AUSTRALIAN PRODUCT INFORMATION

KAPANOL® (MORPHINE SULFATE PENTAHYDRATE) CAPSULES

1. NAME OF THE MEDICINE

Morphine Sulfate Pentahydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kapanol capsules 10, 20, 50 and 100 mg contain identical polymer-coated sustained-release pellets of morphine sulfate pentahydrate for oral administration.

For the full list of excipients see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Modified release capsule.

Each capsule contains creamy-white to light tan spheroidal pellets.

- 10 mg morphine sulfate pentahydrate

  Size 4 capsule, clear cap imprinted with K10, and clear body imprinted with one black band.

- 20 mg morphine sulfate pentahydrate

  Size 4 capsule, clear cap imprinted with K20, and clear body imprinted with two black bands.

- 50 mg morphine sulfate pentahydrate

  Size 2 capsule, clear cap imprinted with K50, and clear body imprinted with three black bands.

- 100 mg morphine sulfate pentahydrate

  Size 0 capsule, clear cap imprinted with K100, and clear body imprinted with four black bands.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

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.

4.2. Dose and Method of Administration

The sustained-release nature of Kapanol capsules allows for administration on a once daily (every 24 hours) or twice daily (every 12 hours) dosing interval.

Kapanol is not bioequivalent to other controlled-release morphine preparations.

THE INDIVIDUAL PELLETS IN KAPANOL CAPSULES MUST NOT BE CHEWED OR CRUSHED.

Symptom Reduction of Chronic Pain

The use of opioid analgesics for the relief of chronic pain, including cancer pain, and chronic breathlessness should be only part of a complete approach to pain control which should include other types of treatment or drug therapy, non-drug measures and psychosocial support. Kapanol should be used for the long-term treatment of chronic moderate to severe pain only after the pain has been proven to be alleviated by a trial of shorter-acting opioids or Kapanol.

Selection of the initial dose of Kapanol should take into account the following:

i. the total daily dose, potency and characteristics of previous opioid analgesics (e.g. pure agonists or mixed agonist/antagonist.)

ii. the reliability of the relative potency estimate used to calculate the dose of morphine required (potency estimates vary with the route of administration.)

iii. the degree of opioid tolerance

iv. the patient's general medical condition

v. concurrent medications

vi. type and severity of pain

The usual starting dose in opioid naive patients is Kapanol capsules 40 mg every 24 hours or 20 mg every 12 hours. The first dose of Kapanol may be taken with the last dose of any immediate-release opioid medication.

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, 'breakthrough pain' occurs, a supplemental dose of a short acting analgesic may be given. The dosing interval of Kapanol should not be reduced below every 12 hours. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief and opioid side effects.

Because of the sustained-release properties of Kapanol, dosage increases should generally be separated by 24 hours.

Symptom Reduction of Chronic Breathlessness

Treatment should be initiated by a specialist knowledgeable in the use of potent opioids for the management of chronic breathlessness. The use of Kapanol for the reduction of chronic breathlessness should be only part of a complete approach to symptom control which should include non-drug measures and psychosocial support.

Kapanol should be commenced at 10 mg once daily in opioid naïve patients. During initiation and up-titration, patients should be reviewed on a weekly basis and breathlessness evaluated using a validated tool such as a numerical rating scale (NRS). If a satisfactory clinical response (e.g., a one point reduction or greater in *worst breathlessness* in the previous 24 hours on the 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 next 7 days is suggested. The dose should be back-titrated if adverse effects become troublesome. Dosing can be once or twice daily but the maximum recommended dose for chronic breathlessness is 30 mg daily.

Initial prescription should be limited to a one week supply; when an effective dose has been determined, a one month supply should be prescribed. Prophylactic treatment for constipation should be commenced simultaneously and considered for nausea and vomiting depending on the patient's past experience with opioids.

Unlike chronic pain, immediate release oral morphine solution should NOT be co-prescribed with Kapanol when Kapanol is prescribed for the reduction of chronic breathlessness.

Kapanol should not be used for acute nor acute-on-chronic breathlessness.

