PUBLIC SUMMARY DOCUMENT
Product: TAPENTADOL, tablet, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg (as hydrochloride) (sustained release), Palexia SR®
Sponsor: CSL Biotherapies
Date of PBAC Consideration: March 2012

1. Purpose of Application

The resubmission sought a Restricted Benefit listing for chronic severe disabling pain not responding to non-narcotic analgesics.

2. Background

This was the second consideration by the PBAC of an application to list tapentadol. At its March 2011 meeting, the PBAC rejected the submission for tapentadol SR because of uncertain clinical benefit and uncertain cost effectiveness.

A copy of the Public Summary Document (PSD) from the March 2011 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-tapentadol-march11

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

Caution
The risk of drug dependence is high.

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

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 did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Chronic, or persistent, pain is pain that continues beyond the usual time of healing (or expected time of recovery). This is often arbitrarily defined as longer than three months. Pain, though not necessarily suffering, is likely to continue without any end in sight.

The resubmission proposed that the place in therapy of tapentadol SR was as a potential alternate analgesic to both the Schedule 8 sustained release opioids for the treatment of chronic severe pain, and tramadol SR.

6. Comparator

The submission nominated oxycodone CR as the main comparator, and added tramadol SR as a secondary comparator in response to the PBAC's request for comparison of tapentadol with tramadol. These comparators were accepted by the PBAC.

7. Clinical Trials

For the comparison with oxycodone CR, the resubmission presented the same three pivotal trials (KF11, KF12, and KF23) from the original March 2011 submission. In response to PBAC's concerns, the resubmission re-analysed the pooled efficacy and safety data by 'prior opioid use' versus 'no prior opioid use' to assess whether a patient's opioid status prior to taking tapentadol was a treatment effect modifier. The submission also presented a randomised Phase II trial (KF20) comparing the efficacy and safety of two titration regimens of tapentadol SR and tramadol SR to placebo in subjects with moderate to severe chronic low back pain. The PBAC noted that no clinical outcome data were presented on cancer related pain even though tapentadol would most likely be used for malignant as well as non-malignant pain relief.

Publication details of KF11, KF12 and KF23 have been previously reported in the March 2011 PSD. The KF20 trial was not published at the time of submission.

8. Results of Trials

TAPENTADOL SR VS. OXYCODONE CR:

The resubmission mainly focused on assessing whether prior opioid status (prior/no prior opioid use) was a treatment modifier in response to the concern of the PBAC about the potential bias introduced by the prior opioid status.

The table below summarises the efficacy results for pain intensity from the pooled analysis of Trials KF11, KF12, and KF23 stratified by prior opioid use.

Pair-wise comparison of the change from baseline in average pain intensity based on NRS (pooled analysis, stratified by prior opioid use)

Prior opioid use	**Yes**		**No**	
Treatment	**Tapentadol**	**Oxycodone**	**Tapentadol**	**Oxycodone**
Pooled dataset, ITT, LOCF				
Change from baseline to overall maintenance -N -least square mean (LSM)	337 -2.57	317 -2.80	638 -2.86	679 -2.43
LSM Difference (95% CI) [a] -P value	-0.23 (-0.59, 0.13) 0.206		0.43 (0.2, 0.67) **<0.001**	
Change from baseline to week 12	337	317	638	679

Prior opioid use	Yes		No	
Treatment	**Tapentadol**	**Oxycodone**	**Tapentadol**	**Oxycodone**
-N -LSM	-2.62	-2.82	-2.93	-2.47
LSM Difference (95% CI) [a] -P value	-0.20 (-0.57, 0.17) 0.283		0.47 (0.21, 0.72) **<0.001**	
Pooled dataset, ITT, no imputation				
Change from baseline to overall maintenance -N -LSM	253 -3.10	206 -3.47	495 -3.32	366 -3.22
LSM Difference (95% CI) [a] -P value	-0.37 (-0.78, 0.04) 0.075		0.10 (-0.18, 0.38) 0.481	
Change from baseline to week 12 -N -LSM	182 -3.65	157 -3.67	392 -3.62	245 -3.64
LSM Difference (95% CI) [a] -P value	-0.02 (-0.52, 0.47) 0.927		-0.02 (-0.38, 0.34) 0.915	

