



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Morphine sulphate pentahydrate

Proprietary Product Name: Kapanol

Sponsor: MaynePharma International Pty Ltd

March 2019

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
6MWT	6 minute walk test
95% CI	95% confidence interval
AE	Adverse event
AKPS	Australia–modified Karnofsky Performance Status
ANCOVA	Analysis of covariance
bpm	Breaths per minute
CQOLC	Carer Quality of Life Index (Cancer)
COPD	Chronic obstructive pulmonary disease
CER	Clinical evaluation report
CRF	Case Report Form(s)
CSR	Clinical Study Report
ECOG (PS)	European Cooperative Oncology Group (Performance Status)
EORTC-QLQ- C15	European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire(core)
ER	Extended release
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HIC	Health insurance commission
ICH GCP	International Conference on Harmonisation, Good Clinical Practice
mg	Milligram
mMRC	modified Medical Research Council breathlessness scale
MR	Modified release
N/A	Not applicable
NR	Not reported

Abbreviation	Meaning
NRS	Numerical rating scale
OR	Odds ratio
O ₂	Oxygen
PaCCSC	(Australian National) Palliative Care Clinical Studies Collaborative
PBS	Pharmaceutical Benefits Scheme
PS	Performance status
QID	Four times daily
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SR	Sustained release
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
VAS	Visual analogue scale

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Initial decision:</i>	Rejected
<i>Final decision</i>	Approved
<i>Date of initial decision:</i>	27 June 2018
<i>Date of final decision:</i>	7 November 2018
<i>Date of entry onto ARTG:</i>	N/A
<i>ARTG number:</i>	68439 and 48134
<i>, Black Triangle Scheme</i>	No
<i>Active ingredient:</i>	Morphine sulfate pentahydrate
<i>Product name:</i>	Kapanol
<i>Sponsor's name and address:</i>	MaynePharma International Pty Ltd 1538 Main North Rd Salisbury South, SA 5106
<i>Dose form:</i>	Sustained release capsules
<i>Strengths:</i>	10 mg and 20 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	20, 28 and 60 capsules
<i>Approved therapeutic use:</i>	<i>For the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	10mg once daily orally titrated up to a maximum of 30mg daily

Product background

This AusPAR describes the application by the sponsor to extend the indication for Kapanol morphine sulfate pentahydrate 10 mg (ARTG no. 68439) and 20 mg (ARTG no. 48134) capsules for

the symptomatic reduction of chronic breathlessness in patients with a modified Medical Research Council (mMRC) Scale rating of 3 or 4 and in which the approved treatments for the underlying cause(s) of the breathlessness are not effective.

The proposed indications were modified during the TGA's evaluation of the submission to:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatments are not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

Kapanol 10 mg, 20 mg, 50 mg and 100 mg capsules are currently indicated for the relief of chronic pain unresponsive to non-narcotic analgesia. For symptom reduction of chronic pain the dosage regimen states:

The usual starting dose in opioid naïve patients is Kapanol capsules 40 mg every 24 h or 20 mg every 12 h. No maximum dose specified. Treatment initiated only after short acting opiate is shown to be effective.

The proposed dosing regimen for the new indication of breathlessness is a starting dose of 10 mg/day (opioid naïve patients). The daily dose may be increased by 10 mg if a satisfactory clinical response has not been achieved after seven days. Dosing should be evaluated within seven days of any dose increase. Dosing can be once or twice daily but the maximum evaluated daily dose is 30 mg/day.

Kapanol is a long acting formulation of morphine. Morphine has been scheduled as S8 (controlled drug) by the TGA. It is an opium alkaloid that interacts with the opioid receptors (subtypes μ , δ and κ), predominantly in the central nervous system (CNS) and gastrointestinal tract. Agonist activity at the μ receptor in the CNS results in the main actions that are of therapeutic value; analgesia and sedation.

Morphine produces a range of pharmacological effects including analgesia, suppression of the cough reflex, and respiratory depression due to a reduction in the responsiveness of the respiratory centre to carbon dioxide, and nausea and emesis through direct stimulation of the chemoreceptor trigger-zone (CTZ). Mood changes due to morphine include euphoria and dysphoria, sedation, mental clouding due to alterations in autonomic nervous systems, and a decrease in gastrointestinal motility leading to constipation.

Dyspnoea (breathlessness) is defined by the American Thoracic Society as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'.¹ Breathlessness leads to significant distress, impaired physical and mental functioning, reduced quality of life and behavioural change. Up to 98% of patients with advanced chronic obstructive pulmonary disease (COPD) experience increasing breathlessness at rest or on minimal exertion. When breathlessness persists at rest or on minimal exertion, despite optimal treatment of the underlying causes, it is termed 'chronic breathlessness'.²

The exact mechanism of action of morphine in the relief of perception of breathlessness is poorly understood.³ The effects of opioids such as reducing ventilator response to CO₂, hypoxia, inspiratory flow-resistive loading and exercise may aid to reduce the perception of breathlessness.⁴ The therapeutic effect of morphine on anxiety is well recognised.⁵

¹ Parshall, M.B., et al., An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*, 2012. 185: 435-452

² Johnson MJ, et al Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Resp J* 2017; 49. 1602277

³ Laviolette, L. and P. Laveneziana, Morphine to relieve exertional dyspnoea in COPD: myth, dream or reality? *Eur Respir J*, 2017; 50

⁴ Gracely, R.H., et al Cough, pain and dyspnoea: similarities and differences. *Pulm Pharmacol Ther*, 2007. 20: 433-437

⁵ Wang, J., et al, Morphine administration induces change in anxiety-related behavior via Wnt/beta-catenin signaling. *Neurosci Lett*, 2017; 639: 199-206

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.⁶ There is an increasing awareness of the importance of the management around symptoms at the end of life to reduce suffering. There are no other medicines on the Australian Register of Therapeutic Goods (ARTG) for the management of chronic breathlessness. It is likely that opiates are frequently used off label for this indication, particularly where pain is also an important issue. The use of opiates for the management of chronic breathlessness in a palliative care setting is included in a number of clinical guidelines as outlined in Table 1 below.

Table 1: Guidance documents for the use of opiate for the management of breathlessness in palliative care

Reference guideline	Drug	Dosage and administration
eTG Therapeutic guideline*	Morphine	<p>Opioid naïve patients</p> <p><i>Intermittent dyspnoea</i></p> <p>morphine immediate release 1-2.5 mg orally repeated as required q 1 hourly</p> <p>or 0.5-1 mg s/c repeated as required q 1 hourly</p> <p><i>Continuous dyspnoea</i></p> <p>morphine immediate release 1-2.5 mg orally and 1-2.5 mg 1 hourly as required</p> <p>or 0.5-1 mg s/c q 4 hourly and 0.5-1 mg repeated as required 1 hourly</p> <p>morphine modified-release 5 to 10 mg orally, twice daily</p> <p>PLUS morphine immediate-release 1 to 2.5 mg orally, 1-hourly as required.</p>
COPD-X 2017 Guidelines**	Morphine	Regular low dose oral morphine may be considered for treating breathlessness in patients with severe COPD that persists despite optimal medical management.
Palliative care guidelines New Zealand 2017***	Morphine	<p>Oral/parenteral – oral seems to be more effective than subcutaneous</p> <p>Doses are usually small 2.5 to 10 mg prn</p>

*eTG Therapeutic guidelines- pharmacological treatment of dyspnoea in palliative care.

<https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Palliative%20Care&topicfile=palliative-care-respiratory-symptoms&guidelineName=Palliative%20Care§ionId=toc_d1e71#toc_d1e111>.

⁶ WHO definition of Palliative Care. <<http://www.who.int/cancer/palliative/definition/en/>>

**COPD-X 2017 plan. <<https://copdx.org.au/copd-x-plan/o-optimize-function/o10-palliation-and-end-of-life-issues/o101-opioids/>>.

***The Australian & New Zealand Society of Palliative Medicine Inc.
<<http://www.anzspm.org.au/c/anzspm>>.

This application is a joint submission from the sponsor and the Australian national Palliative Care Clinical Studies Collaborative⁷. The sponsor had several pre-submission meetings with TGA.⁸ Key points from minutes of pre-submission meeting are as follows:

- The sponsor had emphasised that the proposed treatment will only be focussed for patients with breathlessness severity of mMRC Scale 3 or 4 (Figure 1) and in which the approved treatments for the underlying causes of the breathlessness are not effective in relieving the symptom of breathlessness.
- So far, Thoracic Society of Australia does not have a position statement on the use of morphine for breathlessness for palliative care. It was mentioned that USA and Canada have position statements indicating use of regular, low dose morphine for palliative care.

The supporting data for the proposed change include a review of literature and a pivotal controlled clinical trial to assess whether there is a net clinical benefit from regular low doses of Kapanol in patients with chronic breathlessness provided in the clinical dossier. Nonclinical or quality data were not required for this application.

Figure 1: Medical Research Council breathlessness scale (mMRC)

Grade	Description
0	Is not troubled with breathlessness except with strenuous exercise
1	Is troubled by shortness of breath when hurrying on level ground or walking up a slight hill
2	Walks slower than people of the same age on level ground because of breathlessness, or has to stop for breath when walking at own pace on level ground
3	Stops for breath after walking about 100 meters or after a few minutes on level ground
4	Is too breathless to leave the house or is breathless when dressing or undressing

²⁰Fletcher CM, et al. *Lancet*. 1959;1:257-266.

From Doherty DE et al COPD: Consensus recommendations for early diagnosis and treatment. J Family Practice Nov 2006.

Regulatory status

The product received initial registration on the ARTG on 21 July 1994.

At the time the TGA considered this application, no similar application had been submitted to any other jurisdiction.

⁷ The Palliative Care Clinical Studies Collaborative (PaCCSC) is a national research network that aims to:

- Generate high quality research evidence to support the use of medicines and other interventions at the end of life to better manage or alleviate symptoms in patients such as: pain; confusion; breathlessness; appetite; and gastrointestinal problems including nausea; bowel obstruction; and constipation.
- Build capacity within the health workforce in the conduct of high quality clinical research in patients nearing the end of life and the translation of research results into clinical practice

The chief investigator is an international expert in palliative care but also has a number of potential conflicts of interest including being a consultant and receiving inventor payment from Mayne Pharma.

⁸ TGA guidance at pre-submission meetings is nonbinding and without prejudice.

According to the sponsor's website, the sponsor's product is currently available under the trade names of 'Kapanol' (Australia and Thailand) and 'Kadian' (Canada and Japan).

The approved indication in North America is limited to severe pain:

- Health Canada⁹:

Kadian (morphine sulfate) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- *that is opioid-responsive; and*
- *for which alternative options are inadequate*

- United States Food and Drug Administration (FDA)¹⁰:

Kadian is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- *Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations [see Warnings and Precautions (5.1)], reserve Kadian for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.*
- *Kadian is not indicated as an as-needed (prn) analgesic*

The prescription opioid crisis

Major reviews of the regulation of opioids have been conducted by the USA and Canadian governments in 2016 and 2017 in response to an 'epidemic' of deaths due to prescription opioids.^{11,12} Methods to address the epidemic proposed by the FDA include: re-wording of the boxed warning to highlight the risk of co-administration with other CNS depressants; limited duration packaging (for example, 3, 6, 8 day packs); updated Risk Evaluation and Mitigation Strategy (REMs) programme including increased education of prescribers; new post-marketing requirements (PMR) for both immediate release and modified release formulations. The FDA has also proposed that the broader public health impact of opioid abuse be incorporated into any approval decisions related to opioids.¹³

The current FDA approved label for Kadian (also known as Kapanol) was updated in December 2016 and includes the black box warning as described in Figure 2 below.

⁹ Health Canada Drug Database – accessed September 2017 at https://pdf.hres.ca/dpd_pm/00031792.PDF

¹⁰ https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020616s057lbl.pdf

¹¹ National Institute of Health, National Institute on Drug Abuse: Opioid crisis

<<https://www.drugabuse.gov/drugs-abuse/opioids/opioid-crisis>>

¹² Government of Canada: Federal Actions on Opioids <<https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/federal-actions.html>>

¹³ FDS Opioids Action Plan.

<<https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm>>

Figure 2: Blackbox warning; FDA approved label for Kadian (updated December 2016)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **KADIAN** exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow KADIAN capsules whole to avoid exposure to a potentially fatal dose of morphine. (5.2)
- Accidental ingestion of KADIAN, especially by children, can result in fatal overdose of morphine. (5.2)
- Prolonged use of KADIAN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).
- Instruct patients not to consume alcohol or any products containing alcohol while taking KADIAN because co-ingestion can result in fatal plasma morphine levels. (5.4)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)

Use of prescription opioids, and deaths associated with these medications, is also increasing in Australia. An opioids roundtable conducted by the Pharmaceutical Benefits Scheme (PBS) in May 2015;¹⁴ reported that there had been a general increase in opioid prescriptions in Australia, (from around 2.5 million per quarter to around 3.5 million per quarter between 2009 and 2014) and that in 2014 the most common prescriptions were for paracetamol with codeine (more than 1.7 million patients), followed by oxycodone (around 1 million patients). The Australian Bureau of Statistics (ABS) *Report on Drug Induced Deaths*;¹⁵ reported an increasing number of deaths due to prescription opioids (from 297 in 2007 to 550 in 2016) and that oxycodone, morphine or codeine was present in 30% of all drug induced deaths in 2016. A review of codeine use in over-the-counter preparations was conducted by the TGA in 2016, with this resulting in re-scheduling of codeine to prescription only.¹⁶ This re-scheduling was due to concerns regarding unsupervised use of codeine resulting in 'opioid tolerance, dependence, addiction, poisoning and in high doses, even death'.

The increased awareness of the risks associated with prescription opioids will require consideration with regard to this application, particularly as use is proposed in such a vulnerable population (elderly, frail, limited respiratory reserve and debilitated due to the underlying condition).

¹⁴ <<http://www.pbs.gov.au/info/reviews/authority-required-listings>>

¹⁵ Australian Bureau of Statistics: Drug Induced Deaths in Australia: A Changing Story.

<<http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2016~Main%20Features~Drug%20Induced%20Deaths%20in%20Australia~6>>

¹⁶ <<https://www.tga.gov.au/codeine-info-hub>>

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration time line

The following table captures the key steps and dates for submission PM-2017-01592-1-5 and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline for application PM-2017-01592-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	1 August 2018
First round evaluation completed	3 January 2018
Sponsor provides responses on questions raised in first round evaluation	28 February 2018
Second round evaluation completed	23 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 April 2018
Sponsor's pre-Advisory Committee response	15 May 2018
Advisory Committee meeting	1-2 June 2018
Registration decision (Outcome)	
Initial	27 June 2018
Final	7 November 2018
Number of working days from submission dossier acceptance to registration decision*	185

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

Morphine sulphate pentahydrate is a water soluble salt of morphine that may be orally or parenterally administered. The oral dose forms are presented as immediate release or modified release formulations.

According to the sponsor's application form, no changes to the manufacture, formulation or packaging of the currently registered 10 mg and 20 mg products (ARTG IDs 68439 and 48134) are proposed. Kapanol capsules 10, 20, 50 and 100 mg contain differing amounts of identical polymer-coated sustained-release pellets of morphine sulfate.

Modified release formulations are available in Australia in a number of different strengths and from several different pharmaceutical companies. Trade names include: Kapanol; Anamorph; MS Contin; Sevredol; and Momex. The current application refers only to the sponsor product, Kapanol.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

According to the sponsor's cover letter, this application seeks to extend the indications to include symptomatic reduction of chronic breathlessness in patients with advanced and terminal diseases, such as cancer, chronic heart failure and chronic obstructive pulmonary disease, which has persisted despite optimal treatments for the underlying cause(s) of the breathlessness. This extension is only to apply to the 10 mg and 20 mg strengths capsules.

In the first round evaluation, the clinical evaluator recommended re-wording of the indication using more clinically relevant terminology and clearly identifying the palliative intent is recommended.

The sponsor agreed to the clinical evaluator's proposed re-wording of the indication to:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatment are not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

Drug class and therapeutic indication

The currently approved indication for Kapanol 10, 20, 50 and 100 mg capsules is for the relief of chronic pain unresponsive to non-narcotic analgesia. The TGA approved indications for the other modified release oral preparations of morphine sulphate are similarly limited to chronic severe pain, although the exact wording may differ.

Oral preparations of morphine sulphate (immediate and modified release formulations) are funded by the PBS with the benefit restricted to severe disabling pain that is unresponsive to non-opioid analgesics.

Dosage forms and strengths

The Kapanol product has the active substance of morphine sulphate pentahydrate in polymer coated pellets contained within a hard gelatin capsule, resulting in a modified release formulation. The capsules are presented in a blister pack.

There are four Kapanol capsule strengths and three pack sizes that are currently listed on the ARTG and described in the current PI (see Table 3 below).

Table 3: Currently Registered Kapanol Dose Strengths and Pack Sizes

Dose	ARTG ID	Presentation ^a	Pack size
10 mg ^b	68439	Hard gelatin capsule, size 4, with K10 in black and a single continuous black band; blister pack	20, 28, 60
20 mg ^b	48134	Hard gelatin capsule, size 4, with K20 in black and 2 discontinuous black bands; blister pack	20, 28, 60
50 mg	48135	Hard gelatin capsule, size 2, with K50 in black and 3 discontinuous black bands; blister pack	20, 28, 60
100 mg	48136	Hard gelatin capsule, size 0, with K100 in black and 4 discontinuous black bands; blister pack	20, 28, 60

^a all capsules contain creamy-white to light tan polymer-coated spheroidal pellets

^b Extension of indication is proposed to be limited to 10 mg and 20 mg strengths

Source: ARTG Public Summaries, accessed September 2017 at TGA.gov.au

The current Kapanol PI notes that ‘not all strengths or pack sizes may be distributed in Australia’.¹⁷

According to the PBS website (accessed September 2017), benefits for Kapanol (10 mg, 20 mg, 50 mg and 100 mg strengths) are limited to a maximum of one pack of 28 capsules (no repeats) although authority for increased maximum quantities and/or repeats may be granted in special circumstances.

The evaluator recommended in the first round evaluation that the pack size be limited to a 7 capsule pack during the initial dose titration for chronic breathlessness, and then to 28 capsule pack size once opioid responsiveness has been confirmed and the effective dose determined. The clinical evaluator notes that smaller pack sizes have been discussed by other regulatory bodies in response to the opioid crisis in North America.

The sponsor was asked to clarify which pack size(s) for 10 mg and 20 mg Kapanol capsules are available in Australia and whether a pack size of 7 capsules is available.

In response to the TGA’s request for further information, the sponsor has advised that all strengths of Kapanol are provided exclusively within Australia in packs of 28 capsules, with each pack containing 4 blister trips, each with 7 capsules. According to the sponsor, there are no plans to implement a dedicated 7 capsule pack at this time but ‘*this pack configuration allows a 28 pack to be ‘broken’ and individual blister strips prescribed and dispensed if necessary.*’ The clinical evaluator is uncertain as to whether this is feasible at the pharmacy level and recommends that this be clarified.

Dosage and administration

The current PI provides the following dosing recommendation for Kapanol:

The usual starting dose in opioid naive patients is Kapanol capsules 40 mg every 24 h or 20 mg every 12 h.

Additional advice is provided regarding: factors that impact on initial dose selection; that the capsule pellets must not be chewed or crushed; that if the capsule cannot be

¹⁷ Current PI for Kapanol, accessed September 2017 at <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01928-1>

swallowed whole, the pellets may be suspended in water or soft food to be swallowed, or may be administered via a large gastrostomy tube (but not a nasogastric tube); dosing adjustment in the event of 'excessive opioid effects'; use of a short-acting analgesic for breakthrough pain; and a conversion guide from other morphine or opioid preparations to Kapanol and vice versa.

The sponsor proposes that the following recommendation be added to the PI:

Treatment of Chronic Breathlessness

Kapanol can be safely commenced in patients who are opioid naïve with a starting dose of 10 mg/day.

If a satisfactory clinical response (a one point reduction in worst breathlessness in the previous 24 h on a 0-10 numerical rating scale (NRS)) has not been achieved after 7 days, and the initial starting dose is well tolerated, an increase of the daily dose by 10 mg with evaluation over the coming 7 days is suggested.

Dosing can be once or twice daily but the maximum evaluated daily dose is 30 mg/day

The other information is left unchanged except for the removal of 'analgesic' following opioid and the addition of 'and chronic breathlessness' in one paragraph.

The clinical evaluator largely agrees with this dosing advice but considers that the whole Dosage and Administration section requires greater clarity and a more structured separation of the advice provided for the two indications.

Clinical rationale

Information on the condition being treated

Chronic breathlessness

Breathlessness may be defined as the '*Subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*'.¹⁸ Extrapolating from pain models, breathlessness is considered to result from the physical perception of laboured breathing and the cognitive and emotional reaction to the perception. Breathlessness is recognised as a major source of distress and suffering that can adversely affect the physical, psychological, spiritual, and social well-being of people with breathlessness and their caregivers. Anxiety can aggravate the symptom as well as result from it, often leading to a progressive spiral of cause and effect.

Chronic breathlessness may be the end-result of a number of differing pathologies, including:

- respiratory conditions such as chronic obstructive pulmonary disease, interstitial lung disease, inflammatory lung disease and lung carcinoma
- cardiovascular conditions such as chronic heart failure and pulmonary hypertension
- neuromuscular disorders such as motor neurone disease, amyotrophic lateral sclerosis

These conditions are characterised by inexorable progression and worsening of breathlessness. The prevalence of breathlessness is reported to be high across all advanced and terminal diseases: cancer (16 to 77%), chronic heart failure (18 to 88%), renal disease (11 to 82%), and COPD (56 to 98%). Breathlessness intensifies near death, with prevalence increasing from 50 to 65% during the last months of life.

¹⁸ American Thoracic Society 1999

The presence and severity of breathlessness has been found to correlate poorly with abnormalities in the physiological parameters of oxygen saturation, respiratory rate, and forced expiratory volume in one second (FEV1). A number of scoring systems for assessing severity have been described. The sponsor's wording of the indication proposes that the target population be identified using the modified Medical Research Council (mMRC) breathlessness scale. This scoring system assesses the severity of breathlessness according to the effect of breathlessness on physical activity. It uses a five-item scale, with ranging from 0 to 4 and with higher scores denoting worse breathlessness (see Table 4 below). The 'modified' version differs from the original version only in that the original numbered the categories from 1 to 5.

Table 4: Modified Medical Research Council (mMRC) breathlessness scale for assessing the severity of breathlessness scoring system

mMRC Grade MRC grade	Description
Grade 0. MRC Grade 1	I only get breathless with strenuous exercise.
Grade 1. MRC Grade 2	I get short of breath when hurrying on the level or walking up a slight hill.
Grade 2. MRC Grade 3	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
Grade 3. MRC Grade 4	I stop for breath after walking about 100 meters or after a few minutes on the level.
Grade 4. MRC Grade 5	I am too breathless to leave the house or I am breathless when dressing or undressing.

Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease *Thorax* 1999; 54(7): 581–586.