Kapanol should be used with caution in settings where renal function may change unpredictably or rapidly.

Method of Administration

It is preferable for Kapanol capsules to be **swallowed whole.** However, if the capsules cannot be swallowed whole they may be administered in one of the following ways:

- The pellets may be mixed into approximately 30 mL of water in a glass and taken within 30 minutes of mixing without chewing or crushing the pellets. As some of the pellets may stick to the sides of the glass, a further 30 mL of water should be added, the glass swirled and all the remaining pellets taken with the water. This procedure can also be performed using orange juice or milk.
- The pellets may be sprinkled onto a small amount of soft food (such as yoghurt, custard, ice-cream, apple sauce or jam) and taken within 30 minutes of sprinkling. The pellets must not be chewed or crushed and the mouth should be rinsed to ensure that all pellets have been swallowed.
- The pellets may be administered through a 16 French gastrostomy tube:
  - Flush the gastrostomy tube with water to ensure that it is wet
  - Sprinkle the Kapanol pellets into 10 mL of water

- Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel
- Rinse the beaker with a further 10 mL of water and pour this into the funnel
- Repeat rinsing until no pellets remain in the beaker.

The administration of Kapanol pellets through a nasogastric tube should not be attempted.

Dose Conversion for Use in Chronic Pain

For patients currently receiving opioids, the following dosing recommendations should be considered.

Conversion from Other Oral Morphine Formulations to Kapanol for Use in Chronic Pain

Patients on other oral morphine formulations may be converted to Kapanol by administering one half of the patient's total daily morphine dose as Kapanol capsules on an every 12 hours dosing regimen or the patient's total daily morphine dose as Kapanol capsules on an every 24 hours dosing regimen. Dose is then adjusted as needed.

Conversion from Parenteral Morphine or other Parenteral or Oral Opioids to Kapanol for Use in Chronic Pain

Kapanol can be administered as the initial oral morphine drug product. However, in this case, particular care must be exercised in the conversion process. Because of uncertainty about and inter-subject variation in relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative, that is, an underestimation of the 24 hour oral morphine requirement is preferred to an overestimate. To this end, initial individual doses of Kapanol should be estimated conservatively.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition.

Consequently, it is difficult to recommend any fixed rule for converting a patient to Kapanol directly. The following general points should be considered:

Parenteral to oral morphine ratio: Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other parenteral or oral opioids to oral morphine: Because there are no data on these types of analgesic substitutions, specific recommendations are not possible. Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate (see Table 1). In general, it is safer to underestimate the daily dose of Kapanol required and rely upon ad hoc supplementation to deal with inadequate analgesia.

Table 1: Approximate oral opioid potency ratios relative to oral morphine*

pethidine	1/8	methadone	3-4[1]
papaveretum	2/3	morphine	1
oxycodone	1	dextromoramide	2[2]

[1] Methadone: a single 5 mg dose is equivalent to morphine 7.5 mg. It has a prolonged plasma half-life, which leads to cumulation when given repeatedly. This means that when given regularly it is several times more potent.

[2] Dextromoramide: a single 5 mg dose is equivalent to morphine 15 mg in terms of peak effect but is shorter acting. The overall potency ratio has been adjusted accordingly.

* Adapted from Twycross and Lack, (1989). Oral morphine in advanced cancer. 2nd ed. Beaconsfield.

Conversion from Kapanol to other Controlled-Release Oral Morphine Formulations for Use in Chronic Pain

Although for a given dose the same amount of morphine is available from Kapanol as from morphine solution or controlled-release morphine tablets (i.e. AUC is the same), Kapanol results in reduced fluctuation in dose adjusted plasma morphine levels. Conversion from Kapanol to the same daily dose of other morphine preparations may lead to an initial change in the clinical status of the patient and close observation is recommended.

Conversion from Kapanol to Parenteral Morphine for Use in Chronic Pain

Based on single dose studies, 10 mg parenteral morphine is equipotent to 60 mg oral morphine. However, in chronic use this ratio may not apply and the ratio of 10 mg parenteral morphine to 30 mg oral morphine may be more appropriate. When converting from Kapanol to parenteral morphine, it is best to assume that the parenteral to oral potency is high and estimate the parenteral morphine dose per 24 hours based on the 1:6 ratio (Parenteral: Oral). The frequency of administration depends on the site and method of the parenteral administration. The dose should be adjusted based on the patient's clinical response.

