

5.11 MORPHINE

**Capsule containing morphine sulfate pentahydrate
10 mg (modified release),**

**Capsule containing morphine sulfate pentahydrate
20 mg (modified release),**

Kapanol[®], Mayne Pharma International Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested an extension to the listing of two strengths of morphine (as morphine sulfate) for the treatment of chronic breathlessness for patients receiving palliative care.

2 Requested listing

- 2.1 The submission requested a restricted benefit listing for chronic breathlessness on the Palliative Care schedule of the PBS. The submission proposed a restriction that is consistent with the TGA registration and product information. The restriction presented below replaces the version included in the submission, and has been proposed by the Secretariat to align more closely with the general restrictions for opioids available on the Palliative Care schedule.

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
MORPHINE					
Capsule containing morphine sulfate pentahydrate 10 mg (modified release), 28	1	0	\$23.88	Kapanol	Mayne Pharma International Pty Ltd
Capsule containing morphine sulfate pentahydrate 20 mg (modified release), 28	1	0	\$28.21		

Category / Program	GENERAL – General Schedule Palliative Care (Code PL)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity:	Chronic
Condition:	Breathlessness
PBS Indication:	Chronic breathlessness
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit
Clinical criteria:	Patient must be receiving palliative care

Administrative Advice	<p>Treatment should be initiated by a specialist knowledgeable in the use of potent opioids for the management of chronic breathlessness.</p> <p>Applications for an increased maximum quantity to provide for 1 month's supply of this drug will be authorised.</p> <p>Where consultation with a palliative care specialist or service has occurred, applications for increased repeats for up to 3 months' supply may be authorised.</p> <p>Shared Care Model:</p> <p>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>
Cautions	<p>The risk of drug dependence is high.</p> <p>Morphine sulfate pentahydrate 10 and 20 mg modified release capsules must not be co-prescribed with immediate release oral morphine, when it has been prescribed for the reduction of chronic breathlessness.</p>

- 2.2 Morphine (as morphine sulfate pentahydrate) immediate release tablets (Sevredol®) quantity 20 with 2 repeats are available on the Palliative Care schedule of the PBS (via Telephone Authority) for pain management. Oral modified released formulations of morphine sulfate pentahydrate are available as restricted benefit with no repeats on the general schedule.

3 Background

- 3.1 Morphine modified release capsules (Kapanol®) are registered with the TGA for the following indications:
- (i) relief of chronic pain unresponsive to non-narcotic analgesia;
 - (ii) symptomatic reduction of chronic breathlessness for patients in palliative care with distressing breathlessness due to severe chronic obstructive pulmonary disease (COPD), cardiac failure, malignancy or other cause.
- 3.2 The PBAC has not previously considered morphine for chronic breathlessness.
- For more detail on PBAC's view, see section 6 PBAC outcome.*

4 Population and disease

- 4.1 Breathlessness (dyspnoea) is a common and disabling symptom that affects many people with advanced cardiorespiratory disease, such as severe chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, renal

disease and cancer. Symptomatic treatment is often required in addition to treating the underlying disease¹.

- 4.2 There are many different reasons for breathlessness being associated with advanced chronic conditions and cancer. Irrespective of the cause, breathlessness is a disabling and distressing condition for patients at the end stages of their illness and for their carers. Patients and carers report the symptoms are as concerning as delirium, nausea and pain².
- 4.3 The prevalence of chronic breathlessness was reported to be high when patients are in advanced stages of disease or in terminal disease. The condition intensifies as the underlying disease progresses and its prevalence increases from 50 to 65% during the last months of life^{3,4}.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Clinical evidence

The minor submission outlined the clinical evidence considered by the TGA.

¹ Barnes H et al Cochrane Database of Systematic Reviews 2016 2016 Issue 3 Art CD011008

² Neuman A et al Respiratory Medicine 2006;100(10):1843-9

³ Higginson, I.J., et al, An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med, 2014. 2(12): p. 979-87.

