SEVREDOL® tablets

Morphine sulphate

1 PRODUCT NAME

SEVREDOL® 10 mg and 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains morphine sulphate 10 mg or 20 mg
Excipient with known affect: Lactose, anhydrous
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SEVREDOL tablets are capsule shaped, biconvex, scored, film-coated tablets approximately 12 mm in length with the strength on one side and "IR" on the other side of the score line. The colours of the tablets are as follows: 10 mg blue and 20 mg pink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SEVREDOL tablets are indicated for the relief of both acute and chronic severe pain in adults and children aged three years and above.

4.2 Dose and method of administration

Dose

Adults and children over 12 years:

SEVREDOL tablets should be given every four hours. The dosage is dependent upon the nature and severity of the pain, the patient's condition and their previous history of analgesic therapy. A patient initially presenting with severe and intractable pain will normally be started on **SEVREDOL** 10 mg every 4 hours. This dose should be increased every 4 hours until the patient is free of pain. At that stage the patient should be transferred onto a long acting morphine preparation.
To do this, add the amount of morphine needed to completely relieve pain over a 24-hour period. Divide this total in half, rounding up to nearest tablet strength and administer the long acting morphine preparation as a twice daily dose. The first dose of the long acting morphine preparation should be given as a replacement of the last dose of **SEVREDOL** tablets. Any recurrence of pain will require an increase in the dose but not the frequency of the long acting morphine preparation. Breakthrough pain should be treated with immediate-release morphine, such as **SEVREDOL** tablets, as rescue dose and not with long-acting formulations.
There is no upper dose limit for morphine sulphate tablets. Increase of morphine dosage should be performed slowly and under clinical judgement, until the lowest effective dose is reached. The dose of morphine used for individual patients must be that dose which completely eliminates their pain irrespective of how large it is.

Patients receiving morphine sulphate tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for the reduction in analgesic effects associated with orally administered analgesics.

Paediatric population:
3-5 years: 5 mg 4 hourly.
6-12 years: 5-10 mg 4 hourly.

Elderly:
5 mg 4 hourly increasing as necessary to completely relieve the pain.

Method of administration:

SEVREDOL tablets should be swallowed whole and not chewed unless half tablets are being used. The tablets are film coated to mask the bitter taste of morphine and this masking effect is lost if the tablets are broken.

SEVREDOL tablets are substitutable with oral morphine solution when titrating for pain relief or treating break through pain.

4.3 Contraindications
Morphine is contraindicated in patients

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- with severe chronic obstructive pulmonary disease
- with known morphine sensitivity
- with acute hepatic disease
- with respiratory depression, with hypoxia and/or hypercapnia especially in the presence of cyanosis and excessive bronchial secretion.
- with acute alcoholism
- with head injuries, in which intracranial pressure is raised.
- with severe bronchial asthma
- with heart failure secondary to chronic lung disease
- who are taking or have taken monoamine oxidase inhibitors (MAOIs) within the previous two weeks
- with paralytic ileus, acute abdomen, or delayed gastric emptying
- for use as a pre-operative medication
- with pheochromocytoma, as morphine appears to increase catecholamine levels
- with chronic pain not due to malignancy who have a prior history of substance abuse

4.4 Special warnings and precautions for use
Morphine has to be administered with caution in patients with:

- Severely impaired respiratory function,
- Severe cor pulmonale,
- Sleep apnoea,
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below),
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below),

- Hypotension with hypovolaemia,
- Biliary tract disorders,
- Pancreatitis,
- Severely impaired renal function,
- Severely impaired hepatic function,
- Constipation.

Respiratory depression

The major risk of opioid excess is respiratory depression**.**

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

CNS depressants co-administration
Concomitant use of morphine and sedative medicines such as benzodiazepines or related drugs such as CNS depressants (e.g. non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol) may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe morphine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5 Interactions with other medicines and other forms of interaction).

In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when SEVREDOL® is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of

substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5 Interactions with other medicines and other forms of interaction).

Special risk patients

Morphine should be given with caution or in reduced doses in patients with impaired kidney or liver function, biliary tract disorders, the elderly, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy, raised intracranial pressure, hypotension with hypovolemia, pancreatitis, severe chronic obstructive lung disease, severe cor pulmonale, severe bronchial asthma or respiratory depression or urethral stricture.