Opioid analgesic agents do not effectively relieve dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This does not mean that patients suffering these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be referred early on for other types of pain therapy. Pain without nociception is usually not opioid-responsive.

Information for Patients

All Patients

A Consumer Medicine Information leaflet for Kapanol is available from your pharmacist. Medical practitioners should be familiar with the contents of this leaflet. If clinically advisable, patients receiving Kapanol should be given the following instructions by the medical practitioner.

1. The use of Kapanol should be determined by consultation with a medical practitioner.
2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery).

3. Morphine should not be taken with alcohol or other CNS depressants (sleeping medications, tranquillisers) because additive effects including CNS depression may occur. A medical practitioner should be consulted if other prescription medications are currently being used or are prescribed for future use.
4. Morphine sustained-release capsules should NOT be co-administered with alcohol
5. For women of childbearing potential who become or are planning to become pregnant, a medical practitioner should be consulted regarding analgesics and other drug use.
6. **The pellets in Kapanol capsules must NOT be chewed or crushed as this may destroy their sustained-release properties.**

For Palliative Use in Chronic Breathlessness

Kapanol should only be commenced after a careful discussion of the risks and possible benefits of its use with the patient, and carer(s) where possible. The following additional information should be provided:

1. Kapanol will be trialled to see if it reduces the intensity of breathlessness.
2. A low dose of Kapanol will be started. Any increase in this dose will only occur in consultation with the prescribing medical practitioner and after consideration of therapeutic response and occurrence of adverse effects.
3. Kapanol may cause nausea, vomiting, constipation, drowsiness and confusion. Laxatives will be commenced at the same time to proactively manage constipation.
4. Kapanol may cause respiratory depression that has been associated with fatal outcome. This risk is increased if Kapanol is taken with alcohol or benzodiazepines or if the pellets in the Kapanol capsules are chewed or crushed.

4.3. Contraindications

Kapanol should not be given to patients with: known hypersensitivity to morphine, morphine salts or any of the capsule components; acute or severe bronchial asthma; respiratory depression; biliary colic, cardiac arrhythmias, gastrointestinal obstruction, particularly paralytic ileus; concurrent MAO inhibitors or within 14 days of such therapy (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Kapanol should not be given to patients who have a prior history of drug abuse.

4.4. Special Warnings and Precautions for Use

Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.

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.

Impaired Respiration when Treating Chronic Pain

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.

Impaired Respiration when Treating Chronic Breathlessness

Reported use of Kapanol carefully titrated at doses up to 30 mg/day in people with severe COPD did not result in episodes of respiratory depression (see Section 5.1 Pharmacodynamic Properties - Clinical Trials). However, observational studies have reported an increased risk of death with opioids in patients with severe COPD. Patients should be advised of this risk

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurological signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme caution.

Hypotensive Effect

Kapanol, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anaesthetics (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). Kapanol may produce orthostatic hypotension in ambulatory patients.

Kapanol, like all opioid analgesics, should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Gastrointestinal Motility

Kapanol should not be given to patients with gastrointestinal obstruction particularly paralytic ileus as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored.

As with any other oral dose morphine formulation, diarrhoea may reduce morphine absorption.

CNS Depressants

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.

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 physical withdrawal symptoms. If withdrawal is necessary it should if possible be undertaken gradually.

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.

Infants born to mothers who are physically dependent on opioid analgesics may also be physically dependent and may exhibit withdrawal symptoms. These infants may have respiratory depression at birth (see Section 4.4 Special Warnings and Precautions for Use).

Tolerance

As with other morphine preparations, tolerance may develop upon repeated administration of Kapanol. The dose of Kapanol may need to be increased to maintain adequate pain relief (see Section 4.2 Dose and Method of Administration).

Tolerance has not been reported when regular, low dose Kapanol is used to reduce chronic breathlessness.

