

PUBLIC SUMMARY DOCUMENT

Product: Tapentadol, tablet, 50mg, 100mg, 150mg, 200mg and 250mg (as hydrochloride) (sustained release), Palexia SR[®]

Sponsor: bioCSL Australia Pty Ltd

Date of PBAC Consideration: November 2013

1. Purpose of Application

The major re-submission sought a Restricted Benefit listing for the treatment of chronic severe disabling pain not responding to non-narcotic analgesics.

2. Background

This was the fifth submission requesting PBS listing for tapentadol sustained release (SR) tablets.

The PBAC had previously considered and rejected two major submissions for tapentadol SR (March 2011 and a re-submission in March 2012), and two minor re-submissions (July 2012 and November 2012). Public Summary Documents are available on the [PBS website](#).

3. Registration Status

Tapentadol SR was TGA registered on 19 January 2011 for the management of moderate to severe chronic pain un-responsive to non-narcotic analgesia. There is currently no clinical trial data available regarding the safety and efficacy of tapentadol SR in patients with pain due to malignancy.

4. Listing Requested and PBAC's View

Restricted benefit

Chronic severe disabling pain not responding to non-narcotic analgesics.

Caution

The risk of drug dependence is high.

Note

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

- (i) chronic severe disabling pain associated with proven malignant neoplasia; or
- (ii) chronic severe disabling pain not responding to non-narcotic analgesics where the total duration of narcotic analgesic treatment is less than 12 months; or
- (iii) 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 analgesic treatment has been confirmed. The date of the consultation must be no more than 3 months prior to the application for a PBS authority. The full name of the medical practitioner consulted and the date of consultation are to be provided at the time of application; or

- (iv) subsequent application for treatment of chronic severe disabling pain not responding to non-narcotic analgesics where a PBS authority prescription for treatment beyond 12 months has previously been issued for this patient.

The PBAC noted that the wording of the requested listing was unchanged from the previous submissions and that listing was requested on a weighted cost-minimisation basis with oxycodone and tramadol.

5. Clinical Place for the Proposed Therapy

Tapentadol is a centrally acting synthetic analgesic with two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition.

The re-submission claimed there is a clinical need for tapentadol SR in the treatment of chronic severe disabling pain not responding to non-narcotic analgesics as it offers similar analgesic efficacy to other opioid analgesics though a different mode of action with improved tolerability (reduced incidence of gastrointestinal adverse events) and lower potential for abuse and dependence.

The PBAC noted that the claim of a clinical need for tapentadol SR may be limited to those patients who are unable to tolerate the gastrointestinal adverse events associated with other opioids. The claim of lower potential for abuse relied on data presented on use of tapentadol immediate release formulation in the US population and regulatory environment over a short period of exposure. The submission assumed that this would also be the situation in Australia; however the PBAC considered this assumption was poorly supported.

The PBAC noted the comments provided by the clinician at the hearing regarding the ongoing need for effective pain management in patients with chronic pain. The clinician considered that a small number of patients were poor responders to existing opiates and tapentadol provided an effective option.

6. Comparator

The submission retained oxycodone CR as the main comparator, and tramadol SR as a secondary comparator. This was previously accepted by the PBAC.

7. Clinical Trials

No new clinical data were presented in this major re-submission and no changes were made to the trial data presented in previous submissions. The re-submission however, presented a new pooled analysis of the risk difference and number needed to harm (NNH) analyses of the pooled safety data from the three pivotal head-to-head trials (KF11, KF12 and KF23), limited to the incidence of treatment emergent gastrointestinal adverse events. Safety data and analyses presented in previous submissions were re-presented as supportive analyses.

The details of KF11, KF12 and KF23 have previously been reported in the March 2011 PSD.

The safety data sets in the pivotal trials KF11 and KF12 include all patients receiving at least one dose of study medication, and are identical to the intention to treat data sets previously considered by the PBAC. In trial KF23, two patients in the placebo arm were randomised twice. Only data from the first randomisation was included in the safety dataset.

The PBAC noted the inclusion criteria of the pivotal trials included dissatisfaction with prior analgesic therapy. More than half of the patients in KF23, around 30% of patients in KF11 and 16% of patients in KF12 reported prior opioid use.

The PBAC noted the perspective of the pain specialist during the sponsor-requested hearing, describing his clinical experience with tapentadol.

8. Results of Trials

With regard to comparative effectiveness, no new efficacy data were presented in the re-submission. In March 2012, the PBAC had accepted the non-inferiority of tapentadol SR to oxycodone CR and tramadol SR in relation to pain efficacy (PSD March 2012).