The local guideline for the management of patients with COPD, *'The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease'*¹⁹ and the *Global initiative for COPD 2017*²⁰ advocate the use of the mMRC Breathlessness Scale (or similar) in the assessment of symptoms in patients with COPD. However, a recent survey of Australian, New Zealand and United Kingdom (UK) specialists/registrars in respiratory and palliative medicine suggests that this scale has not been incorporated into routine clinical practice and may not be used widely in the assessment of chronic breathlessness due to other conditions. The survey reported that only 32% of respiratory doctors and 18% of palliative care doctors used a breathlessness score routinely.²¹

Current treatment options

A multi-modal approach is used in the management of chronic breathlessness, with varying treatments utilised depending on the underlying conditions, the person's co-morbidities, and psychosocial, environmental, and cultural factors. The most important component of the approach is to ensure that management of the underlying condition is optimised and that any reversible contributors are treated. A description of a management

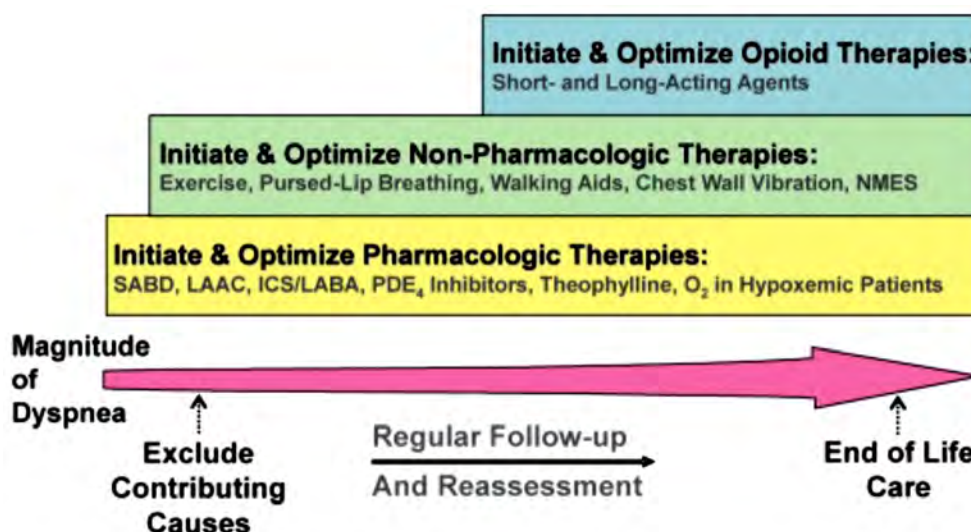
¹⁹ Yang IA, Dabscheck E, George J, Jenkins S, McDonald CF, McDonald V, Smith B, Zwar N. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2017. Version 2.50, June 2017

²⁰ Global Initiative for Chronic Obstructive Lung Disease Inc. (2017). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Accessed September 2017 at <<http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/>>

²¹ Smallwood N et al Physicians' attitudes to dyspnoea management in advanced chronic obstructive pulmonary disease (COPD). *European Respiratory Journal* 2016; 48 :PA3748; DOI: 10.1183/13993003.congress-2016.PA3748

approach for optimising treatment was presented in the sponsor's Clinical overview for breathlessness due to cancer, chronic cardiac failure and COPD.

Figure 3: Current recommended management of breathlessness from sponsor's Clinical Overview



The management of breathlessness seeks to concurrently address the symptom while identifying and treating the underlying causes. Current recommended management for breathlessness is copied from Marcinuik DD et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. Can Respir J Vol 18 No 2 March/April 2011.

Non-pharmacological interventions to relieve the sensation of breathlessness may also be used to relieve breathlessness, both concurrently with treatment of the underlying condition or if breathlessness persists despite this. These measures are described in the sponsor's Risk Management Plan (RMP) and current guidelines such as the COPD-X Plan²² and the Global initiative for GOLD.²³ Non-pharmacological measures demonstrated to have some efficacy in relieving breathlessness in patients with advanced COPD include regular physical activity, pulmonary rehabilitation, airway clearance techniques, walking aids, neuromuscular electrical stimulation and use of a battery powered fan to the face.

In patients in whom the breathlessness remains distressing, pharmacological measures may be tried. Both benzodiazepines and opioids may commonly be trialled in individual patients. According to a recent Cochrane review;²⁴ there is no evidence that benzodiazepines are beneficial in relieving the symptom of breathlessness in adults with advanced disease. However, the review noted that *'there is still an urgent need for more studies in this field to find better ways to relieve this burdensome symptom in people with advanced diseases'* and further concluded that *'benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness'*. Another recent Cochrane review, *Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness*;²⁵ found that

²² The COPD-X Plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease.

²³ GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD

²⁴ Simon ST, et al Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007354.

²⁵ Barnes H, et al Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD011008.

'There was some low quality evidence that showed a benefit of using oral or injectable opioid drugs for the treatment of the symptoms of breathlessness'.²⁶

A number of guidelines recommend opioids for the treatment of breathlessness in the palliative care setting (last days to weeks of life), assuming optimal treatment of the underlying condition and use of non-pharmacological measures:

- The Palliation and end-of-life issues section of the COPD-X Plan states that 'regular low dose oral morphine may be considered for treating breathlessness in patients with severe COPD that persists despite optimal medical management.' The same section notes that 'there is little comprehensive evidence to guide clinicians on the use of opioids in COPD symptom control'.
- The Tasmanian Government Specialist Palliative Care Service Care Management Guideline for breathlessness;²⁷ states that '*Opioids are the drug of choice and should be considered where there is dyspnoea at rest or on minimal exertion*'.
- The Therapeutic Guidelines: Palliative Care;²⁸ states that 'Treatment of the distress of dyspnoea is with oral or parenteral opioids'.
- The European Society of Medical Oncology (ESMO) Clinical Practice Guideline for Treatment of dyspnoea in advanced cancer patients²⁹ states that '*Opioids are the only pharmacological agents with sufficient evidence in the palliation of dyspnoea*'.
- The Canadian Thoracic Society Clinical Practice Guideline (2011) for managing dyspnoea in advance COPD;³⁰ noted the '*dearth of adequately powered, clinically relevant RCTs*' and recommended that '*oral (but not nebulized) opioids be used for the treatment of refractory dyspnea in the individual patient with advanced COPD*'.

Despite these recommendations regarding the use of opioids to relieve distress due to breathlessness in severe disease, studies investigating real world use of opioids for chronic breathlessness report that this treatment is little used. An audit of a random sample (n = 2000) of dispensed opioid prescriptions of 2249 patients starting long-term oxygen therapy for COPD between 1 October 2005 and 30 June 2009 in Sweden;³¹ found that only 2% of the prescriptions with recorded indication were for breathlessness, with 97% for pain. A qualitative investigation in Canadian physicians and patients found that physicians are reluctant to prescribe opioids despite expressing '*frustration with suboptimal control of dyspnea in patients with advancing COPD*'.³² A survey of UK doctors in a single hospital;³³ reported that the doctors were concerned regarding side effects and were more likely to restrict the use of opioids to the last hours/days of life than to use

²⁶ Sponsor comment: 'Low quality' was because those reviewers introduced an arbitrary and uncited category in judging quality of evidence that was individual study sample size (without accounting for cross-over in this process). See also Ekström M et al. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax* 2018; 73: 88-90

²⁷ Tasmanian Government Specialist Palliative Care Service Care Management Guideline for breathlessness. Accessed September 2017

²⁸ Palliative Care Expert Group. Therapeutic Guidelines: Palliative Care, Version 4, Melbourne: Therapeutic Guidelines Ltd; 2016, page 243

²⁹ Kloeke M, Cherny N on behalf of the ESMO Guidelines Committee. Treatment of dyspnoea in advanced cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology* 26 (Supplement 5): v169-v173, 2015. Accessed September 2017

³⁰ Marciniuk DD et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. *Can Respir J* 2011; 18.

³¹ Ahmadi Z, et al Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. *International Journal of COPD* 2016;11 2651-2657

³² Rocker G, et al. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *Canadian Medical Association Journal*. 2012; 184: E497-E504.

³³ Hadjiphilippou S, et al Doctors' attitudes towards prescribing opioids for refractory dyspnoea: a single-centred study *BMJ Supportive & Palliative Care* 2014; 4: 190-192.

them in patients with severe COPD. A survey of Dutch chest physicians³⁴ reported that they rarely prescribe opioids for refractory breathlessness to outpatients with advanced COPD, with this largely due to perceived resistance of the patient, the difficulty in predicting which patients are likely to respond to opioids, fear of possible adverse effects, and fear of respiratory depression. The survey of specialists and registrars in respiratory or palliative care medicine in Australia, New Zealand and the UK reported that palliative care doctors were more likely to introduce pharmacological treatment of breathlessness (91% compared to 69%) and that the preferred agent was short-acting morphine.³⁵

Common adverse effects of opioids that may impact on the patient's quality of life are familiar to most clinicians and are described in the guidelines. The European Society for Medical Oncology Clinical Practice Guidelines (ESMO CPG) notes that: '*patients receiving opioids for breathlessness experience the well-known opioid-related unwanted side effects, e.g. initial nausea and persistent constipation*'. It is also generally accepted in the literature that not all patients with chronic breathlessness will respond to opioids. The article investigating predictors of response by Johnson et al., (2013);³⁶ notes that '*one of the 'known unknowns' in the pharmacological management of chronic refractory breathlessness relates to the observation that, as with many interventions, not everyone benefits.*' Other barriers to use may include changing attitudes over time, financial considerations, the lack of regulatory approval of opioids for this indication and recent adverse publicity in the popular press regarding deaths due to prescription opioids.

Unmet need

Patients with breathlessness due to severe or advanced disease that has not been relieved by optimised treatment of the underlying condition and non-pharmacological approaches have an unmet need. There is no pharmacological treatment that currently has regulatory approval for this distressing symptom and no other pharmacological treatment recommended in current guidelines.

Clinical rationale

The Protocol of the MOP Study provides the following rationale for the conduct of the study and is relevant to the application:

Within the framework of improved community availability of key medications for palliative care, no medication is registered with the Therapeutic Goods Administration for the symptomatic relief of dyspnoea. The current proposal will be of a standard that can inform national medication policy for applications for registration (Therapeutic Goods Administration) and subsidy (Pharmaceutical Benefits Advisory Committee) if the results demonstrate net clinical benefit.

Evaluator's commentary on the background information

The sponsor's clinical expert is an Australian palliative care physician who was the principle investigator of the MOP Study and is the Chief Investigator of the Palliative Care Clinical Studies Collaborative (PaCCSC).

The sponsor's Clinical Overview provides a description of breathlessness and the management of breathlessness as proposed by the Canadian Thoracic Society in 2011³⁷.

³⁴ Janssen DJ, et al. Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians. *Chron Respir Dis*. 2015; 12: 85–92

³⁵ Smallwood N et al, Physicians' attitudes to dyspnoea management in advanced chronic obstructive pulmonary disease (COPD). *European Respiratory Journal* 2016, 48 (suppl 60) PA3748

³⁶ Johnson MJ, et al. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. *Eur Respir J* 2013; 42: 758–766.

³⁷ Marciniuk, D. D., et al. (2011). 'Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline.' *Can Respir J* 2011; 18: 69-78.

Descriptions of optimising treatment according to the underlying condition are provided, with the most detailed description provided for COPD. The sponsor's Clinical Overview notes that in many patients, breathlessness may persist after optimising treatment and that treatment choice is then symptomatic and may include '*opioids, psychotropic agents, nebulized furosemide and oxygen*'. A brief summary of the evidence basis for the use of opioids in the palliative care setting is provided, together with the information that the Australian COPD-X Guideline, the Canadian Thoracic Society (CTS) and the American Thoracic Society (ATS) '*support a role for opioids in treatment of breathlessness*'. The sponsor's Clinical Overview also notes that '*The current registered indications for opioids do not include chronic breathlessness*'. Unmet need, current real world use and barriers to use are not discussed.

It is not clear to the clinical evaluator as to the duration of treatment for which the sponsor proposes that morphine be used for chronic breathlessness. The COPD-X guideline and ATS refers to the palliative setting. The ATS updated statement in 2011 notes that short-term administration reduces breathlessness in patients with a variety of conditions but that '*evidence of long-term efficacy is limited and conflicting*' and that opioids are associated with frequent side effects, particularly constipation. The CTS recommended that oral opioids be used for the treatment of refractory dyspnoea in the individual patient with advanced COPD. This appears to recommend introduction prior to the end-of-life setting, with titration to effect described over 4 to 6 weeks. The evaluator notes that the sponsor's pivotal study, the MOP Study, investigated use for 7 days and that the supportive Abernethy Study;³⁸ investigated use for 4 days.

The sponsor was asked to clarify the timeframe for which use is proposed.

In response to the TGA's request for further information, the sponsor has suggested that treatment duration can only be determined on an individual basis and provided the additional information that '*the literature would suggest 5-year mortality rates of 21% and 65% in COPD patients with a MRC of 3 or 4, respectively (GOLD 2017), and in MOP Study the inclusion criteria included, 'Prognosis of at least 2 months in the opinion of the treating clinician'.*' This would suggest that treatment duration may be weeks to months to years, depending on the individual patient.

Guidance

Literature based submission

According to the TGA guidance for literature based submissions;³⁹ the current application would be categorised as a 'mixed application' and '*mixed applications are treated in the same way as literature-based submissions*'.

The submission describes the sponsor's compliance with pre-submission meeting outcomes.

Contents of the clinical dossier

Scope of the clinical dossier

As agreed to with the TGA, the sponsor has provided a 'mixed application', with this including a Phase III study supported by a literature review. According to the sponsor's Clinical Overview, the Phase III PaCCSC MOP study is pivotal for the demonstration of efficacy and safety.

³⁸ Abernethy AP, et al. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003; 327: 523–528

³⁹ see <<https://www.tga.gov.au/publication/literature-based-submissions>>

The contents of the dossier are:

- CSR for the main PaCCS MOP study
- The publication describing the Abernethy study
- The publications included in the literature review
- Cited references.

Paediatric data

None included. The current PI states that '*The use of Kapanol in children has not been evaluated*' and no change to this is proposed.

Good clinical practice

The MOP Study clinical study report states that:

This study was conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP) and all applicable laws and regulatory requirements' and that: 'The study was submitted to the Therapeutic Goods Administration under the Clinical Trial Notification scheme (CTN), each site was individually submitted to and acknowledged by the TGA prior to recruitment of the first participant at each listed site.

The second of the published articles for the Abernethy Study states that written informed consent to participate in the study was obtained from each participant and the protocol was approved by the Repatriation General Hospital Research Ethics Committee.

The first published article for the Dose Ranging Study states that:

- The research was approved by all participating institutions' research and ethics committees.
- All participants provided written informed consent before participating in the study.
- The study received TGA Clinical Trials Notification approval to use Kapanol for an unregistered indication.

Pharmacokinetics

No new information regarding pharmacokinetics is provided by the sponsor.

Pharmacodynamics

Studies providing pharmacodynamic data

No new information regarding pharmacodynamics is provided by the sponsor.

Evaluator's conclusions on pharmacodynamics

The pharmacokinetics of Kapanol for symptomatic reduction of breathlessness is unlikely to differ from the pharmacokinetics demonstrated in healthy subjects and patients with pain. Of note is that a relatively low dose is proposed for the extension of indication (starting dose of 10 mg per day, with maximum daily dose of 30 mg) compared to the starting dose of 40 mg daily for opioid naïve patients with chronic severe pain.

Dosage selection for the pivotal studies

The pivotal study proposed by the sponsor is the MOP Study. This was a randomised, double-blind placebo controlled study of oral modified release morphine 20 mg daily for one week in the management of refractory breathlessness

The MOP Study Protocol notes that dose selection was based on an earlier dose ranging study:

The current research group in an open labelled dose-ranging study of morphine (10 mg/24 hrs, 20 mg/24hrs or 30 mg/24hrs) has explored the minimum effective dose of opioids (unpublished data) for refractory dyspnoea (Stage I) with open label continuation on the dose that delivers at least a 15% reduction in breathlessness over baseline with acceptable toxicity (Stage II). Eighty five people have completed the study and more than 31 participant years of data collected. With minimal toxicity including no episodes of respiratory compromise, and no hospitalisations attributable to opioid use, the majority of people respond at either 10 mg/24hrs or 20 mg/24hrs. As such, this study proposes to use a dose of 20 mg/24hrs of morphine equivalent in the blinded randomised study

The clinical evaluator notes that the research group that includes David Currow has published a dose ranging study⁴⁰, although this Phase II/IV study has not been included in the presentation of efficacy and safety.

The clinical evaluator asked the following questions to the sponsor:

- Could the sponsor confirm that the dose ranging study referred to in the MOP Study protocol is the same as that described in the publication?
- Could the sponsor also explain why the Phase II/IV study, that provides data regarding long-term use, was not included in the presentation of efficacy and safety?

In response to the TGA's request for further information, the sponsor has confirmed that the dose ranging study is the same as that described in the published article. A summary of this study was apparently not provided in the original application through an oversight.

Evaluator's comments on dose selection for the pivotal study

The sponsor has not provided a discussion of dose selection for the pivotal MOP study and it is not clear why 20 mg daily of modified release morphine was chosen. In the dose ranging study the Study Protocol appears to refer to, a daily dose of 10 mg was found to be effective in 69% of responders, with 20 mg required in 23% and 30 mg in 8%. The 2003 Abernethy Study used a daily dose of 20 mg but states that '*some clinicians may regard this as a relatively high dose in patients who had not been treated with opioids before. As the study was being designed it was the lowest once daily, sustained release formulation available.*'

The evaluator notes that the draft PI proposes an initial dose of 10 mg/day in opioid naïve patients, rather than the 20 mg/day used in the MOP study. According to the sponsor's Summary of Clinical Efficacy, this recommendation is based on the results of the dose-ranging study referred to in the MOP Study protocol.

Many of the recently updated guidelines for the management of dyspnoea in severe COPD state that opioids may relieve chronic breathlessness but do not provide specific advice regarding opioid doses. Some local palliative care guidelines^{41,42} recommend using

⁴⁰ Currow, D. C. et al. (2011). 'Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study.' *J Pain Symptom Manag* 2011; 42: 388-399

⁴¹ Palliative Care Expert Group. Therapeutic Guidelines: Palliative Care, Version 4, Melbourne: Therapeutic Guidelines Ltd; 2016, page 243

immediate release morphine in the initial dose titration, with doses of 1.0 to 2.5 mg repeated as needed every 1 to 6 h, and later conversion to a modified release formulation. One guideline noted that the initial immediate release morphine could be combined with background long-acting morphine at 10 to 20 mg daily.⁴³ The 2011 Canadian Thoracic Society CPG;⁴⁴ recommends a more cautious approach in patients with advanced COPD, with a starting dose of 1mg daily and up-titration over several weeks.

The initial daily dose of 10 mg proposed in the draft PI is, therefore, consistent with local guidelines and the standard recommendation that the lowest effective dose be used. The use of immediate release morphine for initial dose titration, rather than modified release formulation, is commonly recommended. The evaluator notes that this practice may not be evidenced-based and that the recently updated Cochrane review Oral morphine for cancer pain⁴⁵ concluded that either immediate release or modified release morphine could be used to titrate to analgesic effect.⁴⁶

Efficacy

Studies providing efficacy data

The sponsor's presentation of efficacy in the sponsor's Clinical Overview and the sponsor's Summary of Clinical Efficacy is in three parts with efficacy as demonstrated by the MOP study; the Abernethy study; and the literature review. The evaluator's report on efficacy was divided into two parts and included additional publications. The first part describes the 3 original studies by the research group PaCCSC, the MOP study, the Abernethy study and the dose ranging study; the second part describes the literature review and includes an earlier Cochrane review and additional pooled analyses.

Evaluator's conclusions on efficacy

Studies by the research group

These three studies conducted in the Australian population are inconclusive regarding the efficacy of low dose modified release morphine in relieving the distress of chronic or refractory breathlessness. However, they do provide insight into the intended target population, with these being: on average, elderly (aged more than 75 years), male and with the underlying condition of COPD; largely frail (ECOG status 2 or 3;⁴⁷ unable to carry

⁴² Tasmanian Government Specialist Palliative Care Service Management Guideline for breathlessness, page 5. Accessed September 2017 at <http://www.dhhs.tas.gov.au/_data/assets/pdf_file/0009/36936/Care_Management_Guidelines_-_Breathlessness_-_20160622.pdf>

⁴³ New Zealand Best Practice Advocacy Centre (bpac^{NZ}) Better Practice Guideline: Managing breathlessness in palliative care. Accessed September 2017 at <<http://www.bpac.org.nz/BPI/2012/october/breathless.aspx>>

⁴⁴ Marciniuk, D. D., et al. (2011). 'Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline.' *Can Respir J* 2011; 18: 69-78.

⁴⁵ Wiffen PJ, et al. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* 2016, 4. Art. No.: CD003868.

⁴⁶ Sponsor comment: The choice of modified release morphine was also based on important pharmacokinetic criteria: as demonstrated in the Gourlay paper (Gourlay G et al Seventh World Pain Congress 1994 Part VII: 631-643), modified release morphine has lower peaks and higher troughs than immediate release oral morphine solution in steady state, potentially reducing toxicity and improving effectiveness.

⁴⁷ ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

out any work activities or largely confined to bed or chair); and having limited life expectancy (> 2 months for the MOP Study and > 1 month in the dose ranging study).

The MOP Study was a randomised double-blind multi-site parallel arm placebo controlled trial to assess relief of refractory breathlessness comparing fixed doses of morphine and placebo with an active treatment period of 7 days. The study failed to demonstrate a significant improvement with morphine compared to placebo for the primary outcome measure of Visual analogue scale (VAS) Breathlessness Now (Intensity) score at Days 5 to 7. It also failed to demonstrate a significant difference for any of the secondary outcome measures, including different measures of breathlessness, response rate and quality of life. The authors argued that sub-group analysis found that *'there was a statistically significant interaction (or a trending towards significant interaction) between the baseline mMRC subgroup and the treatment effect'* but this is not convincing given that this effect appears to have only been demonstrated with one of many measures of VAS breathlessness scores. This possible beneficial effect in the sub-group with baseline mMRC of 3 or 4 is also questionable due to intra-individual variation in this score between screening and baseline, with 30 participants in whom the mMRC changed from ≥ 2 to 1 between screening and baseline and an unknown number in whom other changes may have occurred.

This study is potentially substantially confounded by the access of participants in both arms of the study to immediate release morphine. The sponsor has argued that the use of this in the placebo group was substantially higher than in the morphine group although this it is not clear as to whether this may represent very high use by a small number of participants in the placebo group. The clinical evaluator also notes that the sensitivity analyses for the primary outcome measure that adjusted for the use of rescue medication, and other baseline prognostic factors, reported no significant difference between the treatment arms. More information regarding the use of immediate release morphine has been requested. The evaluator also notes that the sensitivity analyses for the primary outcome measure that adjusted for the use of rescue medication, and other baseline prognostic factors, reported no significant difference between the treatment arms.

The Abernethy study was a randomised, double blind, placebo controlled crossover trial of sustained release morphine of sustained-release morphine to assess change in the subjective sensation of dyspnoea secondary to advanced disease. The treatment period was four days with no washout period. The primary outcome measure was dyspnoea as measured on a visual analogue scale in the evening on the final day of the period (on Day 4 and 8). There was a significant decrease in breathlessness for the morphine period compared to the placebo period, with the mean VAS Breathlessness score difference of 9.5 mm (standard deviation (SD) 19, 95% CI 3.0 to 16.1, $P = 0.006$). There was a smaller mean reduction of 6.6 mm reported for the morning assessments. The result of the analysis of the evening scores was considered to be both clinically and statistically meaningful, as the minimal clinically important difference for VAS Breathlessness score has been reported to be more than 9 mm. The lack of effect in the morning was attributed to the morning timing of administration.

The results of this study may be confounded by the lack of a washout period between the two periods of the study. The group in which placebo followed morphine would have had a carryover effect of morphine and the timing of the analysis at Day 8 may not have been sufficient for this to dissipate, noting that a substantial proportion of this group (about 40%) continued to have mild-moderate constipation at Day 8. It is also likely that steady

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking h

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking h

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 - Dead

state had not been reached at the time of the analysis, given the difference between the morning and evening results. Also of note is that 21% of participants withdrew from this 8 day study.

The open label dose ranging study found that, for the 83 participants at the end of the dose ranging component of the study, the mean baseline VAS score for intensity of dyspnoea had decreased by 10.3 mm; from 50.3 mm (SD 19.4; median 55.3; range 7-86) at baseline, to 40.0 mm (SD 20.3; median 39.8; range 2-87). There were 52/83 participants who met the criteria of a 10% improvement in dyspnoea over their own baseline at a dose between 10 and 30 mg/day and who had acceptable/minimal side effects and could enter the longer term effectiveness component of the study. The average improvement in scores from their own baselines for these participants was 17.1 mm (SD 11.6). Of these 52 'responders', 19 participants (23% of the original group) were still reporting benefit after 3 months.

The PaCCSC are to be congratulated for conducting this series of studies in a group of patients who are difficult to recruit and whose prognosis may limit their capacity to complete any study. The studies provide some limited evidence of short-term efficacy, with the results of the Abernethy study and the dose ranging study, and a suggestion of long-term efficacy with the small number of patients continuing into the longer term effectiveness component of the dose ranging study. The failure to conclusively demonstrate efficacy may reflect the designs of the randomised controlled studies as described above. Another contributing factor to the difficulties in establishing efficacy may be individual variation in opioid responsiveness. This has been well-recognised in the management of pain and, although the precise mechanism of action of opioids in relieving dyspnoea has not been identified, it may be that this effect is also subject to individual variation. The response rates reported in the MOP study and the dose ranging study suggest that there may be considerable inter-individual variation in opioid responsiveness.