General Precautions

Kapanol is intended for use in patients who require more than several days continuous treatment with a potent opioid.

As with any potent opioid, it is critical to adjust the dosing regimen of Kapanol for each patient individually, taking into account the patient's prior treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of Kapanol, attention should be given to the points listed under Section 4.2 Dose and Method of Administration.

Use in Chronic, Non-cancer Pain

The use of Kapanol for the relief of chronic pain which is not due to cancer should be restricted to situations where:

- all other more conservative methods of analgesia (i.e. non-opioid) have failed, and
- the pain is having a significant impact on the patient’s quality of life, and
- there is no psychiatric contraindication or history of drug abuse.

Prior to long-term prescription, a trial of Kapanol or shorter acting opioid should be undertaken. Long-term administration of Kapanol should only be considered if this trial shows the pain is opioid responsive. Long-term therapy is generally considered inappropriate for opioid naïve patients who require rapid dose escalation with no concomitant pain relief during the trial period.

The prescription and monitoring of the patient's opioid use should be the responsibility of one doctor only.

The prescriber should consult appropriate clinical guidelines on the use of opioid analgesics in patients with chronic, non-cancer pain.

Palliative Use in Chronic Breathlessness

The use of Kapanol for the reduction of chronic breathlessness should be restricted to situations where:

- the approved treatments for the underlying cause(s) of the breathlessness and non-pharmacological measures are not effective, and
- review by a respiratory, palliative care or other appropriate specialist has confirmed that treatment of the underlying cause(s) is optimal, and
- the breathlessness is having a significant impact on the patient's quality of life, and the patient has been informed of the potential risks, and
- there is no psychiatric contraindication or history of drug abuse

The prescriber should be knowledgeable in the use of Kapanol for this indication and should consult appropriate clinical guidelines on the use of opioids for the symptomatic reduction of chronic breathlessness in palliative care. The prescription and monitoring of the patient's opioid use should be the responsibility of one doctor only.

Cordotomy

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly decrease, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive Kapanol within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, can be managed with immediate-release morphine preparations.

Post-operatively

Kapanol should not be used in the first 24 hours following surgery, and should be administered with caution thereafter, especially following abdominal surgery.

Special Risk Groups

Kapanol should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxoedema; hypothyroidism; prostatic hypertrophy or urethral stricture.

Caution should also be exercised in the administration of Kapanol to patients with CNS depression; toxic psychosis; acute alcoholism or delirium tremens; severe kyphoscoliosis; convulsive disorders; about to undergo biliary surgery and patients with acute pancreatitis secondary to biliary tract disease.

Use in the Elderly

See Section 4.4 Special Warnings and Precautions For Use – Special Risk Groups.

Paediatric Use

The use of Kapanol in children has not been evaluated.

Effects on Laboratory Tests

No data available.

4.5. Interactions with Other Medicines and Other Forms of Interactions

CNS Depressants

Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including sedatives, benzodiazepines, hypnotics, general anaesthetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Muscle Relaxants

Morphine may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics

From a theoretical perspective, mixed agonist/antagonist opioid analgesics (e.g. pentazocine and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between the new selective MAOIs (e.g. moclobemide, selegiline) and morphine therefore caution is advised with this drug combination.

Cimetidine

There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine. Although not reported with Kapanol, caution is advised when administering Kapanol with cimetidine.

Diuretics

Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism. As Kapanol contains morphine it has the potential to cause similar effects.

Alcohol

In vitro data have shown that the presence of alcohol leads to an increased rate of release of morphine from the sustained-release pellets in the capsule.

Patients should be advised against co-administration of morphine sustained-release capsules with alcohol as this may lead to a rapid release and absorption of a potentially toxic dose of morphine.

Food

The bioavailability of Kapanol is not significantly affected by food.

St John's Wort

In vitro data suggest that St John's Wort *(Hypericum perforatum)* may induce cytochrome P450 3A4. There is a theoretical possibility therefore, that plasma levels of morphine sulfate pentahydrate may be decreased during concomitant administration and increased upon withdrawal of St John's Wort.

