

New Zealand Data Sheet



1. PRODUCT NAME

SEVREDOL* 10 mg and 20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SEVREDOL 10 mg film-coated tablet contains 10 mg morphine sulphate.

Each SEVREDOL 20 mg film-coated tablet contains 20 mg morphine sulphate.

Excipient with known effect: Lactose, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SEVREDOL 10 mg film-coated tablets are blue, capsule shaped, biconvex, scored, film-coated tablets approximately 12 mm in length with the strength on one side and “IR” on the side of the score line.

SEVREDOL 20 mg film-coated tablets are pink, capsule shaped, biconvex, scored, film-coated tablets approximately 12 mm in length with the strength on one side and “IR” on the side of the score line.

The tablet can be divided into equal doses.

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 of age:

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. The correct dosage per individual patient is that which controls the pain and is well tolerated. 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 desired relief is achieved.

Switching from SEVREDOL to Long-Acting Morphine

Add the amount of morphine needed to achieve pain relief 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 for 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 immediately with an immediate-release morphine preparation, such as SEVREDOL tablets, as a rescue dose, not with long-acting formulations.

There is no upper dose limit for morphine sulphate tablets. Increasing morphine dosage should be performed slowly and under clinical judgement, until the lowest effective dose is reached. The correct dosage per individual patient is that which controls the pain and is well-tolerated.

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

Special populations

Elderly population

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

Paediatric population

3-5 years: 5 mg 4 hourly.

6-12 years: 5-10 mg 4 hourly.

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 impacted respiratory function,
- respiratory depression (see below),
- severe cor pulmonale,
- sleep apnoea,
- acute generalised exanthematous pustulosis (AGEP),
- CNS depressants co-administration (see below and section 4.5),
- monoamine oxidase inhibitors (MAOIs – see below and section 4.5),
- opioid use disorder (abuse and dependence),
- tolerance, physical dependence and withdrawal (see below)
- psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below),
- head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin.
- hypotension with hypovolaemia,
- hepatobiliary disorders,
- pancreatitis,
- severely impaired renal function,
- severely impaired hepatic function,
- constipation.

Hazardous and harmful use

SEVREDOL contains the opioid morphine sulphate and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed SEVREDOL at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed SEVREDOL.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 and section 6.6). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share SEVREDOL with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of SEVREDOL but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and close monitoring in these patients (see section 4.2). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naive patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid increases the risk of CSA in a dose-dependent fashion. Opioids

may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the opioid dosage using best practice for opioid taper.

Severe cutaneous adverse reaction (SCARs)

Acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms. If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

CNS depressants co-administration

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of SEVREDOL with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe SEVREDOL concomitantly with any of the medicines, the lowest effective dosage should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking SEVREDOL.

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).

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).

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.

MAOIs

Morphine must be administered with caution in patients taking MAOIs or have received MAOIs within the previous two weeks.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as morphine.

Repeated use of morphine can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of morphine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or family history (parents or siblings) of a substance use disorder (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with morphine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Tolerance, physical dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dosage is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing SEVREDOL in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see ceasing opioids and section 4.2).

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.

Hepatobiliary disorders

Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, patients with diseases of the biliary tract should be monitored for worsening symptoms while administering morphine.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Effects on hypothalamic-pituitary-adrenal or gonadal axes

Opioids, such as morphine sulphate, may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patients (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see ceasing opioids).

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.

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosage or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

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.

Accidental ingestion/exposure

Accidental ingestion or exposure to SEVREDOL, especially by children, can result in a fatal overdose of SEVREDOL. Patients and their caregivers should be given information on safe storage and disposal of unused SEVREDOL (see section 6.4 and section 6.6).

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. If the patient is experiencing increased pain or serious symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

4.5. Interaction with other medicines and other forms of interaction

Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalinising 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 effects.

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).

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 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 selegiline) and morphine. Therefore, caution is advised with such drug combinations.

Cimetidine and Other H₂ 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 effect of opioids, so should be discontinued several days prior to elective surgery if administration prior to, 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 sulphate 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.

Breast-feeding

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

Tabulated summary of adverse reactions

Table 1: Summary of the safety profile

Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); not known (cannot be estimated from the available data).

	Very Common	Common	Uncommon	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 Central 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 Spasm of Sphincter of Oddi
Skin and subcutaneous tissue disorders		Hyperhidrosis Rash	Urticaria	Acute generalised exanthematous pustulosus (AGEP)

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

Drug Dependence

Repeated use of morphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage and duration of opioid treatment (see section 4.4).

Withdrawal (Abstinence) Syndrome:

Chronic use of opioids 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 (see section 4.4).

With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting of suspected adverse reactions

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://pophealth.my.site.com/carmreportnz/s/>

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; dilation of the pupils occurs as hypoxia develops.

Toxic leukoencephalopathy has been observed with morphine overdose.

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 patent 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 mg 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 $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ and 758.8 respectively.

Mechanism of action

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 (μ) receptors, and the (κ) 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 a 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 pathognomonic (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.

Hepatobiliary System

Opioids may induce spasm of the sphincter of Oddi.

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.

Absorption

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.

Distribution

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.

Biotransformation

Like other phenanthrene derivatives, morphine is mainly metabolised by glucuronide conjugation in the liver. 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.

Elimination

The resultant metabolites of glucuronide conjugation of morphine are excreted primarily in the urine.

5.3. Preclinical safety data

Mutagenicity

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.

Teratogenicity

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.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements

7. MEDICINE SCHEDULE

Controlled Drug B1

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

04 August 1994

10. DATE OF REVISION OF THE TEXT

08 July 2024

* SEVREDOL is a registered trademark in New Zealand and other countries.

Summary table of changes

Section Changed	Summary of new information
ALL	Updated information into new sponsor template and new sponsor contact details added. Minor spelling and grammar corrections throughout.
4.8.	Updated table to move definition of frequencies above table.
5.2.	Moved information according to ADME headings.
6.5.	Added "Not all pack sizes may be marketed".