Literature review and systematic reviews

Meta-analyses

The 3 meta-analyses described above were consistent in that each found some limited evidence of a small improvement in chronic breathlessness with systemically administered opioids compared to placebo. They differed in their assessment of the quality of the evidence provided. The meta-analyses were limited by the available studies, with these largely consisting of small crossover studies of brief duration. Inclusion of studies with disparate design and that investigate a variety of opioids by differing routes weaken the results and risk obscuring a beneficial effect related to a specific opioid or route.

In terms of the proposed indication, these meta-analyses provide very limited support given: the brief duration of administration (single dose administration in approximately half of the studies in each analysis); only 2 of the included studies investigated modified release morphine; Ekström et al., (2015);⁴⁸ and the sponsor's literature review were limited to studies that included patients with COPD whereas the indication does not propose any imitation according to underlying cause of breathlessness.

Systematic reviews (without meta-analysis) and pooled analyses

These publications add little to the demonstration of efficacy. Vargas-Bermudez, Cardenal et al., (2015);⁴⁹ found '*modest evidence of benefit of the strong opioids in the alleviation of*

⁴⁸ Ekström M, et al (2015). 'Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review.' *Ann Am Thorac Soc* 2015; 12: 1079-1092

⁴⁹ Vargas-Bermudez, A., et al. (2015). 'Opioids for the Management of Dyspnea in Cancer Patients: Evidence of the Last 15 Years--A Systematic Review.' *Journal of Pain & Palliative Care Pharmacotherapy* 2015; 29: 341-352.

dyspnoea in cancer patients'. Simon, Koskeroglu et al 2013⁵⁰ found no evidence to support the use of fentanyl for the relief of breathlessness. Both of these reviews noted the paucity of good studies and the need for fully powered randomised controlled trials (RCTs). The pooled analysis of 3 crossover studies by Ferreira et al.,⁵¹ reported that less than half of the participants (43.1%) preferred morphine over placebo or neither, with the occurrence of side effects considered to be a major contributor to the reported preference.

Individual RCTs

As noted, all of these studies were small (< 50 participants in each arm), more than half of them were single dose studies and all were crossover studies. Of the studies included in the meta-analyses and literature review, half indicated a beneficial effect of opioid on breathlessness and half did not. The longest duration tested was 6 weeks.

The study most relevant to the proposed indication was that of Poole et al., (1998).⁵² This study investigated modified release morphine (10 to 40 mg daily) in 16 patients with severe COPD, with a treatment period of 6 weeks. Although this study found no overall improvement in breathlessness over placebo (as assessed by the Chronic Respiratory Disease Questionnaire) it did report that 9/16 participants elected to continue with open label morphine at the end of the study, with 4/16 continuing to receive it after 3 months.

Evaluator's conclusions regarding the demonstration of efficacy

The clinical evaluator does not consider that efficacy for the proposed use has been conclusively demonstrated: the MOP study failed to demonstrate efficacy according to the primary outcome measure but may be confounded by use of rescue medication; the Abernethy study found benefit but only investigated 4 days of treatment; the dose ranging study found benefit with this potentially persisting for some months but was open label; the meta-analyses suggest that there may be a small benefit but are limited by the potential for bias in the included studies.

The difficulties in demonstrating efficacy may reflect the lack of adequately powered RCTs, difficulties in recruiting from the palliative care population being studied, flawed study designs, inter-individual variability in opioid responsiveness and the tools used to assess breathlessness. This is a subjective sensation and, as with pain, it may be expected to vary on a daily basis in response to many different factors.

The proposed patient population is one that is suffering distressing breathlessness in the last weeks-months of life. In this setting, it may be appropriate to accept a lower quality of evidence and different measures of response. Patient preparedness to continue with the study medication may provide such a measure: the dose ranging study reported that 54% of responders were continuing to take modified release morphine at 3 months; the study by Poole et al.; reported that 9/16 of the patients chose to continue with open label modified release morphine, with 4/16 persisting with it at 3 months; the study in patients with CHF by Johnson et al., (2002);⁵³ found that 6/10 reported benefit with morphine, 5/10 chose to continue with the treatment and 4/10 were still on it at one year; the analysis by Ferreira et al., found that 43.1% of participants from three studies preferred morphine over placebo. Qualitative studies may also provide insights: a mixed

⁵⁰ Simon, S. T., et al. (2013). 'Fentanyl for the relief of refractory breathlessness: a systematic review.' *Journal of Pain & Symptom Management* 2013; 46: 874-886.

⁵¹ Ferreira, D H., et al. (2016) 'Blinded Patient Preference for Morphine Compared to Placebo in the Setting of Chronic Refractory Breathlessness - An Exploratory Study.' *J Pain Symptom Manage* 2016; 51: 247-254

⁵² Poole PJ, et al. The effect of sustained release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 1998; 157: 1877-1880

⁵³ Johnson MJ et al. Morphine for the relief of breathlessness in patients with chronic heart failure--a pilot study. *European Journal of Heart Failure* 2002;4: 753-756

qualitative/quantitative open label Canadian study of 4 to 6 months of morphine therapy for refractory dyspnoea in 44 patients found that 68% reported benefit, with some patients describing substantial improvements in quality of life, even though the change in breathlessness was small.⁵⁴ Current expert opinion, as expressed in recently updated guidelines also supports the proposed use, with opioids considered the first-line pharmacological treatment for chronic breathlessness, after optimisation of the underlying condition and use of non-pharmacological approaches.

Safety

Studies providing safety data

The demonstration of safety as presented in the dossier is largely based on the MOP study, with brief reference made to the individual studies included in the literature review.

The clinical evaluator is concerned that this approach may not adequately demonstrate safety for the following reasons:

The duration of the MOP study (7 treatment days) limits the demonstration of safety to short-term use; the use of immediate release morphine by both the placebo and the active arm confounds comparison of the two arms of the study

With regard to the literature review, the clinical evaluator notes that the use of the same search strategy was used for both efficacy and safety, with articles limited to studies that included patients with COPD and to randomised placebo controlled clinical trials. The use of this search strategy for safety was queried by the TGA. The sponsor's clinical expert responded that broad search terms were used and this was accepted by the TGA. The clinical evaluator is not convinced that the study inclusion criteria applied to the demonstration of safety are appropriate. The limitation to patients with COPD is not consistent with the proposed indication. The clinical evaluator is also of the opinion that safety may not be adequately demonstrated by the limitation to RCTs, given that such palliative care studies tend to be small in number, brief in duration, and include highly selected and closely supervised populations. Safety in real world practice may differ and may be better described in observational studies of large populations.

The clinical evaluator notes that the sponsor's clinical expert has co-authored an observational study of the use of opioids and benzodiazepines in chronic breathlessness due to COPD that was published in 2014.⁵⁵ In a rapid response to a Letter to the Editor regarding this study;⁵⁶ the authors have expressed similar concerns with: *'Observational studies are crucial as adverse events are systematically underestimated in randomized trials owing to insufficient sample sizes, relative short duration of therapy and the inclusion of highly selective study populations which are unlikely to be representative of the full spectrum of patients prescribed medications in clinical practice. However, possible confounding by indication cannot be ruled out in observational studies due to the lack of randomization.'*

The presentation of safety by the clinical evaluator was done in 3 parts:

- The first part described the safety findings in the MOP study, Abernethy study and dose ranging study. Given the limited safety information available for the Abernethy

⁵⁴ Rocker GM et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open* 2013.

⁵⁵ Ekström Magnus P, et al. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study *BMJ* 2014; 348 :g445. Accessed October 2017 at <http://www.bmj.com/content/348/bmj.g445>

⁵⁶ *BMJ* Rapid response. Accessed Oct 2017 at <http://www.bmj.com/content/348/bmj.g445/rr/688028>

and dose ranging studies, the MOP study will be presented first, and in greater detail, followed by a brief description of the safety findings in the other two studies

- The second part described safety in two ways:
 - Safety as reported in the individual studies, with this largely as provided in Jennings et al.; (2002);⁵⁷ and Barnes et al., (2016);⁵⁸ but supplemented by information from the individual articles where relevant. Both of these Cochrane reviews included patients with breathlessness due to conditions other than COPD.
 - Safety as more broadly represented in the literature, with this including two observational studies.
- The third part addressed issues of regulatory concern, drawing on information in the first and second parts, together with current public health concerns regarding the use of prescription opioids

Patient exposure

MOP Study

In both treatment groups, the mean exposure (days) was close to the protocol planned exposure of 7 days: mean exposure = 6.47 days in modified release (MR) morphine group; 6.58 days in placebo group. All subjects in the modified release morphine group received the protocol planned dose of MR morphine 20 mg daily. In the MR morphine group, 78.9% of subjects completed 7 days of treatment compared to 88.3% in the placebo group.

- The exposure to immediate release morphine was not reported; the sponsor is asked to provide this. If exposure to immediate release morphine was substantial in the 'placebo' group, then comparison of adverse events (AEs) between the two arms of the study is meaningless.
- The duration of therapy according to the proposed indication is indefinite. Given the proposed patient population, this may be days, weeks, or months. The study duration of 7 days, and subject number, limits characterisation of safety for the proposed use.

In response to the TGA's request for further information, the sponsor has provided additional analyses of exposure to immediate release (IR) morphine in both the morphine and the placebo group. These show that 99/139 (71%) of placebo patients had some exposure to IR morphine on Days 1 to 7 and that the mean total dose during this time was 28.9 mg for the placebo group compared to 22.6 mg for the morphine group. This suggests that there was sufficient exposure to morphine in the placebo arm group for the comparison of rates of AEs in the Morphine group to the Placebo group to be of little meaning.

The sponsor provided additional information regarding those patients in the study who received more than the protocol defined maximum of 8 doses per day of immediate release morphine. Of note are the discrepancies between the dose recalled by the patient in telephone conversation and the doses recorded in the patient's diary. This may reflect confusion as a side effect of morphine use.

Studies included in the literature review and meta-analyses

Exposure was, in general, limited in the studies included in the literature review and meta-analyses. As shown in the table below, many of the studies were single dose and the

⁵⁷ Jennings AJ, et al. A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002; 57: 939–944

⁵⁸ Barnes H, et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane database of systematic reviews* 2016;3:CD011008

longest treatment duration was 6 weeks. Details of studies described in Table 5 below are described in Table 6.

Table 5: Exposure in the studies of systemic opioids included in the literature review and meta-analyses

	Population (#)	# random-ised	# completing study	Intervention	Duration of active intervention
Cuervo Pinna 2014	Advanced cancer	13	13	Oral transmucosal fentanyl citrate 200 to 400 µg	Single dose
Eiser, Denman et al. 1991 (1)	COPD	18	12	Diamorphine PO, dose 2.5 mg/5 mg QDS	2 weeks each dose
Eiser, Denman et al. 1991 (2)	COPD	10	10	Diamorphine PO, dose 7.5 mg	Single dose
Light, Stansbury et al. 1996	COPD	7	7	Morphine PO, dose 30 g	Single dose
Poole, Veale et al. 1998	COPD	16	14	MR morphine, dose variable (10–20 mg, OD–BD)	6 weeks
Woodcock, Gross et al. 1981	COPD	12	12	Dihydrocodeine PO, dose 1 mg/kg	Single dose
Woodcock, Johnson et al. 1982	COPD	16	11	Dihydrocodeine PO, dose 30/60 mg TDS	2 weeks
Johnson, Woodcock et al 1983	COPD	19	18	Dihydrocodeine PO 15 mg PRN, up to 4 times daily	2 weeks
Johnson et al 2002	CHF	10	10	Morphine PO 5mg immediate release solution QID	4 days
Oxberry et al 2011	CHF	37	35	Morphine PO immediate release 5mg QID; oxycodone PO 2.5mg orally QID	4 days

Abbreviations: COPD chronic obstructive pulmonary disease; Route: PO oral, SC subcutaneous; Frequency: OD once daily; BD twice daily, TDS three times daily, QID four times daily #-number

Table 6: Details of studies described in Table 5 above

Author Year	Details
Cuervo Pinna 2014	Cuervo Pinna, M. A. (2014) 'A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dyspnea on exertion in patients with advanced cancer.' <i>Journal of pain and symptom management</i> 47, e4-e5 DOI: 10.1016/j.jpainsymman.2013.12.235.
Eiser, Denman et al. 1991 (1), (2)	Eiser N, Denman WT, West, C Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the 'pink puffer' syndrome. <i>European Respiratory Journal</i> 1991; 4(8):926-31. <i>This paper reported the results of two separate studies</i>
Johnson 2002	Johnson MJ et al. Morphine for the relief of breathlessness in patients with chronic heart failure--a pilot study. <i>European Journal of Heart Failure</i> 2002;4(6):753-6
Johnson, Woodcock et al. 1983	Johnson MA, Woodcock AA, Geddes DM. Dihydrocodeine for breathlessness in 'pink puffers'. <i>British Medical Journal (Clinical Research Edition)</i> 1983;286(6366):675-7.
Light, Stansbury et al. 1996	Light RW, Stansbury DW, Webster JS. Effect of 30 mg of morphine alone or with promethazine or prochlorperazine on the exercise capacity of patients with COPD. <i>Chest</i> 1996; 109(4):975-81.
Oxberry 2011	Oxberry SG, Torgerson DJ, Bland JM, Clark AL, Cleland JG, Johnson MJ. Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. <i>European Journal of Heart Failure</i> 2011;13(9):1006-12
Poole, Veale et al. 1998	Poole PJ, Veale AG, Black PN. The effect of sustained release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. <i>American Journal of Respiratory and Critical Care Medicine</i> 1998;157(6):1877-80.
Woodcock, Gross et al. 1981	Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. <i>The New England Journal of Medicine</i> 1981;305(27):1611-6.
Woodcock, Johnson et al. 1982	Woodcock, A., M. Johnson, et al. (1982). 'Breathlessness, alcohol, and opiates.' <i>N Engl J Med</i> 306: 1363-1364.

Safety issues with the potential for major regulatory impact

The proposed indication is for use in patients with severe respiratory disease and with treatment continued for an indefinite period. Issues that are of possible regulatory concern with this proposed usage are:

- Respiratory depression and increased risk of death in patients with severe respiratory disease
- Prescription opioid deaths
- Development of physical dependence

- Drug abuse and addiction

Respiratory depression and premature death

It is known that opioids cause respiratory depression and that this may contribute to, or cause, death. This is of particular concern in patients with respiratory compromise and is recognised in the Warnings section of the current PI:

Warnings:

Impaired Respiration:

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly and debilitated patients, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may significantly decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnoea. Severe pain antagonises the respiratory depressant effects of morphine.

Some re-wording of this section of the PI that may lessen this warning has been proposed by the sponsor in the draft PI.

This risk is also recognised clinically; a consistent concern in studies investigating barriers to opioid use in chronic breathlessness is respiratory depression, with this potentially contributing to earlier death.

The sponsor has not specifically discussed respiratory depression as a concern in the sponsor's Clinical Overview or Summary of Clinical Safety. The sponsor's Clinical Overview reports that, in the MOP study, *'Eight subjects in each treatment arm had a TEAE of respiratory depression however these were not reported as serious. All TEAEs of respiratory depression were NCI-CTCAE Grade 1 except for three events in the placebo group, where two events were Grade 2 and one was Grade 5.'* Of note is that patients in both arms were provided with immediate release morphine for rescue medication and that these treatment emergent AEs (TEAEs) may have resulted from either, or both, morphine formulations. The MOP Study CSR also refers to 3 patients in whom the deaths were possibly related to study drug (2 in the morphine arm and one in the placebo arm); too little information is provided for these deaths to be evaluated.

The sponsor's documents also note that there were no reports of respiratory depression in the dose ranging study and none reported in the studies included in the literature review and systematic analyses. However, the studies in the literature review included only small numbers and treatment for brief duration. In addition, a rise in CO₂ levels was reported in 2 studies: Woodcock, Johnson et al., (1983);⁵⁹ reported a statistically significant rise in arterial partial pressure of carbon dioxide by both 30 mg and 60 mg four times a day (QID) of dihydrocodeine (2 weeks) compared to placebo; Chua (1997);⁶⁰ found a statistically significant increase in end tidal carbon dioxide levels with a single dose of dihydrocodeine compared to placebo at peak exercise in 12 patients with chronic heart failure (CHF). In both studies, the reported rise was unlikely to be of any clinical consequence.

Two large observational studies that investigated the use of opioids in patients with severe respiratory disease have been described above. In each of these reports, the use of

⁵⁹ Woodcock, A., et al. (1982). Breathlessness, alcohol, and opiates. *N Engl J Med* 1982; 306: 1363-1364.

⁶⁰ Chua TP, et al. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 1997; 29: 147-152

prescription opioids was associated with an increased risk of all-cause mortality. In the Swedish study, this risk was limited to patients receiving 'high dose' opioids, with this defined as > morphine equivalent 30 mg per day. In the Canadian study, the risk of death was more substantial and associated with both low and high doses of opioids. The latter study has been criticised due to the exclusion of patients receiving opioids for palliative. However, if these patients had been included the signal for increased risk of death with opioids would have been stronger. Other commentators have also noted that the use of opioids in patients with severe respiratory disease may be a surrogate marker of the severity of the underlying condition. This would be consistent with the high mortality of 50% reported in the Swedish study. As noted by the authors of both reports, causation can only be inferred. However, these observational studies suggest that serious respiratory adverse events, including mortality, may be increased in patients with severe COPD who receive opioids.

Given the proposed usage, the risk of respiratory depression and premature death would not preclude approval as the principle of double effect could be argued. However, this potential risk must be explicitly referred to in the PI and the Consumer Medicine Information (CMI) and must be discussed with the patient so that informed consent can be obtained prior to commencement. To ensure appropriate assessment and discussion, treatment with Kapanol should only be initiated by a specialist who is knowledgeable regarding the underlying condition and in the use of a potent opioid for the management of breathlessness.

Prescription opioid deaths and the 'Opioid crisis'

As noted above, there is currently an epidemic of deaths due to prescription opioids in the USA;⁶¹ and Canada.⁶² According to the Centre for Disease Control (CDC), an estimated 40 Americans die every day from prescription opioids and the amount of opioids prescribed and sold in the USA has quadrupled since 1999. This has largely been attributed to increasing prescription of opioids to treat chronic non-cancer pain in the middle aged to elderly, with deaths due to accidental or deliberate overdose or co-ingestion with alcohol or benzodiazepines. Methods to address the epidemic proposed by the FDA include: re-wording of the boxed warning to highlight the risk of co-administration with other CNS depressants; limited duration packaging (for example, 3-, 6-, 8-day packs); updated REMs programme including increased education of prescribers; new post-marketing requirements (PMR) for both immediate release and modified release formulations. The PMR for extended release products include ten post-marketing studies and one clinical trial that largely relate to abuse/addiction with opioids prescribed for chronic pain. The FDA has also proposed that the broader public health impact of opioid abuse be incorporated into any approval decisions related to opioids.⁶³

A similar epidemic may be occurring in Australia and has received some media attention.⁶⁴ The National Drug and Alcohol Research Centre report that the rate of accidental deaths due to opioids is increasing, with 668 deaths in 2013 compared to 639 in 2012, and that more than two-thirds of these deaths are due to prescription opioids. The ABS report on

⁶¹ Centre for Disease Control (CDC) Information Page
<<https://www.cdc.gov/drugoverdose/epidemic/index.html>>

⁶² Government of Canada National report: apparent opioid-related deaths <<https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/national-report-apparent-opioid-related-deaths.html>>

⁶³ FDS Opioids Action Plan.

<<https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm>>

⁶⁴ <<http://www.smh.com.au/national/prescription-opioid-epidemic-coming-to-australia-20170803-gxobvt.html>>; <<http://www.abc.net.au/news/2017-04-13/800-australians-overdose-on-prescription-drugs-per-year-experts/8443578>>; <<http://www.news.com.au/finance/economy/australian-economy/painkillers-now-killing-more-australians-than-heroin/news-story/eaedbcf67ca77d67019f7819a4926354>>

Drug Induced Deaths⁶⁵ also reported the increasing number of deaths due to prescription opioids (from 297 in 2007 to 550 in 2016) and that oxycodone, morphine or codeine were present in 30% of all drug induced deaths in 2016. The re-scheduling of codeine by the TGA⁶⁶ has been in response to concerns regarding unsupervised use of codeine resulting in *'opioid tolerance, dependence, addiction, poisoning and in high doses, even death'*.

The potential for accidental overdose and drug-induced death with the proposed use is highlighted by a recent case report involving a patient at a Melbourne hospital.⁶⁷ A 69 year old male with severe COPD was commenced on morphine for chronic breathlessness during hospitalisation and discharged home with modified release morphine tablets at 10 mg daily, immediate release morphine solution as rescue medication, with recommended dose of 2 to 3 mg every 4 to 6 h, and a laxative solution that he was advised to take regularly. The patient subsequently required hospitalisation due to drowsiness and respiratory depression secondary to inadvertent opioid overdose; the patient had mixed up the two solutions and taken immediate-release morphine at the recommended laxative dose, resulting in an additional 30 mg of morphine daily (total 40 mg). This occurred despite verbal and written education regarding his medications, as provided by a pharmacist, prior to discharge.

The RMP also notes the possibility of accidental overdose due to the availability of Kapanol in a range of strengths, with the 50 mg and 100 mg capsules exceeding the proposed maximum recommended dose of 30 mg per day for opioid-naïve patients in the treatment chronic refractory breathlessness. The RMP argues that approval of Kapanol for the proposed indication may in fact improve safety as *'converting this off-label use to on-label, will increase the effectiveness of Mayne Pharma's established pharmacovigilance activities'* through the provision of appropriate information in the PI and CMI.

The Overdosage section of the current PI notes the narrow window between therapeutic effect and toxicity in some patients with *'Morphine toxicity may be a result of overdosage but because of the large inter-individual variation in sensitivity to opioids it is difficult to assess the exact dose of any opioid that is toxic or lethal.'*

The risks of accidental overdose in this vulnerable patient group are considerable. However, as with the risk of respiratory depression, this would not prevent approval for the proposed use provided there are appropriate safeguards and the patient is informed of the potential risks. The safeguards proposed by the clinical evaluator would include: initiation by an appropriate specialist; careful explanation of the potential risks to the patients and carer; written and verbal education to both the patient and a carer; and regular review during use. The involvement of a carer or other person in the discussion is important so as to provide some level of supervision regarding use, given that the adverse effects of drowsiness and confusion could contribute to inadvertent overdose.

These safeguards should be explicitly described in the PI. The risks associated with respiratory depression, particularly when benzodiazepines are co-administered, need greater emphasis; the sponsor's proposed re-wording of the Warning regarding respiratory impairment is not considered appropriate by the clinical evaluator as it may inadvertently reduce the importance of this warning in relation to the use for chronic pain. Additional information should be provided in the Dosage and Administration section and Information for Patients section of the PI. Additional information should also be provided in the CMI.

⁶⁵ Australian Bureau of Statistics: Drug Induced Deaths in Australia: A Changing Story.

<<http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2016~Main%20Features~Drug%20Induced%20Deaths%20in%20Australia~6>>

⁶⁶ <<https://www.tga.gov.au/codeine-info-hub>>

⁶⁷ Politis J, Le B, Smallwood N. Respiratory depression secondary to morphine use in a patient with COPD and refractory breathlessness. *Eur Respir J* 2017; 49: 1601858.

Physical dependence and opiate withdrawal

The risk of physical dependence is recognised in the Warnings section of the current Kapanol PI see below.

Drug Dependence:

Kapanol like all morphine preparations has a potential for physical and psychological dependence. However, this is not a prime concern in the management of terminally ill patients or patients in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. If withdrawal is necessary it must be undertaken gradually.

According to the sponsor's Summary of Clinical Safety, 'No withdrawal was observed in any of the clinical studies of chronic breathlessness'. This statement is true for the MOP Study, the Abernethy Study and the Dose Ranging Study. However, as described above, opiate withdrawal was reported in the studies included in the literature review and the systematic reviews. In 2 of the 4 studies that described treatment duration for 2 weeks or longer, opiate withdrawal symptoms were reported in some patients.

The risk is not adequately described in the draft PI. The clinical evaluator recommends that advice specific to patients receiving Kapanol for breathlessness be added with:

When treating patients with chronic breathlessness, opiate withdrawal symptoms have been reported after 2 weeks of treatment. Care should be taken during cessation and patients advised regarding the symptoms of opiate withdrawal.