Opioid analgesics such as morphine sulphate should be used with caution in patients with myasthenia gravis.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

Tolerance, physical dependence and withdrawal

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse

There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine. Morphine has an abuse profile similar to other strong agonist opioids. Morphine may be sought and abused by people with latent or manifest addiction disorders. SEVREDOL should be used with particular care in patients with a history of substance misuse disorder (including alcohol misuse) or mental health disorder.

Parenteral abuse of dosage forms not approved for parenteral administration can be expected to result in serious adverse events, which may be fatal.

Pre and post-operative use

Morphine is not recommended preoperatively or within the first 24 hours post operatively.

Impaired Respiration

The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries.

Hypotensive Effect

The administration of morphine may result in severe hypotension in the post-operative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, shock, or the administration of such drugs as the phenothiazines or certain anaesthetics. Morphine may produce orthostatic hypotension in ambulatory patients.

Supraventricular Tachycardias

Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

Acute Abdominal Conditions

The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine should be used with caution in patients with inflammatory or obstructive bowel disorders, or with ulcerative colitis, and should only be used when necessary in patients with acute pancreatitis.

Renal or Hepatic Disease

Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may be prolonged.

Caution should be observed when morphine is administered to patients with impaired renal function, as the pharmacologically active metabolite, morphine-6-glucuronide, may accumulate in these patients. This may lead to CNS and respiratory depression.

4.5 Interaction with other medicines and other forms of interaction

Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalising agents decrease clearance and so potentiate the effects of morphine.

Benzodiazepines and other Central Nervous System (CNS) Depressants:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.The dose and duration of concomitant use should be limited (see section 4.4). Follow patients closely for signs of respiratory depression and sedation (see Section 4.4 Warnings and Precautions).

Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids, e.g., pregabalin), general anaesthetics (including barbiturates), tranquilizers, muscle relaxants, drugs with antihistamine-sedating actions such as antipsychotics (including phenothiazines), antidepressants, centrally acting anti-emetics and alcohol.

Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion.
Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of morphine.
Diazepam, when used following high doses of morphine, exacerbates the hypotensive effects produced by morphine, and is associated with reduced plasma catecholamine levels.

Antihypertensive Agents:
Concurrent administration of morphine may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

Muscle Relaxants:
Morphine may enhance the neuromuscular blocking action of skeletal muscle 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):
MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion, and significant depression of respiration, sometimes leading to coma. Co-administration with MAOIs or within two weeks of discontinuation of their use is inappropriate. It is unknown whether there is an interaction between the new selective MAOIs (e.g. moclobemide and selegeline) and morphine. Therefore, caution is advised with such drug combinations.

Cimetidine and Other H_2 Receptor Antagonists:
There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine. A potentially lethal interaction between cimetidine and morphine, in which the patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported. Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours. Confusion has also been associated with concomitant use of ranitidine and morphine.

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.

Phenothiazines:
The analgesic effect of morphine is potentiated by chlorpromazine.

Amphetamines:
Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.

Anticoagulants:
Morphine may potentiate the anticoagulant activity of coumarin anticoagulant agents.

Metoclopramide:
Morphine may antagonise the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of morphine on gastric emptying.

Zidovudine:
Morphine may alter the metabolism of zidovudine, by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Zidovudine and morphine should therefore not be administered concurrently, because the toxicity of either or both of these drugs may be increased.

Ritonavir:
Ritonavir may increase the activity of glucuronyl transferases and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic activity.

Oral Drugs:
Morphine delays gastric emptying, so may affect the absorption of orally administered drugs. For example, morphine delays the absorption of paracetamol and mexiletine.

Anticholinergic Agents:
Concurrent administration of morphine and anticholinergic agents or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

Antidiarrhoeal Agents:
Concurrent administration of morphine and antidiarrhoeal agents with antiperistaltic actions may increase the risk of severe constipation and CNS depression.