Abbreviations: ITT, intention to treatment; LOCF: last observation carried forward; LSM, least squares mean; NRS: numerical rating scale

a Difference of the change from baseline: Tapentadol SR – Oxycodone CR

For the ITT analyses, using last observation carried forward (LOCF) data, tapentadol was associated with statistically significant larger reductions over oxycodone CR in pain intensity change from baseline in opioid naïve patients compared with no differences in treatment response between tapentadol and oxycodone CR for patients with previous opioid exposure. However, when there was no imputation of missing data, there were no statistically significant differences in pain response for patients with previous opioid exposure and patients who were opioid naïve.

The trial discontinuation rates were high, particularly during the titration period in both the prior opioid and opioid naïve groups. Oxycodone CR treated patients with prior opioid use showed a lower discontinuation rate, but this result was not consistent in tapentadol treated patients. The differences in discontinuations were more marked in opioid naïve patients, where oxycodone CR treated patients had the shortest time to discontinuation of treatment and placebo had the longest.

The PBAC noted that the absolute values of the improvement in EQ-5D scores between tapentadol SR and oxycodone SR were small and were unlikely to be clinically important for both previous opioid and non-opioid users. The March 2011 submission defined 0.074 as the minimal clinically important difference in EQ-5D. In the pooled analysis for all patients, tapentadol SR was associated with statistically significantly larger reductions in EQ-5D scores than oxycodone CR; however, the differences in EQ-5D scores were also small.

The proportion of the patients with adverse events was similar between prior opioid users and no prior opioid patients during the titration period. Gastrointestinal events and nervous system events were more frequent in tapentadol SR and oxycodone CR treated patients without previous opioid use during the titration period. The resubmission provided an additional pooled analysis of the safety data from the pivotal trials in response to PBAC comments about more hyperhidrosis with tapentadol. Similar proportions of patients reported hyperhidrosis in active treatment arms (5.3% tapentadol SR and 6.0% oxycodone CR) across the whole trial period.

The PBAC recalled that it had previously noted that tapentadol caused less frequent nausea and constipation than oxycodone CR. The PBAC noted that the resubmission, as in the previous submission, presented the PAC-SYM, a patient-reported constipation symptom measure, which measured the mean change in constipation symptoms from baseline. The PAC-SYM results for the safety analysis set in trials KF11, KF12 and KF23 showed little difference in the severity of constipation symptoms between treatment with tapentadol or oxycodone CR, although less patients were getting symptoms of constipation in the tapentadol arm of the trials. The PBAC considered the PAC-SYM results were difficult to interpret and therefore there was uncertainty about the magnitude of benefit.

TAPENTADOL SR VS. TRAMADOL SR

For study KF20, reductions in pain intensity were similar between tramadol 200 mg SR and tapentadol 200 mg SR, however the large standard deviations around the estimates of change from baseline indicated a wide variability in patient response. There were similar statistically significant improvements in EQ-5D for tapentadol SR 100mg, tapentadol SR 200mg, and tramadol SR compared to placebo and no differences between tapentadol SR and tramadol SR in change from baseline in EQ-5D scores. The large SDs around the estimates of change from baseline indicates wide variability in patient response.

Tapentadol SR 200 mg treated patients showed statistically significantly larger changes in the SF-36 domain of "bodily pain" from Visit 2 than placebo treated patients. There was no significant difference between tramadol SR and placebo. The PBAC considered that the results of the quality of life assessments (EQ-5D and SF-36), for prior opioid and opioid naïve patients, in the oxycodone CR and in the tramadol SR analyses, were unlikely to be clinically important, and there was no evidence to suggest that any small difference would translate to an increase in quality of life.