Drug abuse and dependency

No specific actions were taken in the trials to investigate the potential for abuse or drug dependency and no adverse events related to these were reported in the clinical studies. Given the target population, drug abuse and dependency is unlikely to be an issue.

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

The proposed wording of the indication is:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in patients with a modified Medical Research Council (mMRC) Scale rating of 3 or 4 and in which the approved treatments for the underlying cause(s) of the breathlessness are not effective

According to this, breathlessness must be severe (mMRC Scale rating of 3 or 4 corresponds to an exercise tolerance of 100 m walk or too breathless to leave the house) and treatment would be continued indefinitely. Safety, therefore, needs to be demonstrated with both short-term and long-term use in suitable populations.

Evaluator's summary of the evidence for safety**Studies by the research group**

AEs were commonly reported in patients receiving Kapanol. These AEs were consistent with the AEs known to be associated with opioids and no new safety signals were identified. Comparisons of AE rates in the morphine and the placebo arms of the MOP Study are confounded by the use of immediate release morphine in both arms as rescue medication.

AEs were commonly of sufficient severity as to result in discontinuation of treatment and this did not decrease with longer term use. The discontinuation numbers (%) for the individual studies were as follows:

- MOP study
 - MR Morphine arm 18 (12.7%)
 - Placebo arm 8 (5.8%)
- Abernethy study 10/48 (20.8%)
- Dose ranging study
 - Dose ranging component 15/83 (18.1%)
 - Long term component 14 of 52 responders (26.9%).

Analysis of the relative likelihood of experiencing some AEs was investigated in the MOP Study. This found that the odds of being constipated or confused were at least two times higher than the Placebo group, with this statistically significant for mild and moderate symptoms and that the odds of experiencing sedation were more than two times higher than the placebo group for mildly or moderately drowsy and almost 14 times for 'slept most of the day' versus 'not drowsy at all'.

Distressing AEs were not prevented by prophylactic management. Constipation was commonly reported in each of the studies despite proactive laxative use. Quantification of the severity of constipation was performed in the Abernethy study. This found that the proportion of participants experiencing severe constipation increased with each day of morphine treatment (from <10% on Day 1 to around 20% by Day 3 to 4). The symptom did not immediately improve on cessation of MR morphine, with the proportion of patients reporting severe constipation persisting at around 10% for the first two days of placebo treatment following morphine treatment.

There were 8 reports of respiratory depression in each arm of the MOP Study; an association with somnolence and the use of immediate release morphine was not described. This information and additional information regarding respiratory serious AEs (SAEs) has been requested from the sponsor.

There was a higher number of deaths in the modified release morphine arm of the MOP Study, both overall (22 compared to 15) and during, or within 3 days of ceasing, treatment (8 compared to 5). There were 3 deaths during treatment that were assessed as possibly related to study drug by the investigators and a number of other deaths during treatment that were due to respiratory complications. A possible contribution of morphine-related respiratory impairment (in both the morphine and the placebo arms) could not be excluded given the limited information provided.

Systematic reviews and other sources

The description of safety provided in the two Cochrane reviews did not identify any new safety concerns. As with the studies by the research group: the common AEs were consistent with those known to be caused by opioids; AEs were often sufficiently distressing as to result in discontinuation of treatment.

The studies included in the literature review and systematic reviews provide some additional information regarding dose related effects and longer term use. The severity of AEs appeared to be dose related and to be more severe in opioid naïve patients. Opioid withdrawal syndromes were reported in 2 studies. There were 4 patients who experienced this after cessation of modified release morphine, at a maximum dose of 40 mg. In three patients this occurred after 6 weeks of treatment and in one patient, after 21 days. Two patients were reported to develop opioid withdrawal syndromes after as little

as two weeks of dihydrocodeine 60 mg three times a day (TDS) (morphine equivalent dose of about 20 mg daily).

There were no deaths attributed to the use of opioids reported in the studies, although only 3 deaths in total were reported. There were no reported events of respiratory depression, although a clinically insignificant rise in CO₂ was reported in a small number of patients with short-term use.

Two large observational studies that investigated opioid use in patients with severe COPD using administrative datasets have reported that the risk of all-cause mortality was increased with the use of opioids. In the smaller Swedish study, this increased risk was small and limited to patients receiving higher doses of opioids. In the larger Canadian study, the increased risk was substantial and seen with both high and low doses of opioids. This study also reported an increased risk of deaths due to COPD or pneumonia.

The potential for opioids to contribute to death is highlighted by the current epidemic of deaths associated with prescription opioids that is occurring in the USA and Canada.

Evaluator's conclusions regarding the demonstration of safety

The characterisation of safety for the proposed use is limited by the studies available. The MOP Study involved a reasonable number of patients but is limited by the short duration (treatment period of one week) and by confounding through the use of immediate release morphine in both arms. The Abernethy study had a treatment period of 4 days. The Dose Ranging Study was open label and subject to bias due to this. Regarding the studies included in the literature review and systematic reviews, these were largely of short duration and included small numbers of patients only. The observational studies cannot establish causation and may be confounded by other factors.

Within these limitations, the descriptions of safety provided in these sources did not identify any new safety concerns with MR morphine, with reported AEs consistent with those recognised as caused by opioids.

However, there is evidence of substantial harm with the use of modified release morphine for chronic breathlessness:

- AEs of nausea, vomiting and constipation were common, could occur despite prophylaxis and were sufficiently distressing as to result in treatment discontinuation in a high proportion of patients.
- Physical dependence with opioid withdrawal syndrome on cessation has been reported after as little as 2 weeks of low dose opioids.
- Serious respiratory complications were reported in the MOP Study; the relative contributions of the underlying condition and the respiratory depressant effects of morphine cannot be determined. One large observational study reported an increased risk of hospitalisations for COPD or pneumonia with opioid use in patients with severe COPD.
- Deaths that were possibly related to the study medication were reported in the MOP Study; an increased risk of death with opioid use in patients with severe COPD was reported in the two observational studies.

Also of relevance is the 'epidemic' of deaths associated with prescription opioids that is occurring in the USA and Canada. An estimated 40 deaths per day in the USA have been attributed to the use of prescription opioids and has resulted in a national emergency being declared. The use of prescription opioids have been reported as contributing to an increasing number of drug-related deaths in Australia. The proposed patient population is not likely to be one that will develop drug addiction behaviour but is at high risk of inadvertent overdose. This could occur due to increased risk of toxicity, as a consequence

of age, debility and limited respiratory reserve, or due to dosing errors, with morphine induced confusion and drowsiness contributing to this risk.

First round benefit-risk assessment

First round assessment of benefits

The evaluator's assessments of benefits is summarised in Table 7 below.

Table 7: First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Small clinically relevant improvement in chronic breathlessness with short-term use of systemic opioids.	Consistently demonstrated in 3 meta-analyses that had considerable overlap in included studies. However, the meta-analyses differed in their assessment of the quality of the evidence, with the most recent meta-analysis considering the evidence to be of low to very low quality.
Small clinically relevant improvement in VAS breathlessness score with Kapanol 20 mg daily in the Abernethy study.	Inconsistent results between the morning and evening breathlessness scores, with the change in the morning scores not reaching minimal clinically important difference; duration limited to 4 days; potential confounding due to lack of washout period and assessments not made at steady state.
No consistent improvement in efficacy end-points with Kapanol compared to placebo in the MOP study.	Potential confounding by use of immediate release morphine as rescue medication in both arms. Depending on the definition used, around 30% or 60% in each arm could be categorised as 'responders'.
The dose-ranging study found that 52/83 participants responded to Kapanol, as defined by a > 10% improvement in VAS score.	Response rate of 62%. Potential bias due to open label design without control arm.

First round assessment of risks

The evaluator's assessments of risks is summarised in Table 8 below.

Table 8: First round assessment of risks

Risks	Strengths and Uncertainties
<i>Common distressing side effects:</i>	
Constipation	Constipation reported in about 60% of Kapanol treated patients in the MOP Study and Abernethy Study despite pro-active management with laxatives. Barnes et al meta-analysis: participants who

Risks	Strengths and Uncertainties
	received opioids were three times more likely to experience constipation compared to placebo.
Nausea and vomiting	<p>Vomiting reported in 37% of patients in the MOP study who received Kapanol.</p> <p>Barnes et al meta-analysis: participants who received opioids were 4.73 times more likely to experience nausea and vomiting compared to placebo.</p>
Agitation, delirium	Agitation was reported in 26% and delirium in 8.5% of patients receiving Kapanol in the MOP study.
Somnolence	<p>Somnolence was reported in 60% of patients receiving Kapanol in the MOP study.</p> <p>Barnes et al meta-analysis participants who received opioids were 2.86 times more likely to experience drowsiness compared to placebo.</p>
<i>Discontinuations due to AEs</i>	
Common and did not decrease with longer term use.	<p><i>MOP study</i></p> <p>MR Morphine arm 18 (12.7%)</p> <p>Placebo arm 8 (5.8%)</p> <p>Abernethy study 10/48 (20.8%)</p> <p><i>Dose ranging study</i></p> <p>Dose ranging component 15/83 (18.1%)</p> <p>Long term component 14 of 52 responders (26.9%).</p>
<i>Potential risk</i>	
Respiratory depression	<p>Reported in 16 patients in the MOP Study, Grade 1 in 14/16, Grade 2 in 1 and Grade 5 in 1.</p> <p>Not reported in any of the studies included in the literature review or systematic reviews, although clinically unimportant increases in CO₂ with short-term use were reported in 2 studies.</p>
Premature death	No deaths attributed to study medication were reported in the MOP study, Abernethy Study, Dose ranging Study or any study included in the literature review or systematic analyses. A number of deaths in the MOP study were due to respiratory complications; a contributory factor

Risks	Strengths and Uncertainties
	<p>to this by Kapanol cannot be excluded.</p> <p>Two observational studies of opioid use in patients with COPD have reported an increase in all-cause mortality. This was limited to 'high dose' morphine in one study but not the other.</p> <p>Current information is that an 'epidemic' of premature deaths due to prescription opioids is occurring in the USA and Canada. This has largely been attributed to use of opioids for chronic non-cancer pain and concomitant ingestion of alcohol and other CNS depressants, although deliberate misuse and overdose is also a concern.</p>

First round assessment of benefit-risk balance

The evidence for efficacy suggests that opioid administration may result in a small clinically relevant improvement in chronic breathlessness that will not be experienced by all patients. This evidence is limited and inconclusive for the proposed indication: the MOP Study found no consistent benefit but is confounded by the provision of immediate release morphine to both arms; the Abernethy Study found a marginal improvement for the evening score but not the morning score; the dose ranging study found that some patients benefited but was an open label, uncontrolled study; the placebo controlled RCTs included in the literature review were limited by inconsistent results, small numbers of participants, brief duration of use; only one of the placebo controlled RCTs investigating modified release morphine; this study found no benefit. Despite this, 3 systematic reviews with meta-analysis have found a small benefit, although these analyses differed in their assessment of the quality of the evidence. The limited evidence reflects the difficulties of research in the target population.

The presentation of safety indicates that substantial distress and harm may occur with the proposed treatment with AEs such as constipation, vomiting, drowsiness or confusion occurring commonly. There may also be an increased risk of serious respiratory complications and death during treatment.

The proposed population is expected to be at greater risk of morphine toxicity than the target population of the current approved indication of chronic pain, in view of their advanced age, debility and limited respiratory reserve. It is also possible that benzodiazepines will be co-prescribed, to manage anxiety that is contributing to breathlessness or to manage breathlessness that is not adequately relieved by opioids. Such co-administration would be expected to further increase the risk of respiratory depression and premature death.

A number of clinical questions have been asked to clarify the efficacy and safety of Kapanol for the proposed indication. The clinical evaluator is unable to complete that benefit and risk balance until the sponsor's responses to these questions have been evaluated.

If these responses do indicate that the risk-balance is acceptable and noting that the intent of the proposed indication is to relieve the distressing symptom of breathlessness in patients with limited life expectancy, then it may be appropriate to approve Kapanol for this indication. If this was to occur, the clinical evaluator recommends that substantial safeguards are implemented, as discussed below.

First round recommendation regarding authorisation

The clinical evaluator is unable to make a recommendation regarding authorisation at this time, pending evaluation of the sponsor's responses to Clinical questions.

On the basis of the information provided in the sponsor's dossier and additional information sourced by the clinical evaluator, then the clinical evaluator is of the opinion that any approval of Kapanol for the proposed indication would need to be accompanied by substantial safeguards.

The safeguards recommended by the clinical evaluator are:

- The indication should be re-worded and explicitly indicate that treatment has palliative intent. The following wording is recommended by the clinical evaluator:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatment not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

- The treatment should be initiated by an appropriately experienced specialist, with this explicit in the wording of the indication (as above). This is to ensure that treatment of the underlying condition is optimised and that the prescriber is familiar with the potential risks and benefits.
- Informed consent must be obtained from the patient. This would require a discussion of the goals of therapy and possible benefit together with the potential risks, including distressing side effects and the possibility of early death, must be openly and clearly discussed with the patient and carer. This discussion would be best performed by an appropriately experienced specialist. The patient should be educated regarding the dose, likely adverse effects and proactive management of constipation. This should be supported by written advice. The clinical evaluator does not consider that an open discussion will unnecessarily discourage patients, noting that a qualitative study of the use of opioids for refractory dyspnoea has reported that '*Both patients and family caregivers expressed some concern about addiction, respiratory suppression and imminent death, but they indicated that these fears were easily and quickly alleviated by honest and open communication with their health care professionals.*'⁶⁸
- The patient's carer(s) should be involved in the above discussion to ensure a general understanding of treatment goals, assist in the early detection of serious AEs and provide some supervision of medication use, given the potential for Kapanol induced confusion/drowsiness and consequent drug errors.
- The patient should be reviewed on a weekly basis during commencement and throughout any up-titration to ensure early detection of concerning adverse effects and any confusion regarding dosing. This is in keeping with the Dosing and Administration advice suggested by the sponsor in the draft PI.
- The pack size should be limited to 7 capsules (one week supply) during initial dose titration and then to 28 capsules (one month supply) after response without unacceptable side effects and the effective dose has been determined.

⁶⁸ Rocker G, et al. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *Canadian Medical Association Journal*. 2012; 184: E497-E504. <<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3381775/>>

- Greater clarity and separation regarding the indications of chronic pain and chronic breathlessness should be provided throughout the PI.
- Specific warnings and precautionary advice regarding the potential risks associated with the proposed use must be included in the PI and CMI.

Given that all of the uncertainties around efficacy and longer term safety are unlikely to be resolved by responses to the Clinical questions, the clinical evaluator considers that it is important that a post-approval surveillance study be performed and that the results of the BEAMS Study should be provided to the TGA when available.

Second round clinical evaluation

Sponsor's responses to the Clinical questions raised with evaluator's commentary

The sponsor has provided comprehensive responses to the Clinical questions. The clinical evaluator has provided summaries of the Clinical question and the sponsor's response below, together with commentary on the responses.

Question 1

Dosage Form: Pack sizes for 10 mg and 20 mg capsules that are available in Australia

Could the sponsor indicate which pack sizes are available for the 10 mg and 20 mg capsule strengths in Australia and whether smaller pack sizes, in particular 7 capsule pack size, are available internationally (currently or planned)?

Sponsor's response

All strengths of Kapanol are provided exclusively within Australia in packs of 28 capsules. Each pack is composed of four blister strips with each strip containing 7 capsules. There are no plans to implement a dedicated 7 capsule pack at this time.

This pack configuration of 4 strips allows a 28 pack to be 'broken' and individual blister strips prescribed and dispensed if necessary.

Evaluator comment

The evaluator is uncertain as to whether this breaking up of a prescribed pack is feasible at the pharmacy level. This should be clarified with a pharmacist. If this is the case, then it would be an acceptable solution.

Question 2

Proposed duration of use. Could the sponsor please clarify the intended duration of use?

Sponsor's response

At an individual level, prediction of survival in patients with COPD is unreliable, therefore it is not feasible or clinically relevant to specify a time based on prognosis or duration of treatment.

However, the sponsor notes that the literature would suggest 5-year mortality rates of 21% and 65% in COPD patients with a (MRC of 3 or 4, respectively). (GOLD 2017), and in MOP Study the inclusion criteria included, 'Prognosis of at least 2 months in the opinion of the treating clinician'.

The sponsor then refers to the safeguards proposed in the PI with:

- Guidance on use to be provided in the Product Information (Section 4.4 'Special Warning and Precautions for Use')

- Weekly clinical review during dose titration
 - Initiation by a suitability qualified palliative care and/or respiratory physician
- and that the level of ongoing clinical review required is adequately controlled through existing restrictions on Schedule 8 Therapeutic Goods.

Evaluator comment

The clinical evaluator accepts that the duration of treatment is uncertain and may vary from week to months or even years in some individual patients. The clinical evaluator notes that the safety related additions to the PI proposed by the clinical evaluator in the first round evaluation have been accepted by the sponsor.

Question 3

Regulatory history, foreign applications for this extension of indication. The sponsor is asked if there is any intention to apply to other regulatory bodies for this extension of indication.

Sponsor's response

There are no plans to apply to other regulatory bodies for this extension of indication.

Evaluator comment

The sponsor's response was noted.

Question 4

Dose ranging study: Identity of the Phase II Dose ranging study referred to in the MOP Study Protocol. The sponsor is asked to confirm that the study referred to in the MOP study protocol above is the same as that described in the article published in 2011 and also explain why the Phase II study, that provides data regarding long-term use, has not been included in the presentation of efficacy and safety?

Sponsor's response

The sponsor provided the requested confirmation together with a summary of the study, noting that this summary should have originally appeared within 'Summary of results of individual studies' in the original application. The summary is reproduced here:

One supportive study was also identified (Currow, McDonald et al. 2011). This was a Phase II dose increment study in which 10 mg daily of sustained-release morphine was administered, and increased in non-responders by 10 mg daily each week to a maximum of 30 mg daily. Participants were withdrawn if there were unacceptable side effects or no response to the maximum dose. If a 10% (or greater) improvement in dyspnoea over baseline was observed, then they joined a Phase IV effectiveness / safety study at that dose. There were 83 participants in the study. Of these 52 (63%) derived 10% or more benefit (average 35% improvement). Most patients responded to 10 mg daily (70%), with benefits maintained at 3 months. Of those who did not respond or withdrew (n=31), 15 had unacceptable side effects, including drowsiness (n=4), confusion (n=3), constipation (n=2), nausea (n=2), vomiting (n=2), dizziness (n=1) or hallucinations (n=1). Other reasons for withdrawal included death (n=4), clinical request (n=1), lack of benefit at maximal dose (N=8), no benefit at less than maximal dose and withdrew (n=3). The reported number needed to treat was 1.6 and number needed to harm was 4.6. No significant differences were seen in response based on baseline breathlessness or by diagnosis. For those who derived at least 10% benefit and entered the Phase IV study (n=52), the averaged once daily sustained release morphine dose was 14±6.3 mg. In this subgroup, 69.2% had benefit at 10 mg of sustained release morphine in 24 h, 23.1% at 20 mg, and 7.7% at 30 mg. For

patients entering the Phase IV substudy, the average improvement in scores from their own baselines as they entered Phase IV was 17.1 ± 11.6 mm. In the Phase IV study, 13 patients withdrew due to constipation (n=6), drowsiness (n=4), and nausea and vomiting (n=4). Withdrawals occurred in the first 3 months. All side effects settled rapidly following cessation of opioids. Three months after entering the Phase IV study, 24 patients were still taking opioids for breathlessness, half were taking 10 mg and half were taking 20 mg. Nineteen remained on the dose they had left the phase 2 dose-ranging study on, four had increased their dose by 10 mg per day and one had decreased their dose by 10 mg per day. Four remained on their dose but did not complete their patient diary.

Evaluator comment

The sponsor has confirmed the identity of the study referred to as the dose-ranging study in the first round evaluation. The summary provided is consistent with the information provided by the clinical evaluator regarding this study in the first round evaluation.

Efficacy

Question 5

Enrolment before and after Protocol Amendment 4. The sponsor is asked to provide a breakdown of the number of patients enrolled before and after Amendment 4, including a breakdown of mMRC scores at baseline (mMRC score of 2 or 3 or 4) for the before and after groups.

Sponsor's response

One hundred and sixty-three participants were recruited to the study before Amendment 4 and 121 after of whom, only 25 (25/284; 8.8% of all participants) had an mMRC breathlessness scale score of 2.

Table 9: Recruited participants before and after protocol Amendment 4

		mMRC Breathlessness Scale Score				Missi ng	Total
		1	2	3	4		
Before Amendment 4	Research staff-rated screening scores	0	0	90	73		163
	Participant-rated baseline scores	17	28	36	66	16	
After Amendment 4	Research staff-rated screening scores	0	25	52	44		121
	Participant-rated baseline scores	13	19	30	35	24	

Evaluator comment

The clinical evaluator accepts that the populations recruited to the study before and after Amendment 4 are not substantially different.

Question 6

Changes in the mMRC dyspnoea score between screening and baseline assessment in the MOP study and implications of this for the proposed wording of the indication.

The sponsor is asked to provide more information regarding changes in the mMRC dyspnoea score between screening and baseline and during the conduct of the study. This information should include:

- The total number of patients in whom the mMRC score changed between screening and baseline

- The extent of change (increase of 1, 2, 3 or 4 in the score or decrease of 1, 2, 3 or 4 in the score and number of patients for each of these)
- The time between screening and baseline (mean, median and range)
- The total number of patients in whom the mMRC score changed between baseline and Day 7 (inclusive)
- The extent of change (increase of 1, 2, 3 or 4 in the score or decrease of 1, 2, 3 or 4 in the score and number of patients for each of these)

If these results indicate that the mMRC dyspnoea score is highly variable within an individual over time, the sponsor should provide a justification for this score to be used to determine the target population in the proposed wording of the indication.

Sponsor's response

The sponsor's response is summarised here:

The sponsor has clarified that the mMRC at screening was determined by the research staff whereas the mMRC at baseline and subsequently was determined by the patient. The differences between screening and baseline may, therefore reflect differences between the assessment made by the patient and the health professional.

In terms of change between screening and baseline, 91 had no change and 40 had missing baseline assessment. Of the other 153 patients, 110 had a change of ± 1 point, 33 had a change of ± 2 points and 10 improved by 3 points.

The time that elapsed between screening eligibility and baseline was a mean of 3.3 days (SD 4.25) with a median 2 days (range -46 days).

Additional analyses of change in mMRC compared to baseline during the study were provided. These found that:

- 79% of patients in the morphine arm and 77% in the placebo arm had stable mMRC score of 3 or 4 between baseline and Day 1
- 56% of patients in the morphine arm and 62% in the placebo arm had stable mMRC score of 3 or 4 between baseline and Day 7.

The sponsor also noted that the MRC scale has been reported to have very high inter-rater reliability between health professionals and that as the assessment of patient response will be by the treating health professional, then the assessment is likely to be robust and objective.

Evaluator comment

The clinical evaluator is reassured by the clarification that some of the apparent variability in the mMRC is due to assessment by the patient versus research staff. The clinical evaluator also notes that the mMRC can be expected to be a dynamic measurement and to fluctuate according to treatments and other variables. However, this variability is no longer of such concern as the sponsor has agreed to re-word of the indication such that the mMRC is no longer a required component.

Question 7

Use of Rescue Medication in MOP Study

The sponsor was asked to provide more information regarding the use of immediate release morphine as rescue medication in the MOP study to better enable assessment of the possible confounding of the results by this use.

Sponsor's response

The sponsor has clarified that the numbers [in Table 14.2.17; not shown here] refer to the number of patients who answered the question in the diary regarding the use of rescue medication for that day.

The sponsor has provided several displays of the use of rescue medication by study day and study arm. These show that around 60% of patients in the morphine arm did not use rescue medication on study Days 2 to 6, compared to around 40 to 50% of patients in the placebo arm. The displays showed that for each number of rescue doses (1 to 6 doses) on each day of the study there was, in general, a lower proportion of patients in the morphine arm.

Evaluator comment

The sponsor's additional presentations of the use of rescue medication indicate that there was more use of this by the placebo group. Additional information regarding use of rescue medication is provided in the sponsor's response to the question *Exposure to immediate release morphine in the MOP Study*. This information also indicates higher use of rescue medication in the placebo group. The clinical evaluator agrees that the use of rescue medication in the placebo group is a major confounding factor in the study results.