4.6. Fertility, Pregnancy and Lactation

Effects on Fertility

Conventional animal reproduction studies have not been performed using morphine. However, there is evidence of reproductive toxicity in animals from other studies (see Use in Pregnancy). It is not known whether morphine can cause foetal damage when administered throughout pregnancy or if it can affect reproductive capacity in humans.

Use in Pregnancy

Category C.

Treatment of laboratory animals with high doses of morphine during pregnancy has been associated with foetal and neonatal death, foetal growth retardation, exencephaly, skeletal effects, and alterations in behaviour and CNS development in offspring. Some of these findings were attributed to the hypoxic effects of large doses of morphine.

Pregnant women should only be given Kapanol when the benefits clearly outweigh potential risks to the foetus.

Kapanol is not recommended for use in women during and immediately before labour. The effects of opioid analgesics are unpredictable. They may prolong labour by temporarily reducing the strength, duration and frequency of uterine contractions, or conversely they may tend to shorten labour by increasing the rate of cervical dilatation. Infants born to mothers

receiving opioid analgesics during labour should be observed closely for signs of respiratory depression. In such infants a specific opioid antagonist, naloxone hydrochloride, should be available for reversal of opioid-induced respiratory depression.

Use in Lactation

Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving Kapanol. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine sulfate pentahydrate is stopped.

4.7. Effects on Ability to Drive and Use Machines

Morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedatives/hypnotics and alcohol (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.8. Adverse Effects (Undesirable Effects)

The adverse reactions caused by morphine are essentially the same as those observed with other oral and parenteral opioids. They include the following major hazards: respiratory depression, apnoea and to a lesser degree circulatory depression, respiratory arrest, shock and cardiac arrest.

Most Common Adverse Effects

Constipation, lightheadedness, dizziness, headache, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Sedation

Most patients receiving morphine will experience initial drowsiness. This usually disappears in three to five days and is not a cause for concern unless it is excessive, or accompanied with unsteadiness or confusion. Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, exacerbated respiratory failure, tolerance to the dose used especially in older patients, disease severity and the patient's general condition. If the dose of Kapanol has been reduced and pain is not adequately controlled, the dose may be carefully increased again after a few days.

Dizziness and Unsteadiness

Dizziness and unsteadiness may be associated with morphine-induced postural hypotension, particularly in elderly or debilitated patients. The dosage should be adjusted according to individual needs but, because of reduced clearance, dosage may be lower in patients over 50 years of age.

Nausea and Vomiting

Nausea and vomiting is common after single doses of morphine or as an early undesirable effect of regular opioid therapy. The prescription of a suitable antiemetic should be considered. The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid-induced gastric stasis. Metoclopramide is often useful in such patients.

Constipation

Virtually all patients experience constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may experience impacted faeces. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be initiated at the beginning of opioid therapy.

Other Adverse Reactions Include

Cardiovascular

Flushing of the face, chills, tachycardia, bradycardia, palpitations, faintness, syncope, hypotension and hypertension.

Central Nervous System (CNS)

Euphoria, dysphoria, weakness, insomnia, dizziness, confusional symptoms and occasionally hallucinations.

Gastrointestinal

Dry mouth, anorexia, constipation, laryngospasm, colic, taste alterations and biliary colic.

Genitourinary

Urinary retention or hesitancy, reduced libido or potency.

Endocrine

A syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion may occur (monitoring of electrolytes may be necessary).

Visual Disturbances

Blurred vision, nystagmus, diplopia and miosis.

Allergic

Pruritus, urticaria, other skin rashes and oedema.

Withdrawal (Abstinence) Syndrome

Chronic use of opioid analgesics may be associated with the development of physical dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered.

Withdrawal symptoms that may be observed after discontinuation of opioid use include: body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia or unexplained fever. With appropriate dose adjustments and gradual withdrawal, these symptoms are usually mild.

4.9. Overdose

Symptoms

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension.

Treatment

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone hydrochloride, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously. However, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Kapanol will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdosage should be modified accordingly. If the response to naloxone is sub-optimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on Kapanol. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary oedema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Gastric contents may need to be emptied by gastric lavage as this can be useful in removing unabsorbed drug, particularly when a sustained-release formulation has been taken.

