NEW ZEALAND DATA SHEET

Hazardous and harmful use

ORAMORPH oral solution poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see Section 4.4. Special warnings and precautions for use).

Limitations of use

Because of the risks associated with the use of opioids, ORAMORPH oral solution should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see Section 4.4 Special warnings and precautions for use).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis, centrally-active anti-emetics, general anaesthetics, tranquilisers, beta blockers, or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking ORAMORPH oral solution.

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of ORAMORPH oral solution. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see Section 4.4 Special warnings and precautions for use).

1 PRODUCT NAME

ORAMORPH morphine sulfate pentahydrate 2mg/mL oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5mL of ORAMORPH contains 10mg of morphine sulfate pentahydrate

Excipient with known effect:
Each 5 ml also contains 1500mg sucrose, 500mg corn syrup (contains glucose), 0.525mL Ethanol (96%), 9mg methyl parahydroxybenzoate (E218) and 1mg propyl parahydroxybenzoate (E216).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ORAMORPH oral solution is a clear, nearly colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Morphine is an analgesic used for the symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery. Morphine is indicated in adults and children aged 1 year and above. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain.

4.2 Dose and method of administration

Dosage must be titrated to the patient's needs because of the wide inter-individual variability in plasma concentration required to achieve analgesia.

The usual adult dosage is 5-20 mg (2.5-10 mL of the 2 mg/mL mixture) every 4 hours. The initial dose will depend largely on the patient's previous treatment and should be the lowest compatible with pain control. Treatment should start at a dosage of 5 mg every 4 hours, with further increments as required. With repeat administration, tolerance may develop, and the dose may need to be increased gradually in order to control the pain.

Dosage adjustments

Dosage should be lower in elderly patients, those with respiratory, hepatic or renal impairment and in patients receiving central nervous system (CNS) depressants.

Paediatric Population

Dosage in children should be adjusted according to body weight, 0.1-0.2 mg/kg every 4 hours.

Method of administration

For oral administration

4.3 Contraindications

ORAMORPH is contraindicated:

- in patients who are taking, or have taken monoamine oxidase inhibitors (MAOIs), within the previous fourteen days;
- in patients with known hypersensitivity to morphine or other opioids;
- in patients with severe respiratory disease, acute respiratory disease, respiratory depression or insufficiency, especially in the presence of cyanosis and/or excessive bronchial secretion;
- in patients with acute or severe bronchial asthma or other obstructive airways disease; other conditions where respiratory reserve is depleted such as severe emphysema, chronic bronchitis or kyphoscoliosis; cor pulmonale;
- in severe CNS depression;
- in diabetic acidosis where there is a danger of coma;
- in severe liver disease or incipient hepatic encephalopathy.
- following biliary tract surgery or surgical anastomosis; biliary colic; gastrointestinal obstruction; paralytic ileus; suspected surgical abdomen; acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis; diarrhoea caused by poisoning (until the toxic material has been eliminated);
- phaeochromocytoma (due to risk of pressor response to histamine release);
- cardiac arrhythmias; heart failure secondary to pulmonary disease;
- acute alcoholism or delirium tremens;
- comatose patients; head injuries; brain tumour; raised intracranial or cerebrospinal pressure and in convulsive states such as status epilepticus, tetanus or strychnine poisoning;

- in children under one year of age including premature infants or during labour for delivery of premature infants.

4.4 Special warnings and precautions for use

Hazardous and harmful use

ORAMORPH oral solution contains the opioid morphine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed ORAMORPH oral solution 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 ORAMORPH oral solution. 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 Special precautions for storage and Section 6.6 Special precautions for disposal). 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 ORAMORPH oral solution with anyone else.

Accidental ingestion/exposure

Accidental ingestion or exposure of ORAMORPH oral solution, especially by children, can result in fatal overdose of ORAMORPH. Patients and their caregivers should be given information on safe storage and disposal of unused ORAMORPH oral solution (see Section 6.4 Special precautions for storage and Section 6.6 Special precautions for disposal).

Convulsions

Seizures may result from high doses. ORAMORPH may lower the seizure threshold in patients with a history of seizure and may aggravate pre-existing convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders. Patients with known seizure disorders should be carefully observed, especially when doses are increased in response to tolerance. ORAMORPH should be used with extreme caution, if benefits outweigh risks, in convulsive states such as status epilepticus.