Question 8***Number of participants in each sub-group in the MOP Study***

The sponsor was asked to clarify the number of participants in each subgroup in the MOP study given some apparent discrepancies in the study report.

Sponsor's response

The sponsor has clarified that [Table 14.2.9] in the study report includes only participants with non-missing endpoint data in each sub-group, with this accounting for differences in the numbers within the sub-groups for some of the endpoints. The following table of the number of participants per sub-group was provided.

Table 10: Number of participants in each subgroup

PaCCSC Protocol: MOP Population: Intent-to-Treat		
	Morphine 20 mg/day (N=145)	Placebo (N=139)
COPD Sub-group		
COPD - Yes	82 (56.6%)	82 (59.0%)
COPD - No	63 (43.4%)	57 (41.0%)
Baseline mMRC Sub-group		
Baseline mMRC - 1 or 2	40 (27.6%)	37 (26.6%)
Baseline mMRC - 3 or 4	88 (60.7%)	79 (56.8%)
Missing	17 (11.7%)	23 (16.5%)
COPD/mMRC Sub-group		
COPD - Yes; Baseline mMRC - 1 or 2	23 (15.9%)	23 (16.5%)
COPD - Yes; Baseline mMRC - 3 or 4	52 (35.9%)	47 (33.8%)
COPD - No; Baseline mMRC - 1 or 2	17 (11.7%)	14 (10.1%)
COPD - No; Baseline mMRC - 3 or 4	36 (24.8%)	32 (23.0%)
Missing	17 (11.7%)	23 (16.5%)

Evaluator comment

Sponsor's response has been noted.

Question 9***Number (%) of responders in the Abernethy Study.***

The sponsor was asked to provide more information regarding individual participant scores and the number and proportion of the participants that could be considered 'responders' to morphine for the Abernethy Study.

Sponsor's response

The sponsor noted that this was a crossover study with VAS measurements collected so that measurements at the end of each study period (Day 4 and Day 8) were compared to the start of each period (Day 1 and Day 5 respectively) to calculate response. The following analysis was provided, with the average of the morning and evening scores used for the calculations.

Table 11: Abernethy study

	Morphine	Placebo
VAS score at end of treatment period (day 4 or day 8)		
n	41	40
Median (range)	44.5 (2 - 90)	47.5 (6 - 85)
≥ 15% improvement from start of period (day 1 or day 5) to end of period (day 4 or day 8 respectively)		
n/N (%)	13/41 (31.7%)	8/40 (20.0%)
Improvement of 9 mm from start of period (day 1 or day 5) to end of period (day 4 or day 8 respectively)		
n/N (%)	10/41 (24.4%)	6/40 (15.0%)

Evaluator comment

The above analysis was requested to try to determine what proportion of patients in the Abernethy study might be expected to have a response to morphine when used to treat breathlessness, with response definitions as used in the MOP study. The evaluator notes that the analysis provided uses the average of the morning and evening scores and that the original analysis in the Abernethy Study found that the change in mean morning score was not meaningful.

The following table shows the results for 'response rate' for the two studies, MOP and Abernethy.

Table 12: Results from Studies MOP and Abernethy for 'response rate'

	MOP study		Abernethy study	
	Morphine group	Placebo group	Morphine period	Placebo period
Improvement ≥ 15%	35%	31%	32%	20%
Improvement ≥ 9 mm	68%	61%	24%	15%

Literature review

Question 10

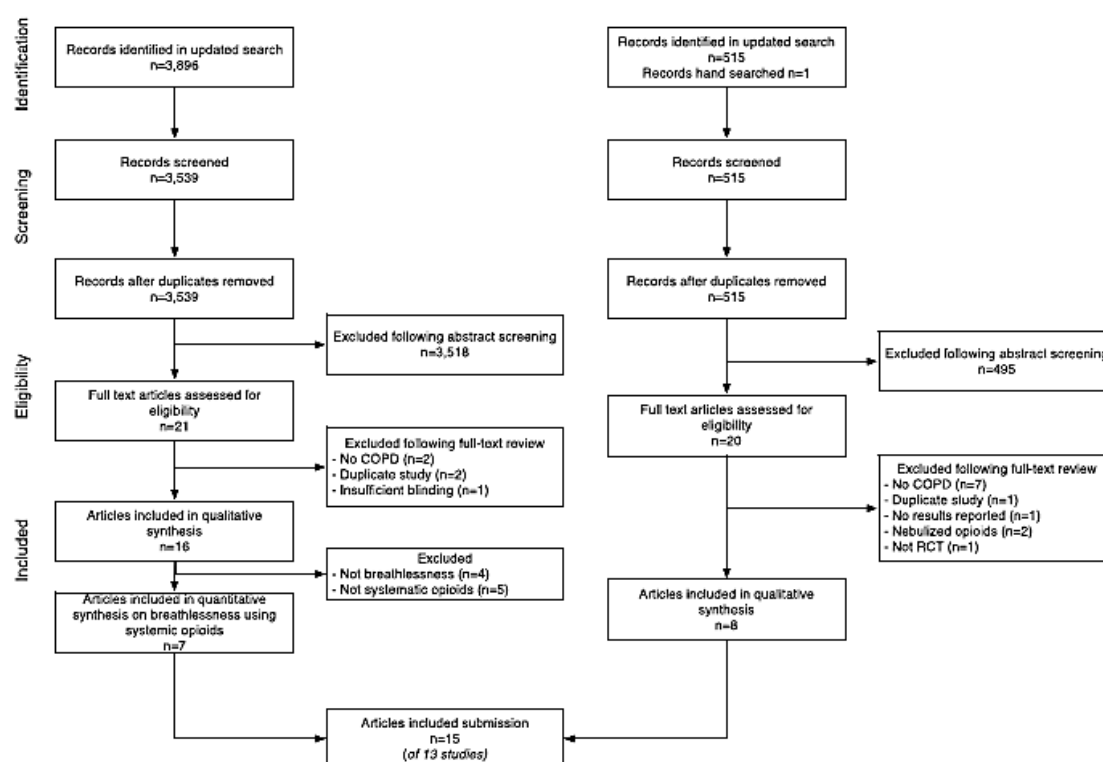
Publications included in the sponsor's literature review

The sponsor was asked to clarify the selection of studies for inclusion in the literature review.

Sponsor's response

A replacement Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was provided and some clarification of the narrative in the original documents with: 'In the original systematic review by Ekström and colleagues , 3,896 abstracts were identified, of which 21 underwent full text review, and 7 (formerly a figure of 13 reported) were included. In the updated searches run for this submission, an additional 515 abstracts were screened, of which 20 underwent full text review and 8 (formerly a figure of 11 reported) included.'

Figure 4: PRISMA diagram of included studies from initial and updates searches



Evaluator comment

The sponsor's response was noted. Criteria used to determine studies for inclusion were not provided.

Safety

Question 11

Maximum doses of Rescue Medication in the MOP Study.

The sponsor was asked to provide more information regarding those participants in the MOP study who were reported to use more than the protocol determined maximum of 8 daily doses (daily dose of 20 mg immediate release morphine).

Sponsor's response

The sponsor has provided brief narratives for each participant in the MOP study who received more than 8 doses of rescue medication.

For the patient in whom 30 doses was reported, this was found to be a transcription error, with the correct number of doses being 3. This patient was in a local rehabilitation hospital at the time with administration of the rescue medication by nursing staff. The

patient deteriorated 4 days after completing the study intervention with increasing breathlessness and died that day.

There were 4 other patients recorded as receiving more than 8 doses of rescue medication

- 40 mL dose: The diary was only completed for baseline. The pharmacy reported that 40 mL of rescue medication was unaccounted for but the patient has denied taking this.
- 12 rescue doses in one day: The nurse collected data indicated 4 doses per day. The patient diary had numerous nursing annotations to indicate incorrect entries by the patient.
- 9 and 10 rescue doses on the last two study intervention days: this was a discrepancy between the doses recorded in the diary and the information provided by the patient at the exit visit at which the patient reported 4 doses in the last 3 days.
- 9 rescue doses: this was a discrepancy between the doses recorded in the diary and the information provided by the patient at the exit visit at which the patient reported 2 to 3 doses per day.

The sponsor noted that patients are given clear instructions regarding the rescue medication, and this is written on the bottle and that every effort is made to ascertain participant compliance regarding morphine rescue doses. Despite this, there is discrepancy between what has been reported by the patient over the telephone and what the patient has recorded daily in the diary.

Evaluator comment

These discrepancies between recorded doses and recollected doses and the inaccurate recording of doses by patients may reflect confusion as a side effect of morphine. They highlight the importance of ensuring that there is a carer involved in discussions regarding the trial of morphine as this carer may then be able to provide some supervision of the use of the medication.

Question 12

Exposure to immediate release morphine in the MOP Study.

The exposure to immediate release morphine was not reported; the sponsor is asked to provide this to assist in the comparison of AEs between the two arms of the study. The overall total number of patients exposed; the mean (median, range) number of days of exposure; and the mean (median, range) total daily dose should be provided for each treatment arm for immediate release morphine.

Sponsor's response

The following table of exposure was provided. The sponsor notes that the analysis assumes that there was accurate recording of use in the patient diaries.

Table 13: Exposure to rescue medication by treatment group

PaCCSC Protocol: MOP Population: Intent-to-Treat			
	Statistic	Morphine, 20 mg/day (N=145)	Placebo (N=139)
Number of participants in study	n	145	139
Summary statistics for total days of rescue medication exposure for all participants	Mean (SD)	2.4 (2.6)	3.2 (2.6)
	SE	0.2	0.2
	95% CI	(2.0, 2.8)	(2.8, 3.7)
	Median	1.0	3.0
	Min, Max	0, 7	0, 7
Number of participants exposed to rescue medication on days 1 to 7	n	84	99
Summary statistics for total days of rescue medication exposure for participants exposed to rescue medication on days 1 to 7	Mean (SD)	4.1 (2.1)	4.5 (2.0)
	SE	0.2	0.2
	95% CI	(3.7, 4.6)	(4.1, 4.9)
	Median	4.5	5.0
	Min, Max	1, 7	1, 7
Number of participants in study	n	145	139
Summary statistics for total dose of rescue medication (mg) over days 1 to 7 for all participants	Mean (SD)	13.1 (19.8)	20.6 (23.3)
	SE	1.6	2.0
	95% CI	(9.8, 16.3)	(16.7, 24.5)
	Median	5.0	12.5
	Min, Max	0.0, 105.0	0.0, 107.5
Number of participants exposed to rescue medication on days 1 to 7	n	84	99
Summary statistics for total dose of rescue medication (mg) over days 1 to 7 for participants exposed on days 1 to 7	Mean (SD)	22.6 (21.5)	28.9 (22.8)
	SE	2.3	2.3
	95% CI	(17.9, 27.2)	(24.4, 33.5)
	Median	15.0	22.5
	Min, Max	2.5, 105.0	2.5, 107.5

Evaluator comment

The sponsor's response showed that around 60% of patients in the morphine arm did not use rescue medication on study Days 2 to 6, compared to around 40 to 50% of patients in the placebo arm and that, in the placebo patients who did use rescue medication, the number of doses was in general around 1 to 4 per day. This information, together with the table above, suggest that there was sufficient exposure to morphine in the placebo arm group for the comparison of rates of AEs in the Morphine group to the Placebo group to be of little meaning.

Question 13***Participants who discontinued treatment due to AEs in the MOP study.***

The sponsor was asked to clarify some apparent discrepancies in the reporting of participants who discontinued treatment in the MOP study due to adverse events and to provide more information regarding the AEs that led to treatment discontinuation.

Sponsor's response

The sponsor has provided the following responses:

There were 20 participants in total who discontinued treatment due to an AE of any grade.

The sponsor has provided the clarification that the "Treatment failure" category [of Figure 10.1] included adverse events related to the study medicine unacceptable to

participant/carer or clinician in charge. Of the 22 participants who withdrew from treatment due to 'Treatment failure', 20 participants, 14 in the morphine group and 6 in the placebo group, withdrew due to adverse events.

The sponsor has provided a table of AEs as reported in patients in whom treatment was discontinued due to AEs at the time of treatment cessation. All AEs at the time were included as attribution of the responsible AE is difficult.

Table 14: List of participants who discontinued due to AEs

List of Participants Who Discontinued Due to AEs

Allocation	Exit day	AE
Morphine	3	Drowsiness (3), dizziness (2), Constipation (2)
Morphine	3	Tremor (1), Dizziness (1), Agitation (1), Constipation (1), Dry mouth (1)
Morphine	4	Bronchospasm (1), Drowsiness (2), Nausea (2), Constipation (1)
Placebo	1	Bronchospasm (2), Arrhythmia (1), Drowsiness (1), Tremor (1), Itch (1), Headache (1), Dry mouth (1), fall.
Morphine	2	Bronchospasm (2), Arrhythmia (1), Drowsiness (2), Nausea (2), Tremor (1), Itch (1), Constipation (1), Dry mouth (1),
Morphine	2	Arrhythmia (1), Drowsiness (2), Nausea (2), Urinary retention (1), Dizziness (1), Tremor (1), Dizziness (1), Agitation (1), Headache (1),
Morphine	6	Bronchospasm (2), Drowsiness (2), Nausea (2), Urinary retention (1), Dizziness (1), Agitation (1), Headache (1), Mood changes (1), Constipation (2), Dry Mouth (2)
Placebo	4	Bronchospasm (1), Drowsiness (1), Nausea (1), Tremor (1), Dizziness (1), Dry mouth (2).
Morphine	5	Bronchospasm (1), Drowsiness (2), Nausea (2), Itch (1), Agitation (1), Constipation (2), Dry mouth (2)
Morphine	4	Drowsiness (2), Nausea (1), Tremor (2), Agitation (2), Mood changes (1), Constipation (2), Dry mouth (2)
Placebo	1	Bronchospasm (1), Drowsiness (2), Tremor (2), Dizziness (1), Agitation (2), Mood changes (1), Constipation (1), Dry mouth (1)
Morphine	6	Bronchospasm (1), Drowsiness (3), Tremor (2), Dizziness (1), Mood changes (1), Constipation (2), Dry mouth (1)
Placebo	4	Bronchospasm (2) Nausea (2), Dizziness (1), Mood changes (1), Constipation (2), Dry mouth (1)
Morphine	6	Respiratory failure (1), Arrhythmia (1), Drowsiness (1), Delirium (2), Nausea (2), Dizziness (1), Constipation (1), Dry mouth (2)
Morphine	1	Headache (1), Constipation (4)
Morphine	5	Bronchospasm (1), Drowsiness (1), Nausea (2), Tremor (1), Itch (1), Dizziness (1), Headache (1), Constipation (1), Dry mouth (1)
Placebo	3	Drowsiness (2), Dizziness (2), dry mouth (1).
Morphine	2	Drowsiness (2), Nausea (1), Tremor (1), Dizziness (1), Headache (1), Flushing (2), Dry mouth (1)
Placebo	6	Hypertension (1), Drowsiness (1), Dizziness (1), Agitation (1)
Morphine	2	Drowsiness (1), Delirium (1), Nausea (2), Tremor (1), Colic (1), Agitation (2), Dry mouth (2)

Brief summaries of the participants who discontinued due to AEs of Grade 3, 4 or 5 while on study were provided.

Evaluator comment

The listing of AEs per patient show that all of the patients were experiencing multiple AEs (ranging from 2 to 9 separate AEs) and that most of these AEs were consistent with the known AE profile of opioids and Grade 1 or 2 in severity. There were 2 patients with Grade 3 drowsiness and one patient with Grade 4 constipation. There were no Grade 5 AEs reported in the listing.

The narratives provided included very little clinical detail. Of note is that each of the placebo patients with opioid type AEs was receiving rescue morphine.

Question 14

TEAEs of respiratory depression and somnolence in the MOP Study.

The sponsor is asked to provide more information regarding patients in whom respiratory depression was reported.

Sponsor's response

The sponsor has provided the following information. The clinical question subsections are included in *italics* with the sponsor's response for greater clarity.

a. *If respiratory depression and somnolence was co-reported in any of the patients:*

- There are 7 participants who were on study medication when respiratory depression was reported. The ones in follow-up can be excluded, as we don't know what else they were taking because at this time care had reverted fully to their treating physicians. Such care may have included the open label introduction of extended release morphine.

Table 15 provided the grading for somnolence that was used, Table 16 listed patients in whom both respiratory depression and somnolence were reported during study intervention, Table 17 listed patients in whom both respiratory depression and somnolence were reported during Follow-up.

Table 15: Grading for somnolence (a disorder characterised by excessive sleepiness and drowsiness)

	1
Somnolence or sedation interfering with function, but not interfering with ADL	2
Obtundation or stupour, difficult to arouse, interfering with ADL	3
Coma	4
Death	5

Table 16: Study Participants, Rescue Doses and Adverse Events

Morphine

Baseline characteristics	Baseline respiratory status	Baseline Respiratory depression grade	Time point of Respiratory depression	Cessation respiratory status	Cessation Respiratory depression grade	Comment; Rescue doses Adverse events Other description or information
Age - 73 Gender - Male Cause of breathlessness - Restrictive lung disease AKPS - 60 mMRC - 3 (4) VAS - 22	RR - 31 SPO2 - 93 ETC02 - 35 Somnolence grade - 1	0	Day 8	RR - 32 SPO2 - 89 ETC02 - 25 Somnolence grade - 1	1	Continued to primary endpoint without incident. Rescue doses: Baseline - 0 Day 1 - 1 Day 2 - 0 Day 3 - 3 Day 4 - 1 Day 5 - 0 Day 6 - 0 Day 7 - 1 4 rescue morphine doses since last contact
Age - 86 Gender - Male Cause of breathlessness - COPD Respiratory failure noted at medical examination AKPS - 60 mMRC - 4 (3) VAS - 6.25	RR - 17 SPO2 - 95 ETC02 - 20 Somnolence grade - 1	0	Day 8	RR - 19 SPO2 - 96 ETC02 - 19 Somnolence grade - 1	1	Respiratory depression noted at cessation, no action taken. Rescue doses: Baseline - 1 Day 1 - 1 Day 2 - 1 Day 3 - 1 Day 4 - 1 Day 5 - 1 Day 6 - 1 Day 7 - -

Table 16 continued: Study Participants, Rescue Doses and Adverse Events

Morphine

Baseline characteristics	Baseline respiratory status	Baseline Respiratory depression grade	Time point of Respiratory depression	Cessation respiratory status	Cessation Respiratory depression grade	Comment; Rescue doses Adverse events Other description or information
Age - 87 Gender - Female Cause of breathlessness - COPD AKPS - 60 mMRC - 3 (3) VAS - 22.1	RR - 22 SPO2 - 92 ETC02 - NA Somnolence grade - 0	0	Day 6	RR - 17 SPO2 - 92 ETC02 - 27 Somnolence grade - 3	1	Ceased intervention on Day 6 due to adverse events including sedation and confusion. This participant is also described in 'Withdrawal from treatment due to AE grade of 3, 4 or 5'. SAE report describes locum review, with RR of 17, pulse of 96 and BP of 127/89, clear chest. Participant refused admission of other review. Withdrawn from intervention. Recorded no rescue doses being taken.
Age - 72 Gender - Male Cause of breathlessness - COPD Respiratory failure noted at medical examination AKPS - 50 mMRC - NA (4) VAS - 63.5	RR - 18 SPO2 - 96 ETC02 - NA Somnolence grade - 2	0	Day 4	RR - 18 SPO2 - 92 ETC02 - 30.64 Somnolence grade - 2	1	Respiratory depression was recorded as Grade 1 during the mid-week telephone call, but the participant continued in the study to primary endpoint without further record of respiratory depression. Rescue doses: Baseline - 2 Day 1 - 1 Day 2 - 2 Day 3 - - Day 4 - 0 Day 5 - - Day 6 - 1 Day 7 - 1

Table 16 continued: Study Participants, Rescue Doses and Adverse Events

Placebo

Baseline characteristics	Baseline respiratory status	Baseline Respiratory depression grade	Time point of Respiratory depression	Cessation respiratory status	Cessation Respiratory depression grade	Comment; Rescue doses Adverse events Other description or information
COPD and restrictive lung disease Respiratory failure noted at medical examination AKPS - 60 mMRC - NA (4) VAS - 19	Somnolence grade - 1			Somnolence grade - 1		Respiratory depression noted at cessation, no action taken. Rescue doses: Baseline - 0 Day 1 - 0 Day 2 - 0 Day 3 - 0 Day 4 - 0 Day 5 - 0 Day 6 - 0 Day 7 - 0
Age - 68 Gender - Male Cause of breathlessness - COPD AKPS - 60 mMRC - 3 (3) VAS - 12	RR - 14 SPO2 - 96 ETC02 - 30.6 Somnolence grade - 0	0	Day 1	SPO2 - 96 Somnolence grade - 1	1	Respiratory depression was recorded as Grade 1 during the telephone call on the first day of intervention, but the participant continued in the study to primary endpoint without further record of respiratory depression. Rescue doses: Baseline - 0 Day 1 - 0 Day 2 - 0 Day 3 - 0 Day 4 - 0 Day 5 - 0 Day 6 - 0
Age - 84 Gender - Male Cause of breathlessness -	RR - 32 SPO2 - 72* ETC02 - 20	0	Day 8	RR - 31 SPO2 - 84* ETC02 - 20	1	*Oxygen saturation measured while on room air, usually on continuous oxygen of 4 to 4.5 litres/minute.
Age - 78 Gender - Female Cause of breathlessness - COPD and end stage heart failure AKPS - 50 mMRC - NA (4) VAS - 45	RR - 21 SPO2 - 86 ETC02 - 45 Somnolence grade - 1	0	Day 4	NA	5	Died, lobar pneumonia. Found by paramedics to be unresponsive. SAE 8/6/15, admitted to hospital and died. Pneumonia, altered conscious state and respiratory failure. No diary retrieved from family, but reported during telephone contact is 7-8 doses per day. Pharmacy confirmed 60mg over the 4 days, or about 20mg per day, the actual amount taken per day cannot be determined. This participant is also described within the tables related to: Deaths on study Withdrawal due to SAE grade 3, 4 or 5

Table 17: Treatment Emergent Adverse Events (TEAEs) of Respiratory Depression and Somnolence in the MOP Study during Follow-up (Vital signs and rescue medications not recorded when telephone contact made)

Arm	Respiratory depression grade	Time point of grade	Somnolence grade	Comment (Dose)
Morphine	1	Week 2		Also described: agitation (1), Constipation (2) as new symptoms.
Morphine	1	Week 2		Also described: nausea (1), urinary retention (1), increased dry mouth (2).
Morphine	1	Week 2		Noted increase in stress due to enforced relocation. No other AEs noted.
Morphine	1	Week 2		Also noted: flushing (1) as a new symptom. Also reported reduced energy and sore abdomen without grade.
Placebo	2	Week 4		Chest infection reported.
Placebo	1	Week 1	1	Also described: tremor (1) as a new symptom. Reported feeling more confused.
Placebo	1	Week 2		Reported a fall without injury.
Placebo	1	Week 1	1	Recent flu vaccination noted.
Placebo	2	Week 2		Also noted headache (1) as a new symptom

b. If respiratory depression of any grade resulted study withdrawal of any patient in either arm

- Two patients were withdrawn with respiratory depression
 - Morphine arm: [information redacted] serious adverse event Day 6, withdrew from intervention, did not die
 - Placebo arm: [information redacted], died Day 4 while on study.
- c. Whether the patients in the placebo arm in whom Grade 2 and Grade 5 respiratory depression was reported were taking immediate release morphine at the time or in the previous 12-24 h*
- Grade 2 in Week 2 ([information redacted]) and Week 4 ([information redacted]) of follow-up, oral morphine was not provided during follow-up or post study. Medication may have been prescribed by their treating physician.
- Grade 5, ([information redacted]), died on Day 4, reported as a narrative, no diary retrieved from family. Mid-week call reported 8 doses of rescue medication per day. This event was discussed by the Data Safety Monitoring Committee (DSMC). Further clarification about blood results were sought, no other action was requested.

File was recalled.

- Pharmacy confirmed 60 mg over the 4 days, or about 20 mg per day, the actual amount taken per day cannot be determined.
- Medical notes at baseline record that patient was cautioned about limiting rescue doses to a maximum of 8 doses per day, 4 doses during baseline

d. The narrative for the patient in the placebo arm in whom Grade 5 respiratory depression occurred was requested.

