placebo.\(^2\)

There are a number of points of difference between tramadol and tapentadol SR in that tramadol has comparatively weak opioid activity and additional serotonin reuptake inhibition compared with tapentadol SR.\(^3\)

Further research is needed to ascertain the relative safety and efficacy of tapentadol SR and tramadol.

**Safety issues**

In total, 3613 patients have been treated with tapentadol SR in clinical trials. The most frequently reported adverse events included nausea, vomiting, constipation, hyperhydrosis and dizziness.\(^1,2\)

Compared with oxycodone, tapentadol SR was associated with numerically lower total incidence of adverse events, in particular, a lower incidence of GI adverse events.\(^1\)

An open-label extension study (treatment up to 1 year) for patients with chronic knee or hip osteoarthritis pain or low back pain showed similar rates of adverse events as those seen in the short-term treatment studies.\(^13\) The incidence of adverse events in the tapentadol SR-treated group was 85.7% compared with 90.6% in the oxycodone CR group.\(^13\)

**Potential for abuse**

As with other opioids tapentadol has a potential for abuse. Tapentadol SR may be abused by chewing, crushing and snorting or injecting the tablets. This poses a serious risk and may result in overdose or death.\(^1\)

The potential for a patient to misuse, abuse or divert tapentadol SR should be taken into account before prescribing or dispensing. Monitor patients prescribed tapentadol SR for signs of abuse and addiction.

**Drug dependence**

As with other opioids, repeated administration may lead to tolerance, defined as the need for increasing doses of opioids to maintain the desired analgesic effect in the absence of disease progression or other factors.\(^1\)
People with chronic pain, history of substance abuse and/or mental health disorders are at a higher risk of dependence and misuse of opioid analgesics. Inform your patients of the risk of dependence before prescribing.

Reason for PBS listing

The PBAC recommended listing of tapentadol SR for the treatment of chronic, severe, disabling pain in patients not responding to non-narcotic pain relief, on a cost minimisation basis — that is, similar efficacy and cost — compared with oxycodone CR and tramadol CR.

Dosing issues

Individualise the dose of tapentadol SR according to the severity of pain and the patient’s response. Tapentadol SR tablets should be taken twice daily approximately 12 hours apart with or without food. As with other long-acting opioid analgesics prescribed for managing chronic pain, explain to patients that they should take their doses every day regularly and not on an ‘as needed’ basis.

Tapentadol SR is not intended for break-through pain. In the trials patients were allowed to use paracetamol for break-through pain.

Starting tapentadol SR

Follow safer opioid prescribing guidance based on a contract approach and a therapeutic trial. Ensure the patient understands and agrees that if goals are not met at the end of the trial period, other alternatives will be explored (see ‘Safer opioid prescribing for chronic pain’, page 22).

For people who are not currently taking opioid analgesics the starting dose is 50 mg tapentadol SR twice daily.

For patients changing to tapentadol from a different opioid analgesic choose a dose of tapentadol SR based on the mean daily dose of their current medicine. The recommended conversion between oxycodone and tapentadol is 1 to 5.3.

Choose the nearest lower dose of tapentadol. For example, for a patient changing from oxycodone 15 mg, the converted dose of tapentadol is 79.5 mg. Prescribe 50 mg of tapentadol rather than 100 mg of tapentadol.

Titrating tapentadol SR

When a patient has begun taking tapentadol SR, titrate the dose according to response. Every 3 days, increase the dose by 50 mg for each twice-daily dose until adequate analgesia is achieved.

A total daily dose of > 500 mg has not been studied and is not recommended.

Stopping tapentadol SR

Abrupt cessation of tapentadol SR could result in withdrawal symptoms. Consider a gradual taper for people who are stopping tapentadol.

Overdose management

Clinical experience with overdose of tapentadol is limited. Symptoms are expected to be similar to those of other opioid analgesics, such as vomiting, cardiovascular collapse and respiratory depression/arrest.