The outcomes presented in the re-submission focused on the comparative gastrointestinal safety of tapentadol SR and oxycodone CR to support the re-submission's claim of superior safety. The PBAC noted that the clinical data presented were not new but rather a different approach to comparing the adverse events reported in the clinical trials. The key results of the new pooled analysis are summarised in the table below.

Pooled analysis – pairwise comparisons of the incidence of gastrointestinal treatment emergent adverse events (KF11, KF12 and KF23)

Treatment emergent adverse event	Risk difference		NNH (95% CI)
	% (95% CI)	p value	
Oxycodone CR vs tapentadol SR			
All gastrointestinal adverse events	22.8 (18, 27)	<0.001	4.4 (3.7, 5.4)
- constipation	16.0 (12, 20)	<0.001	6.2 (5.1, 8.1)
- vomiting	12.8 (10, 16)	<0.001	7.8 (6.3, 10.2)
- nausea	15.5 (12, 19)	<0.001	6.5 (5.2, 8.7)
- vomiting or nausea	19.3 (15, 23)	<0.001	5.2 (4.3, 6.6)

Abbreviations: CR, controlled release; NNH, number needed to harm; SR, sustained release.

The PBAC noted that oxycodone CR was associated with a statistically significantly higher incidence of adverse events compared to tapentadol SR for all presented gastrointestinal events (constipation, vomiting, nausea, and the composite of vomiting or nausea). The number needed to harm suggested that for every five patients treated with oxycodone CR rather than tapentadol SR, one additional patient will experience gastrointestinal adverse event(s).

The PBAC also noted that while oxycodone CR was associated with a higher incidence of gastrointestinal adverse events compared to tapentadol SR, the severity and duration of the events were not reported, and the magnitude of benefit remained uncertain. Given the proportions of patients in the pivotal trials dissatisfied with opioid analgesia, the magnitude of the reduction in the incidence of gastrointestinal adverse events in patients treated with tapentadol SR may be associated with prior intolerance to opioids.

With regards to the supportive analyses, the incidence of treatment emergent adverse events leading to study discontinuations in the pooled data are summarised in the table below.

Pooled data - incidence of gastrointestinal treatment emergent adverse events leading to study discontinuations (KF11, KF12 and KF23)

	Placebo N=993 n (%)	Tapentadol SR N=981 n (%)	Oxycodone CR N=1001 n (%)
All treatment emergent adverse events	63 (6.3%)	179 (18.3%)	390 (39.0%)
All gastrointestinal adverse events	21 (2.1%)	79 (8.1%)	247 (24.7%)
- constipation	2 (0.2%)	23 (2.3%)	67 (6.7%)
- vomiting	7 (0.7%)	29 (3.0%)	103 (10.3%)
- nausea	8 (0.8%)	34 (3.5%)	144 (14.4%)

Abbreviations: CR, controlled release; SR, sustained release.

The PBAC noted that a higher proportion of patients taking oxycodone CR discontinued due to gastrointestinal adverse events compared to patients taking tapentadol SR. The pre-PBAC response provided additional information.

The PBAC also noted the incidence of gastrointestinal treatment emergent adverse events leading to study discontinuations in the phase 2 Trial KF20 presented in the March 2012 re-submission, reported higher rates of adverse event related discontinuations compared to the pooled data, for tapentadol SR 100-200mg (all gastrointestinal events 13%; nausea 7% and vomiting 6%). The reason for the difference in rate of discontinuations was not explained. However, the proportions of patients in the pivotal trials dissatisfied with opioid analgesia suggested the rate of oxycodone CR discontinuations related to adverse events may be higher than in the eligible Australian population.

The PBAC noted the comment in the Pre-Sub-Committee Response and pre-PBAC response that 99% of patients included in the clinical trials were dissatisfied with prior analgesic (including opioids) due to poor analgesic effect and not due to poor tolerability. The PBAC noted that the criteria for entry into the trial was dissatisfaction with analgesia but did not agree that this necessarily meant that lack of efficacy was the only reason for the dissatisfaction. Some patients may have been dissatisfied because of tolerability issues. The PBAC considered that the trial data was ambiguous and difficult to interpret.

With regard to comparative harms, no new toxicity data were presented in the re-submission. The most recent Periodic Safety Update Reports (PSURs) were reported in the March 2012 re-submission. No new safety risks had been identified since the November 2012 re-submission. However, the re-submission presented data on serotonin syndrome.