A narrative with updated details was provided in the response to the question *Deaths during treatment (or within 3 days) in the MOP Study*.

Evaluator comment

In the 7 patients in whom both respiratory depression and somnolence were reported, all events of respiratory depression were described as Grade 1 except for the one Grade 5 event. The events of somnolence were Grade 1 (n = 5), Grade 2 (n = 1) and Grade 3 (n = 1). The patient with grade 5 respiratory depression was reported to have Grade 1 somnolence at baseline; no AE of somnolence was reported while on study treatment. The narratives provided limited clinical information, however, it was notable that for 6/7 patients, the respiratory depression appeared to be mild and not require intervention (no reports of reduced respiratory rate, worsening hypoxaemia, nor retention of carbon dioxide nor hospitalisation). The participant with Grade 5 respiratory depression was found collapsed at home with an altered conscious state and was subsequently reported to have lobar pneumonia and died within 24 h receiving palliative care. Arterial blood gases on hospital arrival showed both hypercapnoeic and hypoxic respiratory failure. This patient was in the placebo group but apparently reported taking 7 to 8 doses of rescue medication per day according to telephone contact. A contribution of morphine to this death cannot be excluded.

The evaluator notes that the concern regarding the potential for morphine to contribute to respiratory failure has been acknowledged by the sponsor's acceptance of the inclusion in the PI and CMI of the warning regarding these and the potential for slow release morphine to contribute to early death.

Question 15

Respiratory SAEs in the MOP Study

The sponsor is asked to:

1. Comment on the high proportion of respiratory type TEAEs resulting in treatment discontinuation
2. Provide more information regarding the review performed for the PaCCSC Studies Data and Safety Monitoring Committee, including the number and type of respiratory AEs and the outcome of the review.

Sponsor's response

The sponsor notes that there is no classification of 'respiratory depression' in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE). Given that respiratory depression is of particular concern in people with respiratory illness (especially those with Type II respiratory failure) and was of particular concern for one of the reviewing Human Research Ethics Committees (HRECs), the investigator team included a classification of 'respiratory depression' using the generic NCI CTC AE grading of none, mild, moderate, severe, or caused death. Any site investigator could therefore draw attention to changes in a participant's clinical condition.

According to the response, this resulted in 'Respiratory depression' being used as a 'flag' when the site investigator was concerned about a participant's condition. As noted in the response to the question *TEAEs of respiratory depression and somnolence in the MOP Study*, the clinical data do not reflect any episodes of reduced respiratory rate, worsening hypoxaemia, nor retention of carbon dioxide. The response also comments that *'Participants who experienced somnolence appeared to have also been classified as having 'respiratory depression' as a precaution in the Case Report Forms while investigations were being undertaken'*.

The DSMC MOP Study Final Report was attached.

Evaluator comment

The sponsor has not directly answered the question that was asked but did provide some information indicating that the reporting of 'respiratory depression' in the study was not standardised and that this may have resulted in overcalling.

The DSMC MOP Study Final Report provided a summary listing of 27 SAEs that were reviewed by the committee. The Report states that: *'The review of SAEs was achieved through both face-to-face meetings and email correspondence, and where necessary, additional information was sought from PaCCSC. No individual SAEs, nor the review of the SAEs for any trends, provided the Committee with reason to recommend the trial be stopped.'*

The table included 8 SAEs in whom the relationship to the drug was considered possible or probable and one in which it was considered definite

1. Hospitalisation due to constipation - probable
2. Hospitalisation due to Respiratory failure/lobar pneumonia/altered conscious state with death as outcome – possible
3. Hospitalisation due to increased breathlessness and fever – possible
4. Acute Respiratory Distress with death as outcome – possible
5. Hospitalisation due to shortness of breath triggered by nausea and vomiting – possible
6. Extreme somnolence since morning dose Day 2 – possible
7. Hospitalisation due to desaturation, confusion, oedema right leg, slurred speech, and decreased mobility - probable
8. Somnolence – definite.

The SAEs that the Independent data monitoring committee (IDMC) considered possible/probable/definite relationship to the study treatment are all consistent with the known safety profile of opioids. Of note it that the Grade 5 event of respiratory depression in the placebo patient discussed in the question above was assessed by the IDMC as having possible relation to study drug (this patient was potentially taking 7 to 8 doses of immediate release morphine each day). There was one other AE with fatal outcome (acute respiratory distress) that the IDMC considered to be possibly related to study drug. From the narratives provided in the response to another clinical question, this patient was in the morphine group and developed increasing respiratory distress on study Day 4 with death occurring 24 h later. The patient received 2 doses of immediate release morphine for terminal breathlessness.

Question 16***Deaths during treatment (or within 3 days) in the MOP Study***

The sponsor was asked for clarification and more information regarding the deaths during treatment in the MOPS Study.

Sponsor's response

A summary of the sponsor's response is provided. The clinical question subsections are included in *italics* with the sponsor's response for greater clarity

- a. The sponsor was asked to clarify if 5 or 6 participants died within 3 days of ceasing treatment.*

The sponsor stated that there were 5 participants who died within 3 days of ceasing treatment. The reference to 6 was a typographical error.

- b. *The sponsor was asked to provide more information regarding the use of rescue medication in the 13 deaths reported during treatment or within 3 days of treatment cessation.*

Additional clinical information regarding the 13 deaths was provided.

- c. *There were more deaths reported in the morphine arm, both overall (22 versus 15) and during or within 3 days (8 versus 5). It is possible that Kapanol administration contributed to some of the increased number of deaths in the morphine arm. The sponsor is asked to comment.*

The sponsor noted that all deaths were reviewed by the DSMC at both the time of reporting and at the twice yearly closed meetings and that at no time did the DSMC request cessation of the study or attribute morphine as the cause of death.

Evaluator comment

The narratives provided by the sponsor show that all participants who died during the study or within the first 3 days after completion of the intervention were receiving morphine during the study period, as a once slow-release formulation or as immediate release rescue medication. From the information provided, deaths appeared to result from rapidly progressing respiratory failure in 4/13, pulmonary embolus in 1/13, sudden death with unclear cause in 5/13, progressive disease in 1/13 and from a fall whilst delirious in 1/13. As each of the patients had severe underlying respiratory disease with an estimated life expectancy of > 2 months, determining whether the use of opioids may have contributed to earlier than expected death would be difficult even if comprehensive records were provided. The possibility that the use of opioids may have contributed to some of these deaths cannot be excluded.

Question 17

Deaths during the Dose Ranging Study.

The sponsor/sponsor's clinical expert is asked to provide more information regarding the deaths reported in the dose ranging study.

Sponsor's response

The sponsor reported that 'A total of nine deaths occurred during the Phase II dose ranging study and Phase IV ongoing study (Currow, McDonald et al. 2011). Four of these deaths were during dose titration and five were during the extension phase of ongoing use. All deaths were attributed to disease progression in a population who had advanced disease at the time of entering the study.' A table describing the characteristics of the participants who died was provided.

Evaluator comment

From the table of characteristics, it is apparent that the patients had severe underlying conditions with clinician-rated mMRC of 3 (n = 2) or 4 (n = 7) and diagnoses of lung cancer (n = 5), COPD (n = 2), mesothelioma and pulmonary fibrosis (n = 1 each). According to the attributed cause of death, this was progressive disease in 5, AMI with stroke in 1, worsening cardiac failure in 1 and death preceded by uncontrollable vomiting in 1. The vomiting in this last patient was not considered to be related to morphine.

Evaluator's summary of the sponsor's responses

The sponsor has provided comprehensive responses to the clinical questions. The following has been clarified:

- Pack size available in Australia is 28 capsules packaged in 4 blister strips. The sponsor has suggested that these may be prescribed individually during titration.

- The proposed duration of use is unpredictable for the individual patient. The sponsor notes that the 5 year mortality in severe COPD (mMRC 4) is reported as 65%.

Responses to questions regarding the main study, the MOP Study, indicate that it was substantially confounded by the use of rescue medication as immediate release morphine in the placebo arm. Additional safety data from this study indicated that all but one of the reported events of respiratory depression were mild and did not require intervention. In one case, the event was associated with a fatal outcome. A contribution of morphine to this cannot be excluded. There were other respiratory SAEs and deaths to which a contribution by morphine cannot be excluded.

The sponsor has agreed to almost all of the recommendation made in the first round evaluation regarding the wording used in the PI and CMI. The points of disagreement are discussed below. The sponsor has agreed to additional pharmacovigilance measures using the RAPID programme. From the description of this provided in the attachment and in the article provided in the RMP response, this would provide suitable post-approval information. However, it is not clear as to how the results from the RAPID programme are to be provided to the TGA. The updated RMP also includes a description of the BEAMS study and a copy of the study protocol has been provided. However, it is not clear from the RMP if a final report of this study is to be provided to the TGA. Of note is neither of these studies will provide long-term safety data; the investigation period in the RAPID programme is limited to 3 months and the blinded extension phase of the BEAMS study will investigate duration of use of up to 4 months.

Second round benefit-risk assessment

The sponsor has accepted the recommended rewording of the indication to:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatment are not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

The risk-benefit assessment below applies to this indication.

Second round assessment of benefits

As noted in the first round evaluation, there is limited high quality evidence to demonstrate benefit from the treatment of chronic breathlessness with opioids. The sponsor's main study failed to show any benefit but the sponsor's responses have confirmed that it was substantially confounded by the use of immediate release morphine as rescue medication in the placebo group has been confirmed by the sponsor's responses. The results of the BEAMS study that is currently in progress may provide important efficacy and safety information.

The lack of evidence of beneficial effect may reflect the difficulties of performing studies of adequate size and duration in the proposed patient group and may also indicate varying responses on the part of individual patients.

The proposed patient population is one that is suffering distressing breathlessness in the last weeks-months of life. This patient population has considerable unmet need, with no medication having received regulatory approval for this indication. In this palliative setting, it may be appropriate to accept a lower quality of evidence and different measures of response. Current expert opinion, as shown in reputable guidelines, recommend the use of opioids in this setting, after non-pharmacological measures have not been effective.

Patient preparedness to continue with the study medication may also provide another measure of response, with around 50% of patients electing to continue with open label morphine in the studies in which this was provided as an option. Qualitative studies may also provide insights: a mixed qualitative/quantitative open label Canadian study of 4 to 6 months of morphine therapy for refractory dyspnoea in 44 patients found that 68% reported benefit, with some patients describing substantial improvements in quality of life, even though the change in breathlessness was small.⁶⁹

Second round assessment of risks

Additional safety information from the MOP study indicates that more than half of the patients in the placebo arm were using immediate release morphine as rescue medication. The events of respiratory depression that were reported in both placebo and morphine arm patients were all low grade and did not require intervention, except for one event with fatal outcome. In this patient from the placebo arm, a potential contribution of immediate release morphine (taken 7 to 8 times per day) to the event cannot be excluded. The available information suggests that distressing side effects such as constipation, nausea, dizziness and confusion occurred commonly but that clinically important respiratory depression was rare. The potential for opioid-induced confusion contributing to accidental overdose is concerning and highlights the need for involvement of a carer.

The changes to the PI and CMI recommended by the evaluator (see above), that make explicit the risks of use for this indication and that emphasise the importance of initiation by a specialist with weekly review during titration, have all been adopted by the sponsor.

Additional safety information may be provided by the investigator-driven pharmacovigilance study, the RAPID programme, which has been included in the RMP as an additional pharmacovigilance activity.

The proposed indication is for symptom relief of breathlessness in patients with severe chronic breathlessness, and with limited life expectancy. Given the palliative intent of the treatment, the risk of serious and/or distressing AEs (including a risk of early death) may be acceptable, although this must be determined by the individual patient in consultation with the treating specialist.

The sponsor has argued that, as morphine preparations are currently being used 'off-label' for the treatment of chronic refractory breathlessness, regulatory approval for Kapanol for the revised indication would actually contribute to the safer use of opioids in this setting. To support this, the sponsor notes that the PI and CMI will provide clear guidance on use, including the required level of medical supervision. Annex 10 of the updated RMP also lists proposed risk minimisation measures with these including an education program directed at potential prescribers.

Second round assessment of benefit-risk balance

Determining the benefit-risk balance for the proposed use is difficult. It appears likely that there will be some patients who will benefit from the proposed use, although predictors of response have not been identified. The potential for distressing adverse events is high but the risk of respiratory depression, with possible fatal outcome, appears to be low.

The evaluator is swayed in favour of MR morphine for the revised indication by the results of the meta-analyses, expert opinion, unmet need in the patient group and by the potential for greater safety of use due to the measures that would accompany regulatory approval.

⁶⁹ Rocker GM et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open* 2013. DOI:10.9778/cmajo.20120031

Second round benefit-risk assessment

The evaluator is of the opinion that the potential benefits outweigh the risks, given the safeguards that have been incorporated into the product documentation and the additional risk minimisation measures that have been adopted by the sponsor.

Second round recommendation regarding authorisation

The evaluator recommends that Kapanol be authorised for the indication of:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatment are not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

The evaluator recommends that the final result of the BEAMS study should be provided to the TGA to provide more conclusive evidence of safety and efficacy. It may be appropriate that the approval is conditional pending this.

The evaluator accepts that the RAPID programme will be acceptable as a post-approval surveillance study, although it is important to note that this study is only investigating use over a 3 month period.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted an Australian (AU) RMP version 1.0 (4 July 2017) in support of this application.

The proposed summary of safety concerns and their respective pharmacovigilance and risk minimisation measures are summarised below. The sponsor added 3 safety concerns and amended one safety concern in their response to the first round RMP evaluation (indicated by **bold text**).

Table 18: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A^
Important identified risks	Nausea and vomiting	Ü	Ü	Ü	
	Constipation	Ü	Ü	Ü	
	Drowsiness	Ü	Ü	Ü	
	Respiratory depression with potential fatal outcome*	Ü	Ü	Ü	

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A^
Important potential risks	Patients will be treated with morphine sulfate that do not require opioids for the treatment of pain	Ü	Ü	Ü	
	Administration of the Incorrect Dose	Ü	–	Ü	
	Rate of physical dependence/withdrawal might be higher in patients with chronic refractory breathlessness†	Ü	Ü	Ü	
Missing information	Extent of clinical database in intended treatment population†	Ü	Ü	Ü	
	Clinical data in patients with underlying causes of chronic refractory breathlessness that fall outside the treatment group defined in the Product Information†	Ü	Ü	Ü	

*Safety concern amended in AU RMP v1.1 in response to request from RMP evaluator. †Safety concerns added by the sponsor in AU RMP v1.1. ^As an additional risk minimisation activity, the sponsor has proposed to implement an education campaign targeted at specialists but has not specified which ongoing safety concerns this activity is directed at.

The sponsor has proposed routine pharmacovigilance for all safety concerns. Additional pharmacovigilance activities (RAPID Program and BEAMS study) are proposed for all safety concerns with the exception of 'Administration of incorrect dose'.

The sponsor has proposed routine risk minimisation for all safety concerns and proposes an additional risk minimisation activity, a healthcare professional information brochure, but has not described this in their RMP nor specified which safety concerns will be minimised by this activity.

New and outstanding recommendations

The recommendations made in the first round evaluation, along with consideration of the sponsor response is considered inadequate as there are outstanding issues with the safety specification, pharmacovigilance plan and risk minimisation plan (see recommendations below).

Safety specification

Recommendation 1: The sponsor should consider the recommendations made by the clinical evaluator regarding the safety specification. It is recommended that 'Confusion and delirium' is added to the summary of safety concerns. Any changes to the summary of safety concerns should be reflected in the RMP and be clearly marked as an important identified risk, important potential risk or missing information item.

Recommendation 2: The sponsor should describe the risk of 'Rate of physical dependence/withdrawal might be higher in patients with chronic refractory breathlessness' as 'Physical dependence/withdrawal.'

Recommendation 3: The sponsor should change the risk of 'Patients will be treated with morphine sulfate that do not require opioids for the treatment of pain' to 'Use in opioid-naïve patients'

Recommendation 4: The sponsor should revise their proposed items of missing information. 'Extent of clinical data in intended treatment population' to describe specific items of missing clinical data (for example, 'data on long term safety').

Similarly, 'Clinical data in patients with underlying causes of chronic refractory breathlessness that fall outside the treatment group defined in the Product Information' should be revised to specifically state which groups have missing information, e.g. 'Use in patients with chronic breathlessness due to underlying neurodegenerative disease, heart failure, interstitial lung disease, central hypoventilation syndrome or pulmonary hypertension'.

Recommendation 5: It is recommended that 'Use in patients with single nucleotide polymorphisms (SNP) in morphine metabolism', 'Use in paediatric patients' and 'Tolerance' are added as items of missing information.

Pharmacovigilance plan

Recommendation 6: The sponsor should describe in the RMP how each safety concern will be further characterised (including severity, frequency, and risk factors) and how missing information will be sought, making reference to the BEAMS study and RAPID Program where appropriate. The sponsor should state which studies are directed at which ongoing safety concerns and provide sufficient detail to describe how safety data will be collected, analysed and used to characterise these specific safety concerns.

Recommendation 7: The sponsor should provide further details of the RAPID Program in the RMP, including institutions involved, study drugs, objectives, methods, length of study and its ability to collect real world safety data for specific safety concerns that require further characterisation (see *Important potential risks* and *Missing information items*). The sponsor should also describe whether Kapanol used in accordance with the proposed PI will be included in RAPID, how long individual patients will be included in the study, whether safety data from RAPID will be continuously available to the sponsor for ongoing benefit-risk assessment, and/or if interim and final results of the studies will be reported, and when the data will be available.

Risk Minimisation Plan

Recommendation 8: In [Table 17 and 19 of] the AU RMP (v1.1) the sponsor should remove reference to the RAPID program as an additional risk minimisation activity as this study is considered to be part of the pharmacovigilance plan.

In Part V of the AU RMP, the sponsor should specify whether the proposed risk minimisation measures are directed at any of the ongoing safety concerns. Measures of effectiveness should also be described in this section. For example, the distribution of an educational brochure to inform specialists of the strict dosing instructions is proposed to minimise 'Administration of incorrect dose' and thus decrease the risk of fatal respiratory

depression. Mock-ups of proposed additional risk minimisation measures should be included in [Annex 11 of] the RMP and submitted to the TGA for review.

Recommendation 9: In regard to the proposed information brochure, the sponsor should consider whether other healthcare professionals, other than respiratory and palliative care specialists, involved in the management of chronic breathlessness (such as General Practitioners (GPs), pharmacists, nurses) should be a target of this activity.

Recommendation 10: It is recommended to the Delegate to include a PI statement which indicates that morphine may impair mental ability and increase the risk of medication error causing potentially fatal respiratory depression. This precautionary statement should also be included in an appropriate section of the CMI.

Recommendation 11: It is recommended to the Delegate that, in-line with the precautionary statement in the PI a statement is included in the CMI, which warns that opiate withdrawal symptoms have been reported in patients following two weeks treatment for chronic breathlessness.

Recommendation 12: In the CMI, the sponsor should make corrections to the 'What is Kapanol use for' section.

Recommendation 13: It is recommended to the Delegate that the CMI is included in the product packaging to ensure that all patients receive important information about the safe use of Kapanol.

Wording for conditions of registration

The current AU RMP (v1.1) is considered inadequate and therefore the wording for the condition of registration cannot be provided at this time.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

Morphine, when administered orally is subject to extensive but variable 'first pass' metabolism.

A single 50 mg oral dose of Kapanol in 30 healthy male subjects resulted in a mean peak plasma morphine concentration of 8.1 ng/mL at 8.5 h. Virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide (M-3-G) (about 50%) and morphine-6-glucuronide (M-6-G) (5 to 15%). Morphine-6-glucuronide has been shown to

be pharmacologically active. Morphine is excreted primarily in the urine as morphine-3-glucuronide and morphine-6-glucuronide.

Efficacy

Figures 5 to 9 describes the measures of breathlessness used in the clinical studies.

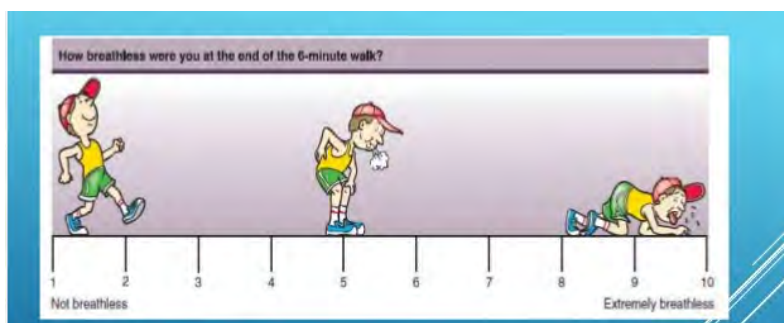
Figure 5: Modified Medical Research Council Dyspnoea Scale (mMRC)

0	"I only get breathless with strenuous exercise"
1	"I get short of breath when hurrying on the level or walking up a slight hill"
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"
4	"I am too breathless to leave the house" or "I am breathless when dressing"

Doherty DE et al. COPD: Consensus Recommendations for early diagnosis and treatment. Journal of Family Practice, Nov 2006

No established MCID for mMRC; useful to assess change in severity of dyspnoea over a period of time.

Figure 6: Visual Analogue Scale (VAS)



Accepted MCID is 10 to 20 units;⁷⁰ best suited to assess exertional dyspnoea; Not suited to assess change in severity of dyspnoea over a period of time.

Figure 7: Numerical rating scale (NRS)

On a scale from 0 to 10

Indicate how much shortness of breath you are having right now.

With 0 = no shortness of breath

And 10 = shortness of breath as bad as can be

Circle the number:

1 2 3 4 5 6 7 8 9 10

⁷⁰ Sponsor comment: The submission had an MCID of < 10 units for chronic (as opposed to acute) breathlessness.

Figure 8: The Australian-modified Karnofsky Performance Scale (AKPS) (Abernethy et al.)⁷¹

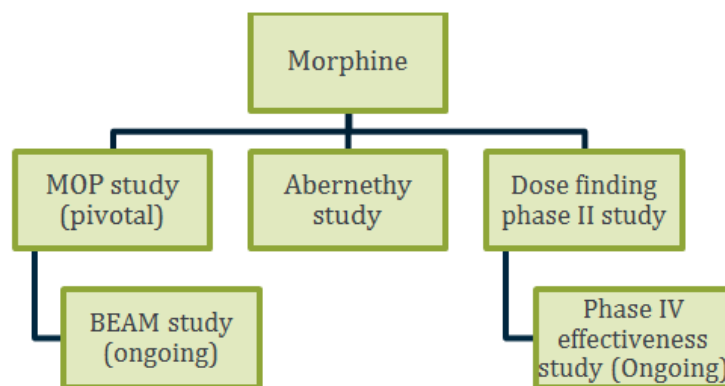
A measure of the patient's overall performance status or ability to perform their activities of daily living.

It is a single score between 10 and 100 assigned by a clinician based on observations of a patient's ability to perform common tasks relating to activity, work and self-care.

A score of 100 signifies normal physical abilities with no evidence of disease. Decreasing numbers indicate a reduced performance status.

The dossier contained a combination of clinical studies (detailed in Figure 9) and literature references.

Figure 9: Efficacy studies



Oral Morphine for Breathlessness (MOP) Study

Randomised, double-blind, multi-site parallel arm, placebo controlled trial to assess relief of refractory breathlessness comparing fixed doses of morphine and placebo over 7 days.

Primary objective

- To compare the efficacy for relieving the sensation of dyspnoea (intensity and unpleasantness), level of function, safety, and quality of life (QOL) of sustained release morphine with placebo among people with refractory breathlessness.

Inclusion criteria

- Refractory dyspnoea where the underlying cause has been maximally treated.
- Breathlessness of a level 2 or higher on the mMRC dyspnoea scale (the initial protocol included mMRC 3 and 4 but was expanded due to problems with recruitment).
- On stable medication for breathlessness over the prior week.
- Prognosis of at least 2 months.

Key exclusion criteria (note this would exclude many terminal patients)

- On regular or as needed opioid medications.
- Anaemia for which blood transfusion is indicated as a treatment for breathlessness within one month of baseline evaluation.
- Evidence of respiratory depression with resting respiratory rate < 8.

⁷¹ Abernethy, A.P., et al., The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care*, 2005. 4: 7

- Severely restricted performance status with Australia–modified Karnofsky Performance Status (AKPS) score of <40 at baseline.
- Uncontrolled nausea, vomiting and/or gastrointestinal obstruction.