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 toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being present.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on overdose management.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Mechanism of Action

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. Morphine produces diverse pharmacological effects in man including analgesia, suppression of the cough reflex, respiratory depression due to a reduction in the responsiveness of the respiratory centre to carbon dioxide, nausea and emesis through direct stimulation of the chemoreceptor trigger-zone (CTZ), mood changes including euphoria and dysphoria, sedation, mental clouding, alterations in both the endocrine and autonomic nervous systems, and a decrease in gastrointestinal motility leading to constipation.

Clinical Trials

Symptom Reduction of Chronic Pain

Cancer-Related Pain:

A total of 94 healthy subjects and 224 patients with cancer pain participated in a total of 8 studies (6 pharmacokinetic and 3 clinical; one study reported both pharmacokinetic and clinical data). Of these individuals, 94 healthy subjects and 171 patients received Kapanol. In the controlled clinical studies patients were followed for a median duration of 7 days. Kapanol was compared to oral morphine solution and to MS ContinÒ using trial designs that followed the clinical and pharmacokinetic performance of each treatment in cancer patients receiving chronic opioid therapy.

In one double-blind, controlled study, patients with moderate to severe cancer pain were titrated with immediate-release morphine (IRM) solution to a stable total daily dose of morphine for at least three consecutive days, then randomised to Kapanol once daily, Kapanol twice daily or MS Contin twice daily for seven days of observation. Kapanol given once a day proved similar to the same total dose of morphine given in divided doses in a 12-hour dosage form, with respect to pain relief, use of rescue medication, patient and investigator global assessment, and quality of sleep. Individual patient differences in the pattern of pain control emphasise the need to individualise the dose (see Section 4.2 Dose and Method of Administration).

Non-Cancer Related Pain: One multi-centre, randomised, open-label, parallel study compared the efficacy and tolerability of 12-hourly Kapanol with morphine sulfate controlled-release tablets (MSTÔ). Patients with severe chronic pain (n=165) of various origins (73.5% non-malignant, 26.5% malignant) were randomised and titrated to adequate analgesia with Kapanol or MST, respectively. The median titrated doses of morphine necessary for analgesia in the initial phase of the study were 40 mg twice daily in the Kapanol group and 30 mg twice daily in the MST group. Once stabilised, patients started the 2-week study period.

112 patients completed the study: 69 patients on Kapanol and 43 on MST. 22 of 91 (24.2%) of patients on Kapanol and 31 of 74 (41.9%) on MST withdrew prematurely. Inadequate efficacy was the reason for premature termination in 5 patients in the Kapanol group and 13 patients in the MST group. Significantly more patients on Kapanol achieved adequate analgesia than with MST, based on the physician's final assessment (73% vs 55.5%, $p = 0.02$), quality of sleep ($p = 0.05$), and effect on mood ($p < 0.05$). Inadequate efficacy was reported in 20% of patients on Kapanol and 21.5% of patients on MST.

Symptom Reduction of Chronic Breathlessness

Clinical trial 1:

282 opioid-naïve participants with modified Medical Research Council (mMRC) breathlessness scores 2-4 despite optimal treatment of the underlying cause(s) were randomised to double-blinded placebo or 20mg Kapanol daily for 7 days. The primary outcome was reduction in *breathlessness now* intensity as measured on a 0-100mm visual analogue scale (VAS) - no significant difference was found between the use of Kapanol and placebo for this measure. However, the study was confounded by the use of immediate release morphine as rescue medication in both arms.

A sub-group analysis for participants with more severe breathlessness (mMRC 3 or 4) found that there was a significant reduction in worst breathlessness when compared to placebo. There were no episodes of respiratory depression in the study.