The PBAC recalled its concern at its March 2011 meeting, about the risk of serotonin syndrome associated with tapentadol use. The re-submission argued that the risk of serotonin syndrome is theoretical, based on its minimal interaction with the serotonergic system. While PBAC noted the information on 50 people provided in the pre-PBAC response, the committee remained concerned that serotonin syndrome remained a real risk following listing.

The PBAC noted the submission presented a review by the US Food and Drug Administration (FDA) of clinical trials supporting the registration immediate release tapentadol found no evidence that treatment with tapentadol caused serotonin syndrome (FDA – Memorandum: labelling Addendum NDA 22-304. Nov 2008, pages 86-87, Appendix 2). This was consistent with the TGA Clinical Evaluation Report (June 2010) and approved Product Information document.

No adverse events related to serotonin syndrome were reported during the pivotal trials (KF11, KF12 and KF23). However, the use of monoamine oxidase inhibitors (MAOI), serotonin noradrenaline re-uptake inhibitors (SNRI) and tricyclic antidepressants was prohibited immediately prior to and during the trials.

Of 101 cases reported in the Individual Cases Safety Reports up to 15 May 2013, only two cases reported symptoms complying with the Hunter criteria for diagnosis of serotonin syndrome, one of which also reports concurrent treatment with the SNRI venlafaxine.

Overall, the PBAC considered that oxycodone CR and tapentadol SR have different characteristics in terms of side effects and the PBAC was uncertain as to how this will translate in clinical practice.

9. Clinical Claim

The re-submission described tapentadol SR as superior in terms of comparative safety to oxycodone CR. The PBAC considered this claim was not adequately supported:

- Fewer patients taking tapentadol SR may experience gastrointestinal adverse events compared to those taking oxycodone CR, but the severity and duration of the events avoided was not reported, and the magnitude of benefit to patients remains uncertain.
- The uncertainty in the patient-reported constipation symptom measure scores (PAC-SYM) and the small differences in quality of life between patients taking tapentadol SR and oxycodone CR previously noted by the PBAC, suggested that the clinical benefits associated with differences in the incidence of gastrointestinal adverse events between these groups were small.

10. Economic Analysis

The re-submission presented an updated weighted cost minimisation analysis based on the primary and secondary comparators; compared with the November 2012 re-submission. The PBAC noted that the weighted cost minimisation analysis, similar to the previous submission was a more acceptable approach however, the PBAC considered that the weighting of the comparators was dependent on the estimates of likely market uptake from each comparator. Furthermore, the estimates of market uptake presented in the re-submission (and previous submissions) based on Medicare Australia statistics and BEACH encounter data were based on the best data available but that this had low reliability as a basis for weighting. The PBAC agreed that weighting of the comparators used in this re-submission was a conservative assumption relative to these estimates and remained uncertain.

The equi-effective dose ratios were estimated as: tapentadol SR 5.3mg to oxycodone CR 1mg (unchanged from the November 2012 minor re-submission) and tapentadol SR 1mg to tramadol SR 1mg.

The PBAC noted that the current re-submission's equi-effective dose ratio of tapentadol SR versus oxycodone CR was based on the mean doses of each agent in the pooled pivotal trial data at each sample point. The PBAC considered this reasonable.

The PBAC also noted that the equi-effective dose ratio of tapentadol SR versus tramadol SR used in the re-submission was based on a conservative assumption relative to the ratio

calculated using the indirect three step method which the PBAC had previously rejected. However, the PBAC recalled that at its March 2012 meeting, the PBAC accepted that the assumed 1:1 ratio was consistent with the doses compared in the clinical trial used to establish the non-inferiority of tapentadol SR to tramadol SR in terms of efficacy and safety therefore, was considered as reasonable.

Overall, the PBAC considered the approach taken in the re-submission is reasonable and accepted the proposed weighting of oxycodone CR and tramadol SR.

11. Estimated PBS Usage and Financial Implications

The re-submission updated the estimated extent of use and financial implications associated with listing tapentadol SR, using a market share approach consistent with previous submissions. The utilisation model remained structurally similar to previous iterations, but there were changes to underlying data and assumptions informing the model compared with previous submissions.

The re-submission estimated that the likely number of packs dispensed to be greater than 500,000 in Year 5 of listing. The cumulative total over five years was estimated to be greater than 4 million. The re-submission stated that the market growth and market share for tapentadol SR were derived from all sustained release opioids listed on the PBS. Estimates of market size, market share and utilisation were based on Drug Utilisation Sub-Committee (DUSC) utilisation data in the re-submission rather than the extrapolation of DDDs used in previous submissions. The market uptake of tapentadol was estimated at 20% of the oral sustained release opioid market, 5% of the transdermal sustained release opioid market and 10% of the tramadol SR market.