Patient population

Sample size was determined based on SD of change of approximately 22 mm in VAS per group. A total sample of 235 would provide 80% power to detect a change of 8.1 mm (note this lies within the SD) between groups, with α of 0.05.

284 patients were randomised to double blind treatment. (76.6%) of the patients in morphine group and 120/139 (86.3%) of the patients in placebo group completed the study. Compared to placebo arm, a higher number of patients on morphine arm withdrew from the study (34 versus 19). Treatment failure was the commonest reason for withdrawal.

Baseline characteristics

Around 68% of patients across treatment arms were having mMRC dyspnoea score of ≥ 3 , thus 32% did not have severe breathlessness. Mean pulse oximetry was 92.6 and AKPS score of 60.85. 56% of patients had a diagnosis of COPD and the next common diagnosis was cancer (17.9%).

Primary efficacy endpoint

The study did not meet the primary efficacy endpoint. The least squares (LS) mean change in VAS from baseline to days 5 to 7 were comparable between morphine and placebo arms (Table 19) at -5 points. There were no significant differences in response, defined as a decrease from baseline in VAS Now (intensity) Breathlessness score of at least 15% ($p=0.701$).

Table19: Primary efficacy endpoint: Change in VAS breathlessness score in the MOP study

Change from Baseline to Days 5 to 7	Morphine 20 mg/day (N=145)	Placebo (N=139)
LS Mean (SE)	-5.52 (2.15)	-5.07 (2.10)
LS Mean Difference From Placebo (SE)	-0.45 (2.32)	
95% CI of difference	(-5.03, 4.12)	
p-value	0.845	

Secondary efficacy endpoints

Response rate

The definition of response was based on a clinically meaningful improvement being arbitrarily defined as a >15% decrease from baseline in the VAS score. Response rates were determined for VAS Now breathlessness score, VAS worst breathlessness score, VAS best breathlessness score, VAS average breathlessness score and VAS Now Breathlessness Score (unpleasantness). There were no statistically significant differences in response rates between morphine and placebo arms for the above outcomes measures.

Rescue medication use

Participants in each arm of the study were provided access to immediate release morphine and could take up to 8 doses of 2.5 mg on an 'as needed' basis in any 24 h period. Both groups used immediate relief morphine.

Patients in placebo arm required significantly greater number of rescue medications, when compared to those in morphine arm. However, the actual number of patients in each arm accessing rescue medication is not clear so it cannot be determined if the use of rescue medication was limited to a small number of participants.

The use of breakthrough morphine makes it very difficult to assess the efficacy of long acting morphine.

Table 20: Number of doses of rescue medication taken from Days 1 to 7 (ITT population)

	Morphine 20 mg/day (N=145)	Placebo (N=139)
Number of Rescue Medication Doses from Days 1 to 7		
LS Mean (SE)	0.88 (0.18)	1.44 (0.17)
LS Mean Difference From Placebo (SE)	-0.56 (0.19)	
95% CI for Difference	(-0.94, -0.19)	
P-value for Treatment Difference	0.003	
P-value for Day	0.001	
P-value for Treatment by Day Interaction	0.638	

Results are from a mixed model with repeated measures with the number of doses of rescue medication taken from days 1 to 7 as the dependent variable; stratification factors: centre, baseline dominant cause of dyspnoea, and the interaction between centre and baseline dominant cause of dyspnoea; factors: day, and treatment group; and interaction terms: treatment group by day.

mMRC scores

There was no significant difference in the average mMRC scores between the two treatment groups over time. In both groups, the mean mMRC score was 3.0 at baseline, and gradually reduced over time to Day 7, where the score was 2.6 in both groups.

Quality of life measures

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 15 (EORTC QLQ-15): The domain scores for overall quality of life, appetite loss, emotional functioning, pain, physical functioning, and insomnia, stayed approximately the same over time in both treatment groups. The morphine group had a higher mean constipation score change from baseline to at the end of treatment at 15.8, compared to 5.8 in the placebo group. The mean change in dyspnoea score was -8.6 in morphine arm, compared to -10.2 in placebo arm. Other quality of life measures such as life space score, carer's quality of life, global impression of change were comparable across morphine and placebo arms.

Sub group analysis

There was a trend toward greater efficacy in those with mMRC score 3 to 4.

Dose ranging study⁷²

This study comprised of both Phase II and Phase IV components and was an investigator initiated study funded by NHMRC.

A Phase II, open label, dose increment efficacy study was performed in opioid naïve patients, with subjective sensation of dyspnoea as outcome measure. The aim of this study was to define the minimum once daily dose of morphine for reducing refractory dyspnoea by 10%. The duration of dose titration to achieve this outcome was 3 weeks.

⁷² Currow, D.C., et al., Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*, 2011; 42: 388-399

Study design

Phase II was an open-label prospective study of once daily sustained release opioid (morphine 10 mg once daily as the initial dose and titrated weekly by 10 mg once daily in non-responders up to a maximum of 30 mg once daily). If at any weekly review the participant had a reduction of $\geq 10\%$ (based on 6.6 to 9.5 mm change in VAS in Abernethy study) over baseline in dyspnoea intensity without unacceptable side effects, they entered the long-term safety and effectiveness Phase IV study. Any unresolved significant side effects at any time, or a lack of response (AKPS falling below 30, a sudden increase in dyspnea, or participant death) by the end of the 3 week titration during the Phase II component of the study resulted in participant withdrawal.

Inclusion criteria

- Opioid naïve patients
- Dyspnoea score of 3 to 4 on mMRC scale
- > 50 score on Australian-modified Karnofsky Performance Scale (AKPS) (see appendix)
- Life expectancy > 1 month

Study treatment

10 mg daily of sustained release morphine, dose was increased by 10 mg up to a maximum of 30 mg/day. It has not been mentioned whether the patients were allowed short acting morphine/opioid for breakthrough pain or breathlessness.

Sample size

100 patients were recruited with an aim to generate 25 patient year data in the long-term effectiveness roll-over study.

Patient disposition

83 patients were recruited to the Phase II dose finding study. 31 (37%) patients withdrew due to various reasons. Lack of benefit at maximal dose (30 mg once daily) was the commonest cause (n = 8), followed by drowsiness (n = 4) and death (n = 4). 52 patients entered Phase IV effectiveness study.

Primary efficacy outcome in dose finding study

83 participants followed for 3 week duration or when they achieved > 10% reduction in VAS. The mean VAS score was observed 50.3 mm at baseline and 40.0 at the end of study. A 10% individual improvement in VAS score was defined as a positive response. Based on this, 63% (52 out of 83) of patients reported a positive response. The mean dose for sustained release morphine was 16.5 mg.

Table 21: Change in VAS score during the Phase II study

		VAS Intensity of Dyspnea at Baseline	Difference—First and Last Measured VAS in Phase II	Progress Through Study		
		Average Standard Deviation	Average Standard Deviation	Withdrew		
		Median Range	Median Range	Proceeded to Phase IV	Toxicity	Other Reason
MMRC Scale at baseline	3 (n = 20)	48.4 20.1 51.0 9–83	13.5 18.5 11.5 –32 to 46	15 (79%)	1	3
	4 (n = 63)	47.7 21.7 51.0 6–85	5.2 19.9 6.0 –46 to 61	37 (59%)	14	12
Dominant underlying cause of dyspnea (n, %), with MMRC 3 at baseline	COPD (n = 45; 25%)	50.0 22.6 58 7–83	8.7 16.6 11 –38 to 43	32 (71%)	7	6
	Cancer (n = 24; 24%)	44.2 22.1 48.5 6–85	4.2 19.3 5.8 –33 to 46	14 (58%)	4	6
	Interstitial lung disease (n = 10; 20%)	44.8 15.4 51.5 18–61	3.2 32.7 3.9 –46 to 61	4 (40%)	4	2
	Other causes ^a (n = 4; 25%)	53.3 9.4 56 40–62	17.7 15.7 19 0 to 33	3 (75%)	—	1

^aHeart failure:1; bronchiectasis: 1; pulmonary hypertension: 1; bronchiolitis obliterans organizing pneumonia: 1

The quality of life questionnaires showed a significant reduction in breathlessness and an increase in constipation.

Table 22: McGill quality of life questionnaire

Symptom	First-Ranked Symptom Concern	P-value ^a	Symptom of Concern Ranked in the Top Three	P-value
Breathlessness				
Baseline n = 83	74	<0.001	79	<0.001
Last recorded n = 81 ^b	39		55	
Constipation				
Baseline n = 83	0	<0.001	7	<0.001
Last recorded n = 79 ^b	12		25	

^aMcNemar Chi-squared test with continuity correction.

^bFour participants died during the initial titration for reasons unrelated to the study medication, and one person withdrew before taking any medication.

Long term effectiveness study

This study (n = 52) is still ongoing. At 3 months of the study, an interim analysis was performed. At the time of entry to this component of the study, the average dose of once-daily sustained release morphine was 14.0 mg (SD 6.3) and the average improvement in scores from their own baselines was 17.1 mm (SD 11.6). 69.2% had benefit at 10 mg,

23.1% at 20 mg, and 7.7% at 30 mg. No signals to suggest addiction or drug tolerance were reported. 13/52 patients withdrew due to adverse effects.

Table 23: Change in VAS score during Phase IV study

Characteristics at Beginning of Phase IV	Mean	SD	Median	Range
VAS as participants enter Phase IV study	34.4	17.2	37.8	1.8–70.5
Improvement (mm on VAS entering Phase IV study) from baseline	17.1	11.6	13.3	2.2–61.6
Individual percentage improvement over baseline entering Phase IV study ^a	35.2	21.3	30.1	10.1–85.7
Dose of sustained-release morphine (mg/24 h) entering Phase IV	14.0	6.3	10.0	10–30

Abernethy study

Study design

Eight day randomised double blind, placebo controlled crossover trial of sustained release morphine.

Inclusion criteria

Opioid naïve adults with dyspnoea at rest despite the optimal management of underlying cause.

Primary outcome

Sensation of dyspnoea measured on VAS on Days 4 and 8.

Secondary outcomes

These included:

- Exercise tolerance measured using mMRC
- Degree of sedation, overall feeling of wellness and quality of sleep measured using Brog scale
- Level of dyspnoea control.

Patient population

The sample size was calculated using a predicted standard deviation of the VAS of 16 mm. It was estimated that 48 participants would provide 80% power to detect a 10 mm difference in the scale, with an α -value of 0.05 and allowing for a 20% dropout rate.

Patient disposition

There were 10 (21%) participants who withdrew from the study: 5 during the morphine period and 5 during the placebo period.

Baseline characteristics

The mean age of the patient population was 76 years. Most of them had diagnosis of COPD (88%) and were on supplemental oxygen (71%). Other diagnosis were cancer (n = 3), motor neuron disease (n = 1) and restrictive lung disease (n = 2). The ECOG status was 2 or 3 for 69% of patients.

Study treatment

Patients were randomised to receive either 20 mg oral morphine sulphate with extended-release in the morning for four days, followed by four days of identically formulated placebo (or vice versa). Patients also received open label docusate sodium 50 mg and senna 8 mg and were permitted to take up to four daily.

Primary efficacy outcome

A difference of 9.5 mm and 6.6 mm in VAS scores (as a measure of sensation of dyspnoea) was observed in the evening and morning of each four day period during the study respectively. These differences were statistically significant but did not achieve MCID (10

to 20 mm.⁷³ (Note: a 4 day treatment period may not have been sufficient for this drug to reach steady state).

Table 24: VAS scores

	Dyspnoea*				
	Morphine (n=38)	Placebo (n=38)	Mean improvement in dyspnoea scores on morphine compared with placebo	95% CI of the mean improvement	P value (paired t test)
Morning	40.1 (24)	47.7 (26)	6.6 (15)	1.6 to 11.6	0.011
Evening	40.3 (23)	49.9 (24)	9.5 (19)	3.0 to 16.1	0.006

*Dyspnoea is measured on a 100 mm visual analogue scale (VAS), with zero as "no breathlessness" and 100 as "worst possible breathlessness."

Secondary efficacy outcomes

The number of patients who reported sleep disturbance due to breathlessness was lower in morphine arm (1 patient), when compared to placebo (8 patients). However, only a minority of study participants ever reported sleep disturbance during the study and hence the significance of this finding is only applicable to a minority of patients in this study.

Literature review

Literature review consisted of meta-analyses, systematic reviews and RCTs.

The three meta-analyses included RCTs that were blinded and placebo controlled. A variety of opiate types and routes were used. Only two studies within the meta-analysis examined modified release morphine. Most of the studies were < 5 days duration. Different scales of breathlessness were used. It was unclear what concomitant treatments were allowed.

A systematic review and meta-analysis conducted by Jennings et al.,⁷⁴ demonstrated a highly statistically significant effect of regular oral and parenteral opioids on the sensation of breathlessness (overall pooled effect size -0.31; 95% confidence interval (CI) -0.50 to -0.13; P = 0.0008). However, the clinical effect was relatively small (approximately 8 mm on a 100-mm VAS with baseline levels of dyspnoea of 50 mm). The pooled analysis by Ekström et al.,⁷⁵ showed a mean reduction in breathlessness by opioids by 0.32.

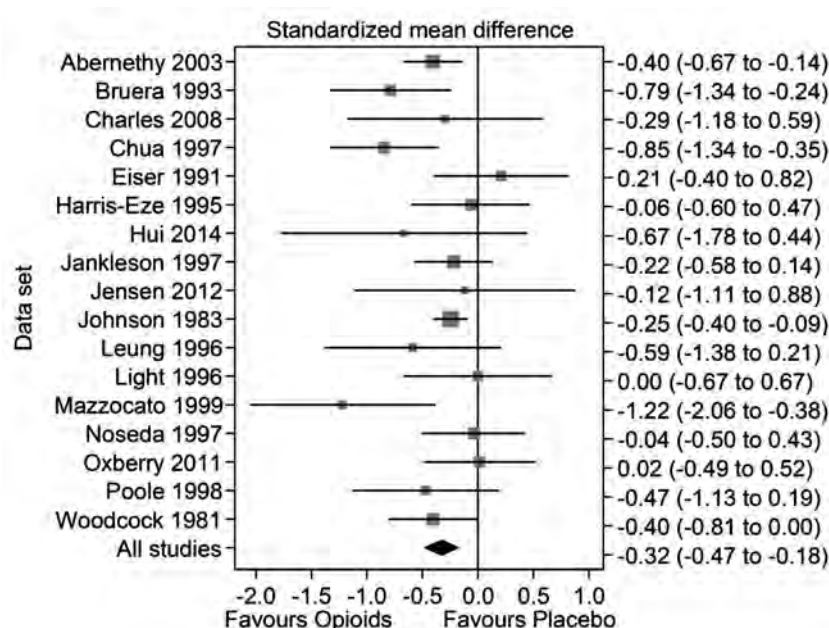
A Cochrane review by Barnes et al.,⁷⁶ included 26 studies (RCTs) with 526 participants. The primary outcome of most studies (11 RCTs, 159 participants) was the mean post-treatment dyspnoea score, which was 0.28 points better in the opioid group (ranging from 0.5 to 0.05 point reduction), compared to placebo group. Three studies utilised six-minute walk test. The change in baseline was 48 m worse in the opioids group (ranging from 36 m to 60 m). The adverse effects reported included drowsiness, nausea and vomiting, and constipation. The authors also identified important issues in the clinical studies which limit the interpretation including inconsistency in reporting outcome measures, risk of imprecise results due to the low number of participants in the included studies.

⁷³ Jones SE et al (2013). The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax*. 2013;68: 1015-1020

⁷⁴ Jennings, A.L., et al., A systematic review of the use of opioids in the management of dyspnoea. *Thorax*, 2002. 57: 939-44.

⁷⁵ Ekström, M., et al., Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc*, 2015. 12: 1079-1092.

⁷⁶ Barnes, H., et al., Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev*, 2016. 3: Cd011008.

Figure 7: Standardised mean difference across literature studies

A RCT by Poole et al.,⁷⁷ examined the effect of 10 to 40 mg of MR morphine over a 6 week period in 16 patients with COPD. Patients were enrolled if they had a FEV₁ of < 1.5 L, pO₂ > 65 mmHg, pCO₂ < 40 mmHg. At baseline, the mean daytime breathless score was 2.3 indicating some breathlessness on exertion. At the end of treatment, there was a non-significant improvement in quality of life measurement for dyspnoea and a significant decrease in score for mastery in the morphine group. The 6 minute walk test distance increased in the placebo group and decreased in the morphine group. There was no difference in the diary breathless scores.

Safety

In the MOP study, the mean patient exposure was 6.4 days. AEs, SAEs and TEAEs were comparable across treatment groups. The morphine group experienced more severe constipation, drowsiness, fatigue and vomiting than the placebo group.

Literature review

The most commonly reported events were nausea and vomiting, constipation and drowsiness. There was no significant increase in partial pressure of carbon dioxide (PaCO₂) or decrease in oxygen partial pressure. In the Cochrane review, participants were 4.7 times more likely to have nausea and vomiting, 3 times more likely to have constipation and 2.9 times more likely to have drowsiness.

Overall, the AEs and SAEs reported were in line with known safety profile of opioids. However, considering the uncertainty regarding the potential duration of treatment with morphine in this patient population, the duration of studies is not adequate to assess long term side effects.

No studies have reported opioid tolerance, dependence or withdrawal symptoms as AEs.

Clinical evaluator comments

At the first round evaluation, the evaluator documented concerns about the limited efficacy, potential safety issues. A number of changes to the indications, PI and RMP were recommended. Most of these recommendations were followed by the sponsor.

⁷⁷ Poole, P.J., et al. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998. 157: 1877-1880

After the second round evaluation, the clinical evaluator recommended approval. The clinical evaluator commented on the 'limited high quality evidence', unmet need in the proposed patient population in the last few weeks-months of life, consideration as to whether a lower level of evidence would be acceptable for palliative indications, and amendments to the PI which highlighted the conditions under which this should be prescribed and safety concerns.

Risk management plan

There was no existing EU RMP. The sponsor submitted an Australian RMP for this submission. This summary of safety concerns, pharmacovigilance and risk mitigation activities the sponsor has proposed is summarised in Table 18.

Additional pharmacovigilance activities include the RAPID program and BEAMS study.

Other considerations:

- Pack size: currently 28
- Schedule: S8
- Prescribers: no restriction

The RMP evaluator considered the revised RMP to be inadequate. The Delegate would agree with this.

Risk-benefit analysis

Delegate's considerations

Proposed indication

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatment not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

'Distressing breathlessness' can only be defined by a patient, and may relate to physical and psychological factors. The use of Kapanol did not lead to a reduction in VAS score for all patients, indicating either it was not effective or the scale was not an accurate measure of the symptom or effect of the drug. It is difficult to describe what Kapanol actually does to inform a patient what to expect from taking this medicine for symptoms.

Palliative care can mean different things to different people; some people may see this as an end of active treatment, whereas others may see it as improving symptoms and quality of life while still taking other treatments for the disease (such as bronchodilators, inhaled steroids, antibiotics, diuretics, oxygen and so on).

Most of the studies enrolled patients with COPD. In the pre-submission meeting and cover letter, the sponsor proposed treatment for severe COPD only.

Efficacy

The difficulty in performing a study in this setting is acknowledged. However, based on the data submitted, efficacy is not adequately established. The quality of studies was poor due to the small size, short duration, subjective and non-specific efficacy endpoints, and

possible confounders. A positive effect on subjective breathlessness was not consistently seen between studies or between the different ways to analyse this.

Although a symptomatic endpoint is appropriate for a palliative care setting where an endpoint needs to be a patient relevant, it is unclear if the improved sensation of 'breathlessness' is actually due to changes in respiratory drive or sensations or purely due to the relaxation/euphoria created by an opiate. It is important to be able to adequately inform patients about the benefits they are likely to receive from medication in order for them to participate in discussions about treatment.

The dose finding study and the Abernethy study were more supportive than the MOP study, perhaps as there was less confounding by the use of short acting opiates.

The literature review adequately performed but the quality of studies was poor. There was considerable heterogeneity (particularly in patient population, dose and formulation and route of opiate) in the meta-analysis which limits the interpretation of results. Like all literature based data, there are major gaps in the reporting of methodology and adverse effects. Many articles were written by co-sponsor. There is the potential for reporting bias.

Use of Kapanol versus other opiates

It is unclear why a long acting opiate would be a better choice than a short acting opiate. The palliative care guidelines do not specify the type of opiate to be used. The sponsor has proposed a benefit in once daily dosing; however compliance would not usually be an issue if a medicine is effective in achieving symptom control. There may be advantages in using a shorter acting agent for breathlessness. It is can be easier for a patient and physician to assess response to a short acting medication than a long acting one; it is also easier to titrate doses; and shorter acting medications are better for episodic symptoms. To the Delegate's knowledge, there has been no head to head study with short versus long acting opiates. It is noted that patients in the MOP study still took breakthrough short acting opiate. The medications used in the meta-analysis and systematic reviews were mainly short acting.

Safety

The short term AE profile of Kapanol is known. Common problems include sedation, itch, nausea, constipation. However, specific safety concerns related to this new indication have not been adequately addressed.

Tolerance to the analgesic, sedative, pruritic and respiratory depression effects may occur over time; thus increasing doses may be needed to maintain adequate pain control or respiratory depression.

End stage COPD is difficult to define. Thus, it is possible patients will be on this medicine for months to years if the indication is not well defined. This creates the potential for opiate dependence which has not been addressed. The use of opiates in older patients has been associated with falls and fractures, dizziness, delirium, somnolence, constipation, nausea and vomiting.

The risk of respiratory depression in patients with COPD described in the PI, however the studies submitted provide some evidence that this may not be the case. It is important to remember that AEs from a clinical trial setting may be different to the real world as patients are more closely monitored.

Complex issues in prescribing

Physicians using this medicine for this indication will need to have the skills and knowledge to have a discussion with the patient about the terminal phase of their disease and the balance between active treatment and palliation. This would also involve a discussion about death and how this would be managed. The proposed aim of treatment is

symptom reduction but patients will remain breathless. How will a physician describe the likely effects that this medicine will have for them?

Regulatory issues

- The TGA's role is to assess quality, safety and efficacy and 'other matters'.
- The TGA's role is not to regulate clinical practice
- The TGA's role is not to write clinical guidelines
- Although the TGA have a role in enabling access and timely availability of medicines, cost is not something we consider
- A literature based submission pathway was developed to enable sponsors to submit applications so that the use of a medicine is in line with clinical practice. However the palliative care guidelines used in Australia are not specific in relation to the type of opiate to use. Furthermore, it is unclear if the guidelines were based on clinical evidence or expert advice.

Impression

The Delegate recognises the suffering that some patients with end stage COPD may experience and the importance of symptom control. The Delegate would not prevent a physician from using off label morphine for this purpose. However, for the purposes of registration, the Delegate needs to be satisfied that quality, safety and efficacy have been adequately established for the proposed indication. There is not strong evidence to support efficacy. In addition there are significant long and short term safety issues that have not been adequately addressed.

The Delegate's impression at this stage is that the application should not be approved.

The main reason for this is the limitations in the evidence for efficacy.

However, if this decision were to create problems for patients with terminal breathlessness in a palliative care setting accessing opiates under appropriate supervision, then this decision could be reconsidered with tighter controls around the use of Kapanol in this setting. This would include:

- Use limited to patients where expected survival is < 1 year.
- Prescribing limited to palliative care physicians in the context of an end of life plan.
- Tools how to assist patients, carers and prescribers assess breathlessness.
- Separate CMI and PI for this indication so that the higher doses are not used for this indication.
- Submission of the BEAM study as a new application to the TGA for evidence of long term efficacy
- Submission of the RAPID study for pharmacovigilance.

Summary of issues

- The submission was a joint submission between the palliative care clinical trial collaboration and the sponsor. The sponsor has stated that the main reason for this submission is to support the PBS funding of sustained release morphine.
- The dossier consisted of three clinical studies and a literature review.
- The main efficacy outcome was a subjective measure of breathlessness.
- The pivotal studies had a number of limitations; in general failed to show significant benefit in the primary endpoint.

- COPD-X and other palliative care guidelines mention use of opiates (but not specifically long acting morphine) as an option for the management of refractory breathlessness.
- Although short term adverse effects of opiates are known, it is difficult to predict the adverse effect profile for this indication as the proposed duration of use and patient population is unclear. There is a potential risk of dependence in situations where life is prolonged beyond expectations and a potential risk of falls if ambulatory patients are commenced on treatment.
- It is difficult to predict when a patient may die, the assessment of breathless is complex in this setting, talking about and planning end of life issues is not a skill all doctors have the relationship between the palliative care consortium and pharmaceutical company is unclear. The lead investigator of the palliative care consortium, most of the clinical studies and author of most publications and guidelines is a consultant for the sponsor.