Serotonin syndrome (SS)

The development of serotonin syndrome (SS), which is potentially life-threatening, has been reported with opioid use, including with morphine. These reports generally occurred when morphine was used concomitantly with serotonergic drugs (see section 4.5 Interactions with other medicines and other forms of interactions). Signs of SS may include clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature elevation. ORAMORPH should be used with caution pre-operatively or within the first 24 hours post-operatively.

Cardiovascular instability

Morphine should be used with caution in patients with acute heart failure as it can be associated with increased morbidity (e.g., increased frequency of mechanical ventilation, admission to an intensive care unit) and increased mortality.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulatory catecholamines. Have naloxone injection and resuscitative equipment immediately available for use in case of life-threatening or intolerable side effects and whenever ORAMORPH therapy is being initiated.

Supraventricular tachycardias

ORAMORPH should be used with caution in patients with atrial flutter and other supraventricular tachycardia because of possible vagolytic action that may produce a significant increase in the ventricular response rate.

Hypotensive effect

ORAMORPH administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, impaired myocardial function or concurrent administration of drugs such as sympatholytics, phenothiazines or certain anaesthetics. ORAMORPH should be used with caution and these patients should be carefully observed for orthostatic hypotension.

Shock patients

In patients with shock, impaired perfusion may prevent complete absorption following subcutaneous or intramuscular injection of morphine. Repeated administration may result in overdosage due to an excessive amount of morphine suddenly being absorbed when circulation is restored.

Tolerance, 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. Psychological dependence, physical dependence and tolerance may develop upon repeated administration of ORAMORPH. However, it should be noted that clinically significant respiratory depression, addiction, rapid tolerance and euphoria rarely develop when doses of morphine are carefully titrated against the pain in patients with terminal disease and severe pain. Except in patients with terminal conditions, morphine should be restricted to short-term administration for the relief of severe pain not responding to non-narcotic analgesics.

Drug dependence does not develop if ORAMORPH is administered regularly at individually optimised doses to the cancer patient with moderate to severe pain. While a certain degree of physical dependence occurs, a psychological dependence does not occur.

If a cancer patient no longer requires an opioid for pain control, a gradual reduction in dose will prevent any withdrawal symptoms, although these are usually mild or absent even after abrupt discontinuance. Clinically significant tolerance to morphine is unusual in the cancer patient being treated for severe pain.

In most cases, a plateauing of dose requirements is seen, as a need to increase morphine dose means an increase in pain and not tolerance. Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose 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, palpitations, irritability, agitation, anxiety, hyperkinesia, tremor, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate, increased heart rate, piloerection, sneezing, convulsions, and unexplained fever.

When discontinuing morphine 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 Dose and Method of Administration).

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 (see Section 4.2 Dose and Method of Administration). If the patient is experiencing increased pain or serious withdrawal 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.

Neonatal opioid withdrawal syndrome

See section 4.6 Fertility, pregnancy and lactation.

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 maximized 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 patient (see Hazardous and harmful use). 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-naive 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).

Hyperalgesia

Hyperalgesia has been reported with the use of opioids, particularly following long-term use and/or at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages 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.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.

Acute abdominal conditions

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

Gastrointestinal Motility

Decreased gastric emptying associated with morphine may be expected to increase the risks of aspiration either associated with morphine induced CNS depression/coma, or during or after general anaesthesia. As

with all oral morphine preparations, ORAMORPH oral solution should be used with caution post-operatively and following abdominal surgery, as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Should paralytic ileus be suspected or occur during use, ORAMORPH oral solution should be discontinued immediately.

Biliary disorders

ORAMORPH should be avoided in patients with biliary disorders (see section 4.3 Contraindications). ORAMORPH can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi. Therefore, in patients with biliary tract disorders ORAMORPH may exacerbate pain. The use of ORAMORPH in biliary colic or following biliary tract surgery or surgical anastomosis is contraindicated (see section 4.3 Contraindications). In patients given ORAMORPH after cholecystectomy, biliary pain has been induced.

Sickle Cell Disease (SCD) and Acute Chest Syndrome (ACS)

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

Decreased sex hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormones and increased prolactin. Symptoms include decreased libido, impotence or amenorrhoea.