9. Clinical Claim

The resubmission described tapentadol SR as equivalent in terms of comparative effectiveness and superior in terms of comparative safety (related to constipation and nausea/vomiting) to oxycodone CR.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

For the tapentadol SR versus oxycodone CR comparison, the resubmission presented a revised cost-utility analysis, based on the clinical claim of superior safety in terms of constipation. The revised model had a time horizon of 15 weeks (vs. 52 weeks in the previous submission); the key difference between treatment arms was the risk of constipation (vs. discontinuations in the previous submission); and it was assumed that there were no discontinuations from treatment. The disutility of opioid-induced constipation was the main health outcome.

The base case incremental cost per QALY gained was less than $15,000.

With respect to the tapentadol SR and tramadol SR comparison, the resubmission presented a cost-minimisation analysis, based on an indirect three-step analysis of equi-effective doses. The equi-effective dose ratio estimation versus tramadol SR was 0.71:1.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated in the re-submission to be greater than 1 million in Year 5, at a net cost to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recalled that oxycodone CR was accepted as the main comparator from the previous submission. The PBAC considered that tramadol SR, nominated as a secondary comparator based on the PBAC's previous consideration that clinicians would also be likely to substitute tapentadol for tramadol SR, was also appropriate.

The PBAC noted that, for the comparison with oxycodone CR, the resubmission presented the same three pivotal trials (KF11, KF12, KF23) from the original March 2011 submission. In response to PBAC's concerns, the resubmission re-analysed the pooled efficacy and safety data by 'prior opioid use' versus 'no prior opioid use' to assess whether a patient's opioid status prior to taking tapentadol was a treatment effect modifier. The submission also presented a randomised Phase II trial (KF20) comparing the efficacy and safety of two titration regimens of tapentadol SR and tramadol SR to placebo in subjects with moderate to severe chronic low back pain. The PBAC noted that no clinical outcome data were presented on cancer related pain even though tapentadol would most likely be used for malignant as well as non-malignant pain relief.

The PBAC noted that the re-analysis of the efficacy data for Trials KF11, KF12 and KF23 showed that imputation of missing data affected the differences in treatment effect. For the ITT analyses, using last observation carried forward (LOCF) data, tapentadol was associated with statistically significant larger reductions over oxycodone CR in pain intensity change from baseline in opioid naïve patients compared with no differences in treatment response between tapentadol and oxycodone CR for patients with previous opioid exposure. However, the PBAC noted that when there was no imputation of missing data, there were no statistically significant differences in pain response for patients with previous opioid exposure and patients who were opioid naïve. The PBAC recalled that it had previously accepted non-inferiority of tapentadol SR compared to oxycodone CR in relation to efficacy in pain intensity.

The PBAC noted that, similar to the previous submission, the trial discontinuation rates were high, particularly during the titration period in both the prior opioid and opioid naïve groups. Oxycodone CR treated patients with prior opioid use showed a lower discontinuation rate, but this result was not consistent in tapentadol treated patients. The PBAC also noted that differences in discontinuations were more marked in opioid naïve patients, where oxycodone CR treated patients had the shortest time to discontinuation of treatment and placebo had the longest.

With respect to the efficacy of tapentadol versus tramadol (Study KF20), the PBAC noted that reductions in pain intensity were similar between tramadol 200 mg SR and tapentadol 200 mg SR, however the large standard deviations around the estimates of change from baseline indicated a wide variability in patient response.

The PBAC considered the submission's claim of a superior comparative safety (related to constipation and nausea/vomiting) for tapentadol compared with oxycodone CR. The PBAC recalled that it had previously noted that tapentadol caused less frequent nausea and constipation than oxycodone CR. The PBAC noted that the resubmission, as in the previous submission, presented the PAC-SYM, a patient-reported constipation symptom measure, which measured the mean change in constipation symptoms from baseline. The PAC-SYM results for the safety analysis set in trials KF11, KF12 and KF23 showed little difference in the severity of constipation symptoms between treatment with tapentadol or oxycodone CR, although less patients were getting symptoms of constipation in the tapentadol arm of the trials. The PBAC considered the PAC-SYM results were difficult to interpret and therefore there was uncertainty about the magnitude of benefit. The claim of superior comparative safety was therefore not accepted.