Questions for sponsor

1. Please explain the choice of a long acting opiate rather than a short acting opiate. Have there been any studies comparing long acting to short acting opiates?
2. Explain the rationale for dosing recommendations.
3. The PI has tables explaining how to swap different classes of opiates. Do the same recommendations apply when used for breathlessness?
4. Explain the data that BEAMS and RAPID studies will provide and how this may affect the assessment of efficacy/safety of this medication
5. In the pre-submission meeting the sponsor proposed use in Stage 3 and 4 COPD, however the sponsor is now including malignancy and other causes of breathlessness. Please justify the broadening of the indication to all causes of breathlessness.
6. Please describe how having Kapanol registered and PBS funding will affect the access of this medication to patients. What is the evidence that the current arrangements are not appropriate?

Proposed action

At this time, the Delegate was unsure if this application should be approved. The options are:

1. Reject.
2. Approve with restrictions around prescribing, further amendments to PI, CMI and RMP.

Request for Advisory Committee on Medicines (ACM) advice

1. Does the evidence submitted support efficacy of Kapanol for the treatment of refractory breathlessness?
2. Although not a regulatory requirement, is the relative efficacy of Kapanol compared to a short acting opiate an important consideration?
3. Should use be either defined by a patient (defined by severity of symptoms); or physician derived expected duration of life; or both?

4. Should prescribing be restricted to palliative care physicians or should GPs and respiratory specialists also be able to prescribe it? Do they have the skills and access to a trained team to enable safe use?
5. Is it appropriate for the PI for breathlessness where only the 10 and 20 mg strength tablet are suitable, to also include the 50 mg and 100 mg strength.

Response from sponsor

The first part of this response includes commentary from the sponsor regarding particular content in the Delegate's request for advice (*Overall conclusions and risk-benefit analysis* above). The second part provides a response to the Delegate's questions for sponsor.

Reaction to content

The submission was a joint submission between the palliative care clinical trial collaboration and Mayne Pharma. The sponsor has stated that the main reason for this submission is to support the PBS funding of sustained release morphine.

The sponsor wishes to clarify its position with respect to the rationale for this submission.

After receipt of sponsorship of Kapanol from GlaxoSmithKline in February 2013, the sponsor was approached for assistance with the Palliative Care Clinical Studies Collaborative's (PaCCSC) Kapanol chronic refractory breathlessness clinical program.

The sponsor has subsequently provided support to PaCCSC, specifically:

- some modest financial support to facilitate completion of the MOP study;
- in-kind support with the preparation of the Category 1 application;
- the payment of the TGA Category 1 application fee; and
- provision of study drug for the ongoing BEAMS Study.

However, the sponsor has no commercial interest in this program. The listing of the proposed new indication for Kapanol on the PBS will simply legitimise existing off-label use of Kapanol that is already significantly funded by the PBS and therefore the sponsor does not expect to generate any additional revenues from a successful TGA application and any expansion to the existing PBS listing of Kapanol.

It is important to note that PaCCSC was created for this specific situation: many medications and other interventions that are commonly used at the end-of-life to assist with managing or alleviating patients' symptoms have little or no evidence to support their use. This use is often off-label and not adequately captured on the PBS.

Pharmaceutical companies are generally not attracted to this area of clinical research because there are few, if any, commercial gains given that these medications are mostly off-patent. Through its independent research, PaCCSC can conduct such clinical research, however it requires the support of the therapeutic good's sponsor to submit the results of its work to the TGA.

Notably, this is the first of the PaCCSC programs to result in a submission to the TGA.

The relationship between the palliative care consortium and pharmaceutical company is unclear. The lead investigator of the palliative care consortium, most of the clinical studies and author of most publications and guidelines is a consultant for the sponsor.

In order to provide funds and study drug to PaCCSC while protecting the intellectual property of each party, the sponsor entered into a license and collaboration agreement with Flinders University. In addition, at the request of Flinders University, the sponsor engaged in a Consultancy Agreement for the provision of advisory activities beyond the responsibilities at PaCCSC, which included helping the sponsor assess the regulatory and

clinical strategy for Kapanol as a treatment of refractory breathlessness outside of Australia.

A literature based submission pathway was developed to enable sponsors to submit applications so that the use of a medicine is in line with clinical practice. However, the palliative care guidelines used in Australia are not specific in relation to the type of opiate to use. Furthermore, it is unclear if the guidelines were based on clinical evidence or expert advice.

The sponsor would need to defer to the clinical experts, however to its knowledge the guidelines are rigorously developed on the basis of available clinical evidence.

BEAM study be submitted as a new application for evidence of long term efficacy + RAPID study submitted as PV.

If this pending application was approved, the sponsor would be willing to provide in-kind support associated with submitting the BEAMS Study report and/or the RAPID study report to the TGA post-approval. However, the sponsor is not in a position to absorb any further TGA new application fees or other out-of-pocket costs associated with writing of the study reports and their submission. If further TGA fees or significant out-of-pocket costs were likely the sponsor would need to consider withdrawal of this application.

Response to questions for sponsor

Question 1

Please explain the choice of a long acting opiate rather than a short acting opiate. Have there been any studies comparing long acting to short acting opiates?

Sponsor's response

In considering the proposed dosing in the draft PI, it is informative to note that a dose of 20 mg/day of Kapanol equates to 3.3 mg of immediate-release morphine sulphate given every 4 h during a 24 h period. Put another way, it is less than the morphine equivalent daily dose that patients get from combination analgesics with codeine phosphate and paracetamol (acetaminophen). Combination analgesics like these are prescribed every day in primary care practice for a variety of aches and pains such as arthritic pain, by general family doctors. The Kapanol formulation was selected for this application due to its unique pharmacokinetic profile: it has a particularly low peak plasma concentration (C_{max}) and an extended-release profile that avoids the peaks and lows of other immediate and sustained release morphine sulphate dose forms.

The sponsor is not aware of any studies directly comparing the safety and efficacy of long versus short acting opiates in the treatment of chronic refractory breathlessness.

Question 2

Explain the rationale for dosing recommendations.

Sponsor's response

The dosing recommendations are based on the available clinical data package, which includes the results from the Abernethy study and of the MOP study, both of which were conducted with Kapanol.

Question 3

The PI has tables explaining how to swap different classes of opiates. Do the same recommendations apply when used for breathlessness?

Sponsor's response

No, those tables are for the treatment of pain only.

Question 4

Explain the data that BEAMS and RAPID studies will provide.

Sponsor's response

As presented by the sponsor in the updated RMP:

- The ongoing BEAMS Study is designed to add significantly to the extent of clinical data available in the patient group proposed for treatment in the PI. The BEAMS Study will collect data:
 - On any physical withdrawal from morphine if a person chooses to cease the medication with this being formally measured while still blinded at study withdrawal;
 - For a pooled analysis of single nucleotide polymorphisms (SNP) in morphine metabolism pathways and opioid receptors to determine if a putative SNP is a predictor of reduced symptomatic response to morphine for the symptomatic reduction of breathlessness;
 - On performance on a driving simulator which will add significantly to the evidence base to inform clinical practice. Participants in this sub-study (n=20) perform the same test at baseline and days two and seven; for an understanding of whether with clinical response, any symptom benefit increases further with dose increases;
 - On habitual physical activity using FitBitR monitoring. This will compare baseline to subsequent activity and be an important indicator as to whether people are more mobile when chronic breathlessness is better controlled; and
 - On long term blinded data (up to 29 weeks) for participants who continue into the extension phase. This sub-study will provide the most robust evidence of long term effectiveness including the ongoing benefits in symptom control.
- The RAPID program is a PaCCSC initiated program which currently captures immediate and short term benefits and harms as a medication is commenced. One medication or class is studied sequentially in six symptom nodes. RAPID will be studying opioids in the breathlessness node commencing in 2018. The issue of longer term dosing and outcomes is being considered by the research team currently, particularly search for rare but catastrophic outcomes.

Question 5

In the pre-submission meeting the sponsor proposed use in Stage 3 and 4 COPD, however the sponsor is now including malignancy and other causes of breathlessness. Please justify the broadening of the indication to all causes of breathlessness.

Sponsor's response

The proposed indications in the draft PI reflect the recommendations of PaCCSC based on its research and its interpretation of the available literature. In the October 2016 pre-submission meeting, PaCCSC and the sponsor acknowledged that: (i) the bulk of the available data, including from the MOP Study, is in patients with COPD, and (ii) the MOP Study results demonstrated the most significant clinical response in patients with an mMRC of 3 or 4.

Question 6

Please describe how having Kapanol registered and PBS funding will affect the access of this medication to patients. What is the evidence that the current arrangements are not appropriate?

Sponsor's response

The current approved PI and PBS listing for Kapanol is restricted to the treatment of pain. However, as discussed in the sponsor's Clinical Overview:

- Chronic breathlessness is common in patients with advanced disease, and it intensifies near death.^{48,53} Breathlessness affects close to 1 in 5 Australian people over the age of 65 years.⁷⁸
- The prevalence of breathlessness is high across all advanced and terminal diseases: cancer (16 to 77%), chronic heart failure (18 to 88%), renal disease (11 to 82%), and chronic obstructive pulmonary disease (56 to 98%).⁷⁹ During the last months of life, the prevalence of breathlessness increases from 50 to 65%.⁸⁰
- Symptomatic management, often including off-label use of oral morphine sulphate, is one of the few pharmacological options for patients with refractory dyspnoea and is recommended in symptom guidelines from several countries.^{30,81,82}

However, no medication is registered for the symptomatic reduction of chronic refractory breathlessness. Furthermore, the palliative care schedule of the PBS does not capture what is common practice.

The lack of TGA regulation of these practices, and the lack of a corresponding PBS listing, represents an unmet medical need, and from a risk management perspective, puts patients, their carer's and health care providers at risk.

Advisory Committee Considerations⁸³

The ACM taking into account the submitted evidence of efficacy, safety and context in which this medicine is to be used considered Kapanol Sustained release capsules containing 10 mg and 20 mg of morphine sulfate to have an overall positive benefit-risk profile for the proposed indication with amendments as follows:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with refractory dyspnoea. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatments are not effective. Treatment with Kapanol in this setting should only be initiated by a medical practitioner with expertise in palliative care.

The products are currently registered for the indication:

⁷⁸ Currow DC et al (2009). A Community Population Survey of Prevalence and Severity of Dyspnea in Adults. *J Pain Symp Manag* 2009; 38: 533-545

⁷⁹ Ekström PM. et al (2015). The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ* 2015;349:g7617

⁸⁰ Currow DC et al (2010). Do the Trajectories of Dyspnea Differ in Prevalence and Intensity By Diagnosis at the End of Life? A Consecutive Cohort Study. *J Pain Symp Manag* 2010; 38: 680-690

⁸¹ Mahler DA et al (2010). American College of Chest Physicians Consensus Statement on the Management of Dyspnea in Patients With Advanced Lung or Heart Disease. Consensus statement. *Chest* 2010;137: 674 – 691

⁸² Parshall MB et al (2012). An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012; 185:435-452.

⁸³ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Kapanol 10, 20, 50 and 100 mg are indicated for the relief of chronic pain unresponsive to non-narcotic analgesia.

In providing this advice the ACM noted the following:

- The application was made by the sponsor (Mayne Pharma) in association with the Palliative Care Clinical Trials Consortium.
- Refractory dyspnoea is a distressing condition. The problem is seen not only with COPD but also a number of other settings including heart failure and cancer.
- International clinical guidelines mention the use of opiates in the management of refractory breathlessness however this is usually a short acting opiate.
- The need for opiates was highlighted particularly in the end-of-life care planning. However, the usual practice would be to use a short acting opiate in this setting. The ACM recommended dose titration with a short acting opiate before initiating a long acting opiate. The importance of close monitoring of the patient in this setting was emphasised.
- Palliative care requires multidisciplinary care.
- Three clinical studies (MOP, Abernethy, and a Dose ranging study) were provided to support the application. These studies used a subjective measure of breathlessness known as the visual analogue scale (VAS) to measure dyspnoea. The MOP (pivotal) study and Abernethy study were of 7 days and 8 days of duration respectively.
- The MOP (pivotal) study demonstrated no significant difference for the primary endpoint benefit, but the outcomes are confounded by the provision of immediate release morphine to both treatment arms. The Abernethy study demonstrated a 9.5 and 6.6 mm improvement in VAS scores for dyspnoea reported in evening and morning respectively. These differences did not achieve Minimal Clinically Important Difference (MCID) for VAS scores of 10-20 mm. In the interim analysis at 3 months of the Phase IV long term effectiveness study (52 participants), 69.2% of patients achieved a benefit at 10 mg, 23.1% at 20 mg and 7.7% at 30 mg doses.
- The literature review provided limited support but the results are difficult to interpret due to the heterogeneity across the studies. Most of the studies used a different opiate, were of short duration and had a small sample size.
- The literature review showed that the most commonly reported adverse events were nausea and vomiting, constipations and drowsiness. There was no significant increase in partial pressure of carbon dioxide or decrease in partial pressure of oxygen.
- Adverse events are to be expected in the palliative care setting, and deemed acceptable provided there is clinical review, active management and treatment titration.
- None of the studies reported opioid tolerance, dependence or withdrawal symptoms as adverse events.
- The ACM acknowledged the challenges of conducting studies in the palliative care setting and considered that despite the limitations of the data, that there was sufficient evidence to support a role of Kapanol (10 and 20 mg) in the palliative care setting.

Proposed conditions of registration

The ACM advised that if Kapanol was to be registered for use in refractory breathlessness on this limited evidence, then more active ongoing pharmacovigilance and assessment of efficacy in a post market setting should occur.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI), noting its recommendations regarding the proposed indication and acceptability of the other forms of Kapanol (50 and 100 mg) to remain in the same PI.

The ACM also advised that consideration should be given to include stopping rules in the PI.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. Does the evidence submitted support efficacy of Kapanol for the treatment of refractory breathlessness?

The ACM noted that the data presented in the submission was not robust, but acknowledged the challenges of conducting studies in the palliative care setting and considered that the data provided weak support of efficacy. Overall, to improve patient access to care to reduce distressing breathlessness, the ACM was satisfied that there was sufficient evidence to support a role for Kapanol (10 and 20 mg) for refractory dyspnoea in the palliative care setting. Patient preparedness to tolerate any adverse reactions should also be considered.

2. Although not a regulatory requirement, is the relative efficacy of Kapanol compared to a short acting opiate an important consideration?

The ACM were of the view that although relative efficacy of Kapanol to a short acting opiate would be informative, it was not a critical consideration from a regulatory perspective. The ACM noted that the advantages of a longer duration of effect and decreasing pill-burden may be addressed by the sustained release formulation.

3. Should use be defined by a patient defined severity of symptoms or physician derived expected duration of life or both?

The ACM considered that patient-defined severity of symptoms and physician derived expected duration of life were both important components of shared decision-making in the palliative care setting.

4. Should prescribing be restricted to palliative care physicians or should GPs and respiratory specialists also be able to prescribe it? Do they have the skills and access to a trained team to enable safe use?

The ACM advised that prescribing should not be restricted to narrow specialist groups. Instead it should be specified that the medicine should only be initiated by medical practitioners with expertise in palliative care. The ACM advised that management should occur in a multidisciplinary setting.

5. Is it appropriate for the PI for breathlessness where only the 10 and 20 mg strength tablet are suitable, to also include the 50 mg and 100 mg strength

The ACM were of the view that this could be addressed in the Dosage and Administration section of the PI.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Kapanol morphine sulphate pentahydrate 10 mg and 20 mg modified release capsules for the proposed indication:

Kapanol 10 and 20 mg are indicated for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause. Kapanol should only be used after treatments for the underlying cause(s) of the breathlessness have been optimised and non-pharmacological treatments are not effective. Treatment with Kapanol in this setting should only be initiated by a specialist knowledgeable in its use.

The reasons for Delegate's decisions

Under section 25 of the Therapeutic Goods Act 1989,

(1) If an application is made for the registration of therapeutic goods in relation to a person in accordance with section 23, the Secretary (or delegate) must evaluate the goods for registration having regard to:

(d) whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established; and

(k) such other matters (if any) as the Secretary considers relevant

The Delegate acknowledges that the outcomes of efficacy and safety relevant in a palliative care setting are different to those of medicines intended for active treatment. In particular, in a palliative care setting the emphasis needs to be on the reduction of suffering and improvements in quality of life. However, the legal framework under which decisions are made under the Therapeutic Goods Act is the same regardless of the indication. The Delegate does not believe it is appropriate to use lower standards of evidence to support an indication for palliative care.

The main reason for this decision is that the Delegate is not satisfied that there is sufficient evidence provided in support of efficacy for the proposed indication. The pivotal clinical study the MOP study failed at the primary efficacy endpoint for breathlessness. This negative finding may have been due to the use of breakthrough short acting opiates which minimised any true treatment effect. The clinical significance of the small improvement in VAS for quality of life measurement for breathlessness in the Abernethy study and dose ranging study is difficult to assess as this was not associated with an overall improvement in quality of life or physician related breathlessness. The high dropout rate of the studies due to lack of efficacy and adverse effects is noted and may skew the results. The results of the meta-analysis and Cochrane reviews are of limited utility as most of the studies included in them used short acting opiates for short periods. The decrease in exercise tolerance is concerning. The clinical trials submitted have been open label or placebo controlled; there are no clinical trials against short acting opiates, which appears to be the treatment of choice in the clinical practice guidelines.

Safety data was limited in duration of study and the range of outcomes. There was inadequate assessment of the impact on falls, confusion, and hospitalisation. These have been documented to occur in elderly patients prescribed opiates for other indications, and are equally relevant for this indication; particularly as the proposed indication is broad and may include ambulant patients receiving treatment for months. The clinical studies submitted were most relevant to use for < 7 days, there was very limited evidence of use over a period of months.

The Delegate is aware that clinical trials in the context of palliative care are difficult, and that the sponsor has made a number of constructive amendments to the indications, PI, CMI, and RMP in the course of the evaluation. However, these changes do not mitigate the very limited efficacy and safety data to support this application. The BEAMS study may provide more long term evidence for the use of Kapanol at doses of 8 to 32 mg over 29 weeks; however the results will not be available until 2019. Thus a 'stop clock' [on this application] would not be practical. The RAPID study may also be able to provide some post market information around efficacy and safety in real world use.

The Delegate respects the aim of this submission which was to improve the palliative care of patients with refractory breathlessness. There are no other products on the ARTG for this indication, and the sponsor has suggested that there is an unmet need. The Delegate considers the extension of indication of a currently registered and marketed medicine to be a small component of a larger project to improve the palliative care of patients with breathlessness. Of more importance is expanding access of patients to palliative care services, training GPs in palliative care, developing multi-disciplinary teams, developing guidelines, educating carers and health professionals about how to recognise breathlessness, evaluate and treat possible underlying causes, and discuss palliative options. The Delegate is concerned that the registration of Kapanol for this indication may have negative consequences as its listing on the ARTG could be viewed as it having robust level of efficacy and safety for this indication. The availability of opiates for pain relief has recently been restricted due to concerns of inappropriate use. The same concerns would be present for this indication.

The Delegate disagrees with the clinical evaluator and ACM that the risk mitigation strategies proposed are acceptable to overcome the significant safety concerns. Information in the PI and CMI is important, but has limitations. The PI is not a substitute to ensuring prescribing practitioners have adequate training and skills in this area. The PI is an information document in relation to a medicine, not a symptom or disease. Patients prescribed medicines in this setting are unwell, and are likely to have limited ability to understand written information. This information may also be needed to be provided in other forms such as videos or face to face. Carers will also need training in recognising and responding to breathlessness and other complications of opiate use, as well as how to store and dispose medications safely.

The Delegate considers that assessing the risks and benefits of the registration of a therapeutic good at a population level to be different to assessing the same risks and benefits at a patient level. There will be therapeutic goods registered for an indication that may not be suitable for a patient. And there will be goods where there is no ARTG entry which may be efficacious and appropriate for an individual patient. There are mechanisms other than registration of therapeutic goods (such as special access, authorised prescriber or off label prescribing) to enable patients to have access to medicines where there is an unacceptable risk/benefit balance at a population level but acceptable benefit/risk at an individual level.

This decision is a reviewable initial decision under section 60 of the Act. Under section 60 of the Therapeutics Goods Act, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the

goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

For clarity, the original application (PM-2017-01592-1-5) relates to two products included in the ARTG: Kapanol 10 mg (ARTG number 68439) and Kapanol 20 mg (ARTG number 48134). The applications for an extension of indications with respect to both products were collectively provided in the one submission and consequently dealt with in the one initial decision. For consistency, this notice of decision reflects my reconsideration of the initial decision as it applied to the products

Result of the Delegate of the Minister for Health reconsideration of the initial decision

The Delegate of the Minister for Health has decided to revoke the initial decision and make a new decision in substitution for that decision.

The substituted decision is to register Kapanol (morphine sulphate pentahydrate, 10 mg and 20 mg extended-release capsules) for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause on the basis that the Delegate of the Minister for Health was satisfied that there is sufficient evidence of efficacy and safety of low dose, extended release morphine in the palliative care setting to support an extension of the registered indications. In making this decision, the Delegate of the Minister for Health has given particular weight to the recommendations of the ACM read in conjunction with the three additional studies that were provided as part of the applicant's request for reconsideration.

Reasons

In making this decision the Delegate of the Minister for Health reviewed the 3 primary studies provided by the applicant in the initial application in support of efficacy and safety of Kapanol for the proposed extension of indication. The Delegate of the Minister for Health have also considered the 3 additional studies included in the request for reconsideration of the initial decision, the minutes of ACM as they relate to this matter and the initial decision of the Delegate.

The Delegate of the Minister for Health notes particularly that the systematic review and meta-analysis by Verberkt et al.⁸⁴ provides reassurance with respect to safety. The Delegate of the Minister for Health was persuaded by the results of the dose ranging study by Currow et al.⁸⁵ that the majority of patients in a palliative care setting would use a low dose of Kapanol for the proposed extension of indication. The Delegate of the Minister for Health further noted that the application for reconsideration seeks to cap prescribing of extended-release morphine for the proposed extension of indication to 30 mg/24 hours (a low total dose) accepts the argument of the applicant that 'off-label' prescribing of opiates for the proposed extension of indication is common practice, and that registration of Kapanol would provide financial and risk mitigation benefits to patients. The Delegate of the Minister for Health also accepts the recommendation of the ACM that the clinical context of the proposed extension of indication be considered. The Delegate of the Minister for Health was satisfied with the applicant's changes to the RMP.

Accordingly, the Delegate of the Minister for Health is persuaded that sufficient evidence of efficacy and safety in a palliative care setting exists to support registration of Kapanol for the restricted extension of indication proposed.

⁸⁴ Verberkt CA et al (2016). A randomized controlled trial on the benefits and respiratory adverse effects of morphine for refractory dyspnea in patients with COPD: Protocol of the MORDYC study. *Contemporary clinical trials* 2016; 47: 228-234

⁸⁵ Currow DA et al (2011). Once-Daily Opioids for Chronic Dyspnea: A Dose Increment and Pharmacovigilance Study. *Journal of Pain and Symptom Management* 2011; 42: 388-399.

Conclusion

For the reasons referred to above, the Delegate of the Minister for Health have decided to revoke the initial decision and make a new decision in substitution for that decision. The substituted decision is to register Kapanol (morphine sulphate pentahydrate, 10 mg and 20 mg extended-release capsules) for the symptomatic reduction of chronic breathlessness in the palliative care of patients with distressing breathlessness due to severe COPD, cardiac failure, malignancy or other cause on the basis that the Delegate of the Minister for Health was satisfied that there is sufficient evidence of efficacy and safety of low-dose, extended-release morphine in the palliative care setting to support an extension of the registered indications.

Consistent with section 60(3C) (b) of the Act, the Delegate of the Minister for Health determine that this decision takes effect on and from the date of this notice.

Specific conditions of registration applying to these goods

The KAPANOL Australian Risk Management Plan, version 1.2, dated 5 December 2018 (data lock point 4 July 2017), included following the approval of submission PM-2017-01592-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Kapanol approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

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