The PBAC considered that the estimated number of tapentadol SR packs dispensed per year was likely underestimated given: (i) the number of patients switching from tramadol SR was likely underestimated and (ii) tapentadol 250mg was assumed to adequately substitute for some sustained release opioids with substantially higher equivalent strengths. The re-submission assumed that the Schedule 8 administrative requirements for the prescribing of tapentadol SR will discourage switching from tramadol SR.

The financial savings to the PBS were estimated in the re-submission to be less than \$10 million in Year 5 of listing. The cumulative net savings over five years was estimated to be between \$10-30 million. The PBAC noted that the estimates of the savings to the PBS were likely overestimated. Furthermore, the estimates of the number of patients switching from the lower priced tramadol SR to tapentadol SR were also likely underestimated, and the number of patients switching from the higher priced oxycodone + naloxone SR to tapentadol SR was likely overestimated. This may result in the cost offsets derived from substitution of these comparators being overestimated. The underlying assumptions the estimates were based on, are poorly supported and favour tapentadol SR.

The PBAC remained concerned with the uncertainties in the estimates presented and agreed that a revised Risk Share Arrangement (RSA) would be needed.

12. Recommendation and Reasons

The PBAC recommended listing of tapentadol SR on the PBS as Restricted benefit for the treatment of chronic severe disabling pain not responding to non-narcotic analgesics, on a

cost-minimisation basis compared with oxycodone CR and tramadol SR. The equi-effective dose are 5.3mg tapentadol SR : 1mg oxycodone CR and 1mg tapentadol SR : 1mg tramadol SR.

The PBAC accepted the submission's claim of comparative effectiveness compared to oxycodone CR and tramadol SR. However, the PBAC considered that oxycodone CR and tapentadol SR have different characteristics in terms of side effects and the PBAC was uncertain as to how this will translate in clinical practice. The PBAC remained concerned about some of the potential for adverse events associated with tapentadol and will seek to work with NPS Medicinewise and other organisations to promote good quality use of medicines.

The PBAC considered the updated weighted cost minimisation analysis approach based on the primary and secondary comparators as reasonable and accepted the proposed weighting of oxycodone CR and tramadol SR.

The PBAC remained concerned that use of tapentadol may vary from that presented and agreed that a revised Risk Share Arrangement (RSA) would be needed.

The PBAC noted and welcomed the input received from health care professionals via the Consumer Comments facility on the PBS website. The PBAC also noted the correspondence received from Pain Australia supporting access to analgesic medications on the PBS.

The Safety Net 20 Day Rule should not apply.

The PBAC considered that tapentadol SR as suitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners

In accordance with subsection 101 3BA of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to its November 2013 meeting, tapentadol SR should not be treated as interchangeable on an individual patient basis with any other drug or medicinal preparation.

Outcome:

Recommended

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
TAPENTADOL				
Tablet 50 mg (as hydrochloride) (sustained release)	28	0	Palexia SR	CS
Tablet 100 mg (as hydrochloride) (sustained release)	28	0	Palexia SR	CS
Tablet 150 mg (as hydrochloride) (sustained release)	28	0	Palexia SR	CS
Tablet 200 mg (as hydrochloride) (sustained release)	28	0	Palexia SR	CS
Tablet 250 mg (as hydrochloride) (sustained release)	28	0	Palexia SR	CS

Episodicity:	Chronic
Severity:	severe
Condition:	disabling pain
Restriction:	Restricted benefit
Clinical criteria:	The condition must be unresponsive to non-narcotic analgesics.
Administrative Advice	<p>Authorities for increased maximum quantities and/or repeats will be granted only for:</p> <p>(i) chronic severe disabling pain associated with proven malignant neoplasia; or</p> <p>(ii) chronic severe disabling pain not responding to non-narcotic analgesics where the total duration of narcotic analgesic treatment is less than 12 months; or</p> <p>(iii) 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 analgesic treatment has been confirmed. The date of the consultation must be no more than 3 months prior to the application for a PBS authority. The full name of the medical practitioner consulted and the date of consultation are to be provided at the time of application; or</p> <p>(iv) subsequent application for treatment of chronic severe disabling pain not responding to non-narcotic analgesics where a PBS authority prescription for treatment beyond 12 months has previously been issued for this patient.</p>
Caution	The risk of drug dependence is high.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

bioCSL welcomes the decision to recommend tapentadol SR for listing. Tapentadol SR offers an important treatment alternative for patients with severe disabling pain.