The PBAC further considered that the results of the quality of life assessments (EQ-5D and SF-36), for prior opioid and opioid naïve patients, in the oxycodone CR and tramadol SR analyses, were unlikely to be clinically important, and there was no evidence to suggest that any small difference would translate to an increase in quality of life.

Overall, the PBAC accepted the resubmission's clinical claim with respect to comparative effectiveness compared with oxycodone CR, however it did not accept the claim of superior safety. The claim of non-inferiority in terms of comparative effectiveness and safety compared with tramadol SR was accepted.

The resubmission presented a revised cost-utility analysis based on the claim of superior safety in terms of constipation for tapentadol compared with oxycodone CR. The PBAC agreed with the ESC that the model was over simplified and did not capture what would occur in clinical practice as the model assumed average rates of constipation and that all patients remained on treatment for 15 weeks. The PBAC noted that this did not reflect the high discontinuation rates shown in the clinical trials, and may not fully capture the outcomes and costs associated with treatment of chronic pain.

The economic evaluation transformed the outcome in terms of the proportion of patients with nausea and vomiting to a QALY, based on the disutility associated with constipation. The PBAC noted that the disutility of opioid-induced constipation was not based on the trial EQ-5D results but derived from the literature (Penning-van Beest et al 2010), with PAC-SYM score adjustment. The PBAC was concerned that this would allow small differences in PAC-SYM scores to have a greater impact than may be reasonably expected, particularly as the EQ-5D was a multi-dimensional QOL instrument whereas the PAC-SYM focused on only one dimension and therefore questioned whether this method was appropriate.

The PBAC considered that while the overall base case ICER was low (less than $15,000 per QALY gained), it was difficult to interpret because of the concern about the method used to estimate nausea and constipation rates in with the model as well as the transformation to utilities. The PBAC noted that the model was sensitive to disutilities for constipation, rates of constipation and inclusion of discontinuers. The PBAC noted that a multi-variate sensitivity analysis in the resubmission resulted in an ICER of between $15,000 and $45,000/QALY.

With respect to the tapentadol and tramadol SR comparison, the resubmission presented a cost-minimisation analysis, based on an indirect three-step analysis of equi-effective doses. The PBAC agreed with the ESC that there was considerable uncertainty associated with the equi-effective dose ratio estimation versus tramadol SR of 0.71:1, as it was based on dose relativities for three different pairs of drugs, each from different sources with adjustment by rounding and available dose matching.

The PBAC noted that the resubmission provided a GP survey to address its previous concerns regarding the estimated uptake of tapentadol SR. The PBAC considered that the GP survey results were highly subjective as the survey relied on the GP recalling previous prescribing practice rather than being an audit of actual clinical practice.

The PBAC considered that the resubmission's justification for its requested price of tapentadol was inherently uncertain as it was derived from several variables which the Committee considered were also uncertain i.e. the cost-effective price of tapentadol vs. oxycodone CR and the cost-minimised price of tapentadol vs. tramadol SR, weighted by an expected 85% substitution for Schedule 8 opioids and 15% substitution for tramadol SR based on the GP survey. The PBAC considered that the survey provided a very limited evidence base on which to calculate the weighted average price.

The PBAC therefore rejected the resubmission because of uncertain clinical benefit, uncertain cost-effectiveness and hence uncertain basis for justifying the requested price.

In making this recommendation, the PBAC noted the consumer comments on this item.

Recommendation:
Reject

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

CSL disagrees with the PBAC's decision, but is committed to working with the PBAC to ensure tapentadol SR is available for patients with chronic severe disabling pain not responding to non-narcotic analgesics.