⁴ Currow, D.C., A.P. Abernethy, and D.N. Ko, The active identification and management of chronic refractory breathlessness is a human right. Thorax, 2014. 69(4): p. 393-4

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol/publication	Citation
MOP Study (Pivotal study)	Phase III, multi-site randomised double-blind parallel arm fixed dose controlled trial of 286 subjects comparing safety and efficacy of modified release morphine 20 mg daily to placebo to relieve symptoms of dyspnoea, improve function, quality of life in adults with breathlessness of 2 or higher on modified Medical Research Council Dyspnoea Scale	Clinical Study Report unpublished
Cochrane Review 2016	Meta-analysis of randomised controlled double-blind trials comparing the use of any opioid drug to placebo or any other intervention for relief of breathlessness (primary outcome). Pre-specified subgroup analyses planned: route of administration, dose, type of opioid and cause of breathlessness.	Barnes H et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. <i>Cochrane Database of Systematic Reviews</i> 2016, Issue 3. Art No CD011008
Ekström M et al Research letter(supporting) Thoraxjnl-2016-209868.R1	Meta-analysis of published studies to evaluate efficacy of systemic opioids for chronic breathlessness. Review of reasons for conflicting finding from earlier studies.	Ekstrom et al One evidence base; three stories: do opioids relieve chronic breathlessness? Thorax (in press)

5.3 As this was a minor submission, no evaluation of the clinical data was undertaken. The following describes the studies and presents relevant results.

MOP Study

5.4 The Palliative Care Clinical Studies Collaborative (PaCCSC) in 15 Australian sites conducted the MOP study. The primary objective of the study was to compare the efficacy of sustained release morphine compared to placebo for relieving the sensation of dyspnoea, level of function, safety and quality of life. The study randomised 286 patients, with 141 assigned to morphine and 141 to placebo. Patients with level 2 or higher modified Medical Research Council Dyspnoea Scale (mMRC) score in spite of optimal treatment of the underlying cause of this dyspnoea were enrolled. Patients received either 20 mg morphine (Kapanol brand) capsule plus laxative tablets or placebo capsule and placebo tablets for 7 days. Scores to record a number of measures of breathlessness were recorded morning and night at baseline and on days 5-7. Primary analysis was a t-score comparing the within subject change between groups measured as the average of morning and evening scores for days 5-7 minus baseline.

5.5 Efficacy results for all patients showed no statistically significant difference in primary endpoint of breathlessness (VAS Now Intensity Breathlessness) between baseline and days 5-7 between groups. Another measure of breathlessness (VAS Worst Intensity Breathlessness) showed a trend toward statistical significance (Least Squares mean difference morphine minus placebo = -4.88, 95%CI -10.73, 0.98, p=0.105). The placebo group received significantly more rescue medication and this may have masked the effect of morphine in reducing the symptoms of breathlessness.

- 5.6 The subgroup of mMRC >3 or 4 and patients with COPD experienced statistically greater improvement.
- 5.7 Safety was assessed in the MOP study. The safety results were similar in the morphine and placebo groups in terms of duration of survival, pulse oximetry and general adverse events. The morphine group experienced statistically significantly more severe constipation and vomiting than the placebo group.

Cochrane Review

- 5.8 The Cochrane Review aimed to determine the difference in effectiveness of opioid drugs in relieving the symptoms of breathlessness in patients with advanced disease. The primary outcome was subjective measures of breathlessness and any randomised controlled trial for any opioid or mode of administration was accepted. Eighteen studies, 276 participants, provided data for the primary outcome and were included in a meta-analysis. The meta-analysis (fixed-treatment effects) demonstrated a small treatment effect for breathlessness. In the 7 studies reporting change from baseline, the outcome was calculated by the Cochrane authors as standard mean difference (SMD = -0.09, 95% CI -0.36, 0.19, p=0.54) favouring opiates. The authors acknowledged difficulty in combining scores from different studies and that this contributed to error in the analysis. The heterogeneity was high, $I^2=75\%$. The quality of evidence was considered low (Cochrane risk of bias assessment tool). The studies had very small sample sizes, variable durations of therapy and different types of opiate product. Information was difficult to extract for the risk of bias assessment for many studies.
- 5.9 Pre-specified subgroup analyses were undertaken for type of opioid, condition, mode of administration, dose and comparisons with other interventions. Results relevant to the submission to list morphine on the PBS are listed below:
- Morphine showed a stronger treatment effect than other opioids: 5 studies, 77 participants, SMD = -0.18, 95% CI -0.51, 0.15, p=0.28). $I^2=81\%$.
 - The opioid dose in most studies was equivalent to 20 – 30 mg of morphine.
 - There was insufficient data to show whether opioids were more beneficial in any specific condition (COPD, heart failure, cancer-related breathlessness, interstitial lung disease).
- 5.10 The Cochrane Review concluded there is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in adults with advanced disease and terminal illness. There appeared to be a small treatment effect but the meta-analysis was constrained by difficulty in pooling the treatment effect owing to the variety of measurement scores for breathlessness.