Table 2: Change in 0-100mm visual analogue scale (VAS) breathlessness - change between baseline and days 5-7. Mean (standard error (SE)

			Complete trial cohort**			Severely breathless cohort*		
			ER^^ morphine	**Placebo**	**Treatment Difference**	**ER morphine**	**Placebo**	**Treatment Difference**
Breathlessness 0-100		**Now^**	**−5.00 (2.13)**	**−4.86 (2.07)**	**−0.15 (-4.59, 4.29)**	−3.93 (2·48)	−3.02 (2.43)	−0.91 (-6.61, 4.78)
	Previous 24 hours	Worst	−10.51 (2.59)	−5.29 (2.61)	−5.23 (-10.77, 0.31)	−11.84 (2.96)	−4.03 (2.97)	−7.81 (-14.65, -0.97)
		Average	−4.49 (2.09)	−2.36 (2.06)	−2.13 (-6.64, 2.38)	−4.21 (2.41)	−1.21 (2.39)	−3.00 (-8·63, 2.62)

*Severely breathless cohort as defined in the originally registered study - people with modified Medical Research Council (mMRC) breathlessness scale 3, 4 at baseline.
** Complete cohort
^ Primary outcome ^^ ER – extended release

Clinical trial 2:

48 opioid naive participants with chronic breathlessness secondary to advanced disease with no reversible components were randomised to receive 20mg sustained release morphine for 4 days or placebo in a double blind, crossover trial. The mean age of participants was 76 (SD 5) years, 73% were men, 88% had a diagnosis of COPD and 71% were receiving supplemental oxygen; Eastern Co-operative Oncology Group functional status was 2 or 3. The primary outcome variable was the sensation of breathlessness as measured on a VAS in the evening on the final day of the period. This was significantly reduced with sustained release morphine compared to placebo with a difference of 9.5mm (SD 19, 95% CI 3.0 to 16.1, P = 0.006). 21% of participants withdrew from the study.[1]

Clinical trial 3:

83 opioid-naive adult outpatients with a palliative diagnosis and chronic breathlessness (mMRC 3-4) were enrolled in an open-label dose finding study of sustained release morphine. Of the participants, mean age was 75 years, 64% were male, 54% had a diagnosis of COPD, median Australia-modified Karnofsky Performance Status function was 60. The duration of participation in the study was a mean of 142 days (SD 190; median 29; range 2 to 665). There were 52 participants who were assessed as responding (with this defined as a 10% improvement over baseline in VAS Breathlessness score and with acceptable/minimal side effects). In these patients, the average improvement from their own baselines was 17.1

[1] Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ. 2003;327(7414):523-528

mm (SD 11.6) and 69.2% had had benefit at a daily dose of 10 mg, 23.1% at 20 mg, and 7.7% at 30 mg.[2]

The most recent meta-analysis of controlled clinical trials of morphine for the reduction of chronic breathlessness explored 12 trials with significant heterogeneity, 11 of which were cross-over studies. The findings were of a statistically and clinically meaningful reduction in breathlessness.[3] Of these studies, two used extended release (ER) morphine (64 participants) and one of these studies was for up to six weeks of treatment.

A further systematic review and meta-analysis that brought together 67 clinical studies of opioids for breathlessness found no evidence of clinically relevant respiratory adverse effects of opioids for chronic breathlessness including changes in blood gases or respiratory depression. In this study, 84 participants in three studies were on ER morphine, two of which for longer than seven days.[4]

5.2. Pharmacokinetic Properties

Absorption

Morphine is rapidly absorbed from the gastrointestinal tract, nasal mucosa, lung and after subcutaneous (s.c.) and intramuscular (i.m.) injection.

Following oral administration, the dose normalised extent of absorption (AUC) of morphine from Kapanol is similar to that obtained from morphine solution or controlled-release tablets. However, the rate of absorption of morphine from Kapanol is significantly slower.

On a 12 hourly dosing schedule, Kapanol at steady state exhibits a lower mean peak plasma morphine concentration (Cmax) and higher mean trough plasma morphine concentration (Cmin) than the same total daily dose of morphine solution administered on a 4 hourly dosing regimen. Although there is no clear relationship between the analgesic effect or the incidence of adverse reactions and plasma morphine concentrations, the reduced fluctuation in blood morphine concentrations following administration of Kapanol may reduce adverse reactions and the incidence of breakthrough pain.