Opioid Antagonists:
Naloxone antagonises the analgesic, CNS and respiratory depressive effects of morphine, and may precipitate withdrawal in patients who are physically dependent on opioids. Naltrexone blocks the therapeutic effects of opioids, so should be discontinued several days prior to elective surgery if administration prior to, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.

Effect on Laboratory Tests:
Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies. Morphine may interfere with hepatobiliary imaging using technetium Tc99m diosfenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of Tc99m

diosfenin to the small bowel. These actions result in delayed visualisation, and thus resemble obstruction of the common bile duct.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Morphine has been associated with foetal CNS defects in rodent studies. It is not known whether morphine can cause foetal harm in humans when administered during pregnancy. Pregnant patients should only be given morphine when the benefits clearly outweigh potential risks to the foetus.

Prolonged use of morphine sulfate during pregnancy can result in respiratory depression and neonatal opioid withdrawal syndrome. Babies born to mothers who are physically dependent on morphine may also be physically dependent on the drug. Use in pregnancy is therefore not recommended.

Breastfeeding

Morphine is excreted in human milk. Narcotic analgesics may cause respiratory depression and dependence in the newborn infant. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine is stopped.

Use in breast-feeding is therefore not recommended.

Fertility

Prolonged use of opioid drugs may result in impairment of reproductive function, including infertility and sexual dysfunction in both sexes and irregular menses in women.

Animal studies have shown that morphine may reduce fertility (see section 5.3)

4.7 Effects on ability to drive and use machines

Patients should be warned that morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine in combination with other opioid analgesics, phenothiazines, sedative-hypnotics and alcohol has additive depressant effects.

4.8 Undesirable effects

The adverse effects listed below are classified by body system according to their incidence (common [≥ 1%] or uncommon [< 1%]).

	Very Common **(≥1/10)**	**Common** **(1/100 to < 1/10)**	**Uncommon** **(1/1,000 to <1/100)**	**Not Known**

Immune system disorders			Hypersensitivity	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Thinking disturbances Drug dependence Dysphoria
Nervous system disorders		Dizziness Headache Involuntary muscle contractions Somnolence	Convulsions Hypertonia Paraesthesia Syncope	Hyperalgesia Allodynia Sleep apnoea syndrome
Eye disorders			Visual impairment	Miosis
Ear and labyrinth disorders			Vertigo	
Vascular disorders			Facial flushing Hypotension	
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Respiratory depression Bronchospasm	Cough decreased
Gastrointestinal disorders	Nausea Constipation	Abdominal pain Anorexia Dry mouth Vomiting	Ileus Taste perversion Dyspepsia	
Hepato-biliary disorders			Increased hepatic enzyme	Biliary pain
Skin and subcutaneous tissue disorders		Hyperhidrosis Rash	Urticaria	
Renal and urinary disorders			Urinary retention	
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenia Fatigue Malaise Pruritus	Peripheral oedema	Drug tolerance Drug withdrawal syndrome Drug withdrawal syndrome neonatal

Withdrawal (Abstinence) Syndrome:

Chronic use of opioid analgesics may be associated with the development of physical dependence, with or without psychological 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 and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Acute morphine overdosage can be manifested by respiratory depression, extreme somnolence progressing to stupor or coma, pneumonia aspiration, miotic pupils, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death. The triad of coma, pinpoint pupils, & respiratory depression is considered indicative of overdosage; dilatation of the pupils occurs as hypoxia develops.

Treatment

A patent airway must be maintained. The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

Immediate attention should be given to the re-establishment of adequate respiratory exchange through provision of a patient airway and institution of assisted or controlled ventilation. In patients physically dependent on opioids, respiratory support is the first line of treatment. In these patients, the use of naloxone is potentially dangerous. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids. The recommended adult dose of naloxone for the treatment of severe opiate induced respiratory depression is 0.4 to 2 mg intravenously every 2 to 3 minutes as necessary, simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01 mg/kg naloxone. A response should be seen after 2 to 3 doses. Note the duration of action of naloxone is usually shorter than that of morphine and thus the patient should be carefully observed for signs of CNS depression returning.

If the response to naloxone is suboptimal 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 morphine. 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.
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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid, ATC code: N02A A01

Morphine sulphate is the pentahydrate of the sulphate of 7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6-diol. It has a molecular formula and weight of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ and 758.8 respectively.