Ekström M et al

- 5.11 Ekström et. al. (2016) re-analysed the meta-analysis from the Cochrane Review using a random effects model and accounting for matched data of crossover trials in eleven studies. In the pooled analysis of systemic opioids compared to placebo for the

outcome of reduction of breathlessness in twelve studies, systemic opioids reduced breathlessness demonstrating a SMD= -0.32 (95% CI, 0.18, 0.47; p<0.001) I² = 44.8%. The authors argued this was a clinically meaningful reduction of 0.8 points on a 0-10 numerical rating scale. The authors also argued that the small sample size of the studies had too large an effect on determining the risk of bias without sound methodological justification, and that the quality of evidence for a meta-analysis of these studies should be classified as moderate.

Comparative harms

- 5.12 In terms of clinical safety, a systematic review and meta-analysis of the clinical studies of opioids for breathlessness found no evidence of clinically relevant respiratory adverse effects including changes in blood gases or respiratory depression⁵.

Economic analysis

- 5.13 As a minor submission, there was no economic comparison presented.
- 5.14 The sponsor proposed an ex-manufacturer price (AEMP) of \$8.82 for a 28 pack of 10 mg capsules, and \$12.84 for a 28 pack of 20 mg capsules. The PBAC noted this is unchanged from the AEMP currently applicable to Kapanol 10 mg and 20 mg capsules listed on the PBS for chronic pain.

Drug cost/patient: \$ [REDACTED].

- 5.15 The drug cost per patient per course was \$ [REDACTED] (20 mg daily for 6 months). Average duration of treatment for a responding patient is 6 months.

Estimated PBS usage & financial implications

- 5.16 The sponsor estimated a net cost to the PBS of less than \$10 million in Year 6 of listing with a total net cost to the PBS/RPBS of less than \$10 million over the first 6 years in listing. This is summarised in the table below. This was based on the assumption that the additional indication would result in a 15% increase in prescriptions in the first year with no further market growth during subsequent years.
- 5.17 The submission stated that assumption was based on discussions with 'key opinion leaders' in Australia about the use of morphine sulfate in the palliative care setting, but did not provide any further justification.

⁵ Verberkt CA, et al., Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. Eur Respir J. 2017 Nov 22;50(5). Cited in the TGA letter of approval. Not provided in the submission.

Table 2: PBS use and financial implications estimated by the sponsor

	2019	2020	2021	2022	2023	2024
Prescriptions Kapanol 10 mg	██████	██████	██████	██████	██████	██████
Prescriptions Kapanol 20 mg	██████	██████	██████	██████	██████	██████
PBS costs						
Total cost to PBS	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Co-payments	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Net cost to PBS	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
RPBS costs						
Total cost to RPBS	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Co-payments	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Net cost to RPBS	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████
Total cost to Government						
Total cost to Government	\$██████	\$██████	\$██████	\$██████	\$██████	\$██████

The redacted table shows that at Year 6, the estimated number of prescriptions was 50,000 to 100,000 and the net cost to the PBS/RPBS would be less than \$10 million.

5.18 The Department prepared an alternative set of estimates using an epidemiological approach, presented in Table 3. The following assumptions were included:

- 0.3% of the population has severe symptoms of chronic breathlessness (Currow D et al JPSM 2009;38(4):533-544 Study of chronic breathlessness in the South Australian Community using the SA Omnibus Survey);
- 25% of patients are suitable for treatment with opioids (Currow D et al JPPM 2011;42(3):388-99 RCT of once daily opioids in sample of 83 outpatients in palliative care with severe breathlessness);
- 46% of the suitable patients respond to opioid treatment and continue therapy (Currow D et al JPPM 2011;42(3):388-99)
- The average time on therapy in palliative care is estimated to be 6 months based on expert opinion.

5.19 The estimates of use are the maximum expected use for this indication but do not represent the likely additional cost to government expenditure. It was noted that a substantial proportion of palliative care patients with symptoms of breathlessness are already treated with oral morphine. There was a lack of data to adequately inform an estimate of the number of patients who are already treated.

5.20 Use of opioids for this condition is unlikely to have an impact on overall use of morphine for pain. Sustained release morphine for breathlessness is used at low doses, and use in palliative care will be limited as patients with severe pain, who require oral morphine solution for breakthrough episodes of pain, are contraindicated for low dose Kapanol for breathlessness (Product Information).