On a 24 hourly dosing schedule, Kapanol at steady state maintained higher dose-adjusted minimum plasma morphine concentrations (Cmin) and was associated with reduced fluctuation in dose-adjusted plasma morphine levels than controlled-release morphine tablets administered on a 12 hourly dosing regimen. Plasma morphine concentrations remained at or above 75% of the maximum plasma concentration for longer with Kapanol than for controlled-release morphine tablets. There was no significant difference in the dose-adjusted AUC, average concentration (Cave) or Cmax between these two treatments.

[2] Currow DC, McDonald C, Oaten S, et al. Once daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage 2011;42:388-399.
[3] Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? Thorax. 2018 Jan;73(1):88-90
[4] Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, Datla S, Dirksen CD, Johnson MJ, van Kuijk SMJ, Wouters EFM, Janssen DJA. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis Eur Respir J. 2017; Nov 22;50(5).

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. It crosses the placental membranes and has been found in breast milk. About 30 to 35% of morphine is reversibly protein bound.

When Kapanol is given on a fixed dosing regimen, steady state is achieved within about two days.

Pharmacokinetic parameters of morphine show considerable inter-subject variation. The average volume of distribution (Vd) is approximately 4 L/kg.

Metabolism

When administered orally it is subject to extensive but variable 'first-pass' metabolism and only about 40% of the administered dose reaches the central compartment.

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. Because accumulation of this metabolite has been observed in patients with renal disease, caution should be exercised in patients with clinically significant impairment of renal function. There has been no evaluation of Kapanol in patients with impaired hepatic and renal function.

Excretion

Morphine is excreted primarily in the urine as morphine-3-glucuronide and morphine-6-glucuronide. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the faeces. The terminal half-life of morphine is 2 to 4 hours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Kapanol inactive ingredients: sucrose, –maize starch, hypromellose, ethylcellulose, methacrylic acid copolymer, macrogol 6000, diethyl phthalate, purified talc, purified water, gelatin, Tek Print* SW-9009 Black Ink.

6.2. Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. Special Precautions for Storage

Store the capsules below 30°C. Protect from light and moisture.

6.5. Nature and Contents of Container

Kapanol capsules are available in in blister packs of 20, 28 or 60 capsules.

Not all strengths or pack sizes may be distributed in Australia.

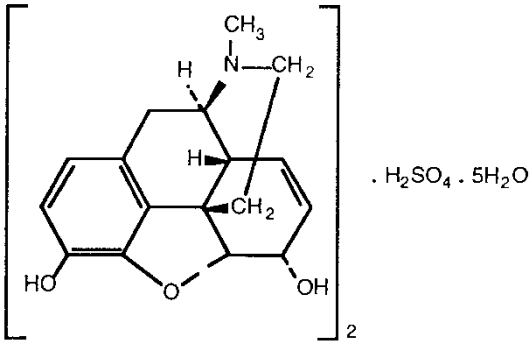
6.6. Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. Physicochemical Properties

Chemical structure

Chemically, morphine sulfate pentahydrate is 7,8-didehydro-4,5(alpha)-epoxy-17-methyl-morphinan-3,6 (alpha) diol sulfate (2:1) (salt) pentahydrate and has the following structural formula:



Morphine sulfate pentahydrate is an odourless, white, crystalline powder or needlelike crystals with a bitter taste. It has a solubility of 1 in 21 of water and 1 in 1000 of alcohol, but it is practically insoluble in chloroform or ether.

CAS number

57-27-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S8

8. SPONSOR

Mayne Pharma International Pty Ltd.

ABN 88 007 870 984

1538 Main North Rd., Salisbury South, SA 5106, Australia

http://www.maynepharma.com/products/australian-products/

9. DATE OF FIRST APPROVAL

21 July 1994

10. DATE OF REVISION

6 February 2019

Kapanol® is a registered trade mark of Mayne Pharma International Pty Ltd.

Summary table of changes

Section changed	Summary of new information
All	PI reformat
4.1, 4.2, 4.4 and 5.1	Updates to account for the addition of the indication, symptomatic reduction of chronic breathlessness.