Morphine is a potent opioid analgesic. It is about 8 times more potent than pethidine and 10 times more potent than codeine. Morphine combines selectively at opioid binding sites found in the CNS and smooth muscle to produce its pharmacologic effects. These are due to morphine mimicking the action of endogenous endorphins, which are released in response to pain and other stimuli. Morphine relieves most types of pain but is more effective against dull, constant pain than sharp, intermittent pain. Analgesia at the supraspinal level results principally from combination with (mu) receptors, and the (kappa) receptors are responsible primarily for expression of analgesia at the spinal level. In addition to relieving severe constant pain, morphine also alleviates the associated anxiety.

Central Nervous System

Pharmacological effects include analgesia, drowsiness, mental clouding and mood alteration (euphoria or dysphoria). Such effects may be common at first but tolerance develops on prolonged administration. Other centrally mediated effects include respiratory depression, nausea and vomiting, to which a high degree of tolerance also develops over time.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathogonomic (e.g. pontine lesions of haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilatation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

5.2 Pharmacokinetic properties

The onset of action of **SEVREDOL** tablets is about 15-30 minutes after oral administration. The duration of action is 3-4 hours.

Morphine is well absorbed from the GI tract following administration of **SEVREDOL** tablets, however, it is subject to extensive first-pass metabolism in the liver. **SEVREDOL** tablets produce peak morphine levels approximately one hour post-dose. The elimination half-life of morphine is 2-3 hours with great interpatient variability.

Like other phenanthrene derivatives, morphine is mainly metabolised by glucuronide conjugation in the liver. The resultant metabolites are excreted primarily in the urine. The principal metabolites are active, although the relative contributions of these, and parent morphine, to the overall analgesic effect is unclear. The 6-glucuronide metabolite has been shown to be 10 times more potent than parent morphine, however, the 3-glucuronide metabolite may antagonise this effect.

Morphine is widely distributed through the body and diffuses across the placenta. Reduced dosing is necessary in patients with renal or hepatic dysfunction, and also in the elderly due to increased sensitivity to its effect.

5.3 Preclinical safety data

Genotoxicity

No regulatory studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the positive findings, in vitro studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in Drosophila.

Carcinogenicity
Regulatory studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Reproductive toxicity
Reduced fertility has been shown in male rats administered repeat doses of morphine subcutaneously. A study reported in the literature in female rats treated i.p. with up to 15 mg/kg/day of morphine before mating, up to 30 mg/kg/day over pregnancy and up to 40 mg/kg/day postpartum showed reduced fertility of the mothers and an increase in stillborns, and in the live offspring reduced growth, morphine withdrawal symptoms, and suppression of sperm production

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core*:*
Lactose anhydrous
Pregelatinised maize starch
Povidone K25
Magnesium stearate
Purified talc.

10 mg tablet:
Coat*:*
Hydroxypropylmethyl cellulose
Polyethylene glycol 400
Opadry 06B20843.

20 mg tablet:
Coat*:*
Hydroxypropylmethyl cellulose
Polyethylene glycol 400
Opaspray M-1-5503.

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

10 mg or 20 mg tablets, packed in bottles or blister packs of 10

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

Controlled Drug B1.

8 SPONSOR

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Pharmaco (N.Z.) Ltd
P O Box 4079
AUCKLAND 1140
Ph: (09) 377-3336
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9 DATE OF FIRST APPROVAL

04 August 1994

10 DATE OF REVISION OF THE TEXT

August 2020 (CCDS dated 14 April 2020 V17)

Orbis NZ-0069-002

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Amendment of text relating to co-administration of sevredol with the first dose of long acting morphine; clarification of treatment of breakthrough pain with immediate-release morphine instead of long-acting formulations
4.3,4.4,4.5,4.8	General editorial and administrative updates to maintain consistency with CCDSs
4.4	Added warning of central sleep apnoea and worsening of pre-existing sleep apnoea.
4.8	Sleep apnoea syndrome (not known) added to undesirable effects.
4.9	Reinstate information on treatment which was originally requested by Medsafe in 2014.