Table 3: PBS use and financial implications estimated by the Department

	2020	2021	2022	2023	2024	2025
Eligible patients	█	█	█	█	█	█
Treated patients	█	█	█	█	█	█
Prescriptions 10 mg Kapanol	█	█	█	█	█	█
Prescriptions 20 mg Kapanol	█	█	█	█	█	█
Total cost	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Co-payments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

5.21 The submission estimated a cumulative net cost to the PBS of less than \$10 million over the first 5 years of listing.

5.22 The revised estimates estimate a maximum cumulative net cost to the PBS of less than \$10 million, noting this is unlikely to be realised owing to displacement of a large but unknown quantity of current prescription volume for this condition.

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended extending the PBS-listing of morphine modified release capsules (Kapanol) to include the treatment of chronic breathlessness for patients receiving palliative care, as a restricted benefit listing on the Palliative Care Schedule. The PBAC was satisfied that morphine provides, for some patients, an improvement in efficacy over conventional care, particularly in patients with severe symptoms.

6.2 The PBAC considered that the proposed restriction was appropriate, and that both specialist palliative medicine physicians and general practitioners trained and experienced in treating palliative care patients would be appropriate to prescribe morphine for breathlessness. The PBAC noted that the TGA recently registered Kapanol for chronic breathlessness and that the proposed listing on the Palliative Care schedule is consistent with approved indication.

6.3 The PBAC considered the advice provided from the Palliative Care Clinical Studies Collaborative (PaCCSC) about Australian use of morphine for breathlessness in palliative care patients, noting that PaCCSC was in full support of this submission.

6.4 The PBAC considered there was a clinical need for treatment in patients requiring symptomatic relief from chronic breathlessness and that recent experience of using morphine in clinical practice in Australia for managing this condition had been informative to PBAC’s decision.

6.5 The PBAC considered there was considerable uncertainty in relation to the evidence provided in the submission, in particular as to whether the magnitude of treatment effect as measured in the studies would translate to clinically significant improvements in symptoms. However, noting expert clinician support for the listing, on balance the PBAC considered that listing would be appropriate if limited to patients

- in a palliative care setting as requested in the submission.
- 6.6 The PBAC noted that Kapanol is already listed on the PBS as a restricted benefit on the General Schedule for chronic pain and that the submission has requested the same price for chronic breathlessness. The PBAC considered that this was an appropriate pricing approach for the extended indication.
- 6.7 The PBAC noted the uncertainties around the submission’s estimates of utilisation and financial implication due to the lack of justification provided for the estimated 15% increase in use. The PBAC considered the Department’s revised estimates reflected the upper limit of the likely financial impact to the PBS as the revised estimates did not take into account the likely large but unknown existing use of currently listed morphine for breathlessness.
- 6.8 The PBAC advised that morphine is suitable for prescribing by nurse practitioners under shared care arrangements.
- 6.9 The PBAC noted that the Early Supply Rule is not currently applicable to morphine on the palliative care schedule and recommended no changes.
- 6.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Proprietary Name and Manufacturer	
MORPHINE				
Capsule containing morphine sulfate pentahydrate 10 mg (modified release), 28	1	0	Kapanol®	Mayne Pharma International Pty Ltd
Capsule containing morphine sulfate pentahydrate 20 mg (modified release), 28	1	0		

Category / Program	GENERAL – General Schedule Palliative Care (Code PL)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity:	Chronic
Condition:	Breathlessness
PBS Indication:	Chronic breathlessness

Restriction Method:	<input checked="" type="checkbox"/> Restricted benefit
Clinical criteria:	Patient must be receiving palliative care
Administrative Advice	<p>Treatment should be initiated by a specialist knowledgeable in the use of potent opioids for the management of chronic breathlessness.</p> <p>Applications for an increased maximum quantity to provide for 1 month's supply of this drug will be authorised.</p> <p>Where consultation with a palliative care specialist or service has occurred, applications for increased repeats for up to 3 months' supply may be authorised.</p> <p>Shared Care Model:</p> <p>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>
Cautions	<p>The risk of drug dependence is high.</p> <p>Morphine sulfate pentahydrate 10 and 20 mg modified release capsules must not be co-prescribed with immediate release oral morphine, when it has been prescribed for the reduction of chronic breathlessness.</p>

8 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.

9 Sponsor's Comment

The sponsor had no comment.