In the event of an overdose, focus on maintaining respiration. Opioid antagonists such as naloxone may be used as a specific antidote to respiratory depression, but respiratory depression after overdose may outlast the duration of action of the opioid antagonist.

For more information on managing overdose contact Poisons Information Centre on 131 126.

Contraindications

As with other opioid analgesics tapentadol SR is contraindicated for patients with significant respiratory depression and with acute or severe bronchial asthma or hypercapnia. Tapentadol SR is also contraindicated in:

- patients with (or with suspected) paralytic ileus and those with acute intoxication with alcohol, hypnotics, centrally acting analgesics or other psychotropic drugs
- patients who are taking MAOIs or have taken them during the last 14 days.
Renal and hepatic impairment
Tapentadol SR has not been studied in patients with severe renal and hepatic impairment and is therefore not recommended. A dose reduction is recommended for people with moderate hepatic impairment; check the Product Information for full details.

Use in pregnancy, older people and children
Tapentadol has not been studied in pregnancy and is listed as a category C medicine. Tapentadol should not be used while breastfeeding.

Do not use in children under 18 years due to lack of safety and efficacy data.

As with all opioids, take care when prescribing tapentadol to older patients.

Driving and use of machinery
Warn people prescribed tapentadol that, as with other opioid analgesics, it may affect their ability to drive and use machinery.

This effect is especially prominent at the beginning of treatment, when changing doses, or when combined with alcohol or sedative medicines.

Interactions with medicines
People who are taking other CNS depressants such as phenothiazines, sedatives, hypnotics or other CNS depressants (including alcohol) concurrently with tapentadol SR may experience an additive CNS depression that may result in respiratory depression, hypotension, profound sedation or coma.

If possible avoid using tapentadol SR with any of these medicines. If it is unavoidable, monitor carefully and consider a dose reduction of one or both medicines.

Combining MAOIs with tapentadol (or use of tapentadol in patients who have taken MAOIs in the last 14 days) may result in additive effects on noradrenaline levels that may cause adverse cardiovascular events. See ‘Contraindications’, page 25.

Serotonin toxicity
Tapentadol has only a weak effect on serotonin reuptake; however, there is a theoretical risk that concomitant use of tapentadol with other serotonergic products such as SSRIs, SNRIs, TCAs, MAOIs, St John’s wort and triptans may result in serotonin syndrome.

There are some reports of isolated cases of serotonin syndrome in patients who have also been taking tapentadol SR. This risk appears to be similar to that reported for tramadol.
Information for patients

Advise patients that tapentadol SR may not completely relieve their pain and that a 30–50% reduction in overall pain intensity may be realistic.

A trial is recommended for patients who have never taken prescription opioid medicines before. Discuss the nature of the trial and draw up an agreement regarding its duration and aims, and the actions to be taken if the agreed goals are not achieved. A written agreement may be helpful.¹⁴

Explain the process of initiation and titration and the need for regular monitoring for efficacy and side effects.

Explain the potential for interactions for patients who are also taking medicines that affect the CNS, such as antidepressants or sedatives, and that there may be a need for dose adjustment. Caution your patients to avoid alcohol and illicit drugs.

Advise patients that they may experience GI symptoms, including nausea and constipation. Consider co-prescription with a laxative such as Movicol or lactulose.

Advise patients that tapentadol SR must be taken twice daily and regularly — it is not for ‘as required’ use.

Advise patients that they should be careful about driving and operating machinery, especially when they first start treatment, or when they change doses.

Fully inform your patients of the risks associated with long-term opioid use and discuss the potential for opioid dependence before they start.

Discuss the Palexia SR (tapentadol) Consumer Medicine Information (CMI) leaflet with the patient.*


† Tapentadol Medicine Update article: www.nps.org.au/medicine-update/tapentadol-sr

MEDICINE UPDATE

An NPS Medicine Update article on tapentadol† is available for consumers. Medicine Update helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with those of other medicines.
REFERENCES


Date published: June 2014

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