Other special risk patients

ORAMORPH should be given with caution, and in reduced dosages, to certain patients, such as those with severe impairment of pulmonary, hepatic or renal function, pancreatitis, hypothyroidism, adrenocortical insufficiency, Addison's disease, myxoedema, and prostatic hypertrophy or urethral stricture (see section 5.2 Pharmacokinetic properties). Caution should also be observed if morphine is administered to patients with toxic psychosis or myasthenia gravis. ORAMORPH should be used with extreme caution in patients with disorders characterised by hypoxia, since even usual therapeutic doses of opioids may decrease respiratory drive to the point of apnoea while increasing airway resistance.

Morphine should be used with caution in patients with tetanus due to stimulatory effects on the spinal cord or strychnine poisoning.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

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 ORAMORPH oral solution with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, beta-blockers, and other CNS depressants should be reserved for patients for whom other treatment options are not possible. 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 interactions).

If a decision is made to prescribe ORAMORPH oral solution concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. 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. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms.

Patients and their caregivers should also be informed of the potential harms of consuming alcohol and illicit drugs while taking ORAMORPH oral solution. 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 interactions).

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 ORAMORPH oral solution, 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, in patients with renal and hepatic impairment and in patients with existing impairment of respiratory function, in those suffering from conditions accompanied by hypoxia or hypercapnia (e.g. chronic obstructive pulmonary disease; asthma). ORAMORPH should therefore be used only in patients for whom its use is judged to be essential, with extreme caution and with close monitoring in these patients (see Section 4.2 Dose and method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see Section 4.3 Contraindications).

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 effects, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries. Large doses and/or rapid administration of morphine may produce rapid onset of respiratory depression including central sleep apnoea (CSA) and sleep-related hypoxemia, bradycardia, or even cardiac arrest. The risk of respiratory depression is greater with the use of high doses of opioids, and in opioid naïve 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 together with consideration of pharmacological differences between opioids. (see Section 4.2 Dose and method of administration). Therapeutic doses of narcotics may decrease respiratory drive and increase airway resistance to the point of apnoea in patients with acute bronchial asthma, chronic obstructive pulmonary disease or cor pulmonale, or those with a substantially decreased pulmonary reserve or respiratory depression. Follow patients closely for signs and symptoms of respiratory depression including central sleep apnoea (CSA) and sleep-related hypoxemia and sedation. If respiratory depression occurs, consider decreasing the opioid dosage using best practices of opioid taper and to account for individual variations in response. Resuscitative equipment and narcotic antagonists must be readily available.

Risks of use in patients with increased intracranial pressure, brain tumours, head injury, impaired consciousness, or medical conditions where there is a danger of coma

Monitor for sedation and respiratory depression. Avoid use of morphine in patients with impaired consciousness or coma.

Use in hepatic impairment

ORAMORPH may have a prolonged duration and cumulative effect in patients with liver dysfunction. In these patients, analgesia may last for 6, 8 or even up to 24 hours following a standard dose.

The pharmacokinetics of morphine are negatively altered in patients with liver impairment. The clearance of morphine is reduced in liver impairment. Administration of morphine is not recommended in patients with liver impairment. If the use of morphine is needed, use with caution, in reduced total daily dosages, and/or with increased dosing interval in patients with liver impairment and monitor for signs of respiratory depression, sedation, and hypotension.

Use in renal impairment

ORAMORPH may have a prolonged duration and cumulative effect in patients with kidney dysfunction. In these patients, analgesia may last for 6, 8 or even up to 24 hours following a standard dose.

The pharmacokinetics of morphine are negatively altered in patients with renal impairment. In renal impairment, an accumulation of morphine metabolites has been demonstrated, however, morphine clearance in these patients is dependent on haemofiltration volumes, and accumulation of morphine does not occur during this form of treatment. Administration of morphine is not recommended in patients with renal impairment. If the use of morphine is needed, use with caution, in reduced total daily dosages, and/or with increased dosing interval in patients with renal impairment and monitor for signs of respiratory depression, sedation, and hypotension.

Use in the elderly

ORAMORPH should be administered with caution and in reduced dosages to elderly or debilitated patients. Respiratory depression occurs more frequently in these patients. The pharmacodynamics of ORAMORPH are more variable in geriatric patients than in younger adults. Therefore, initial dosage should be selected carefully based on clinical assessment of response to test doses and consideration of the patient's age and ability to clear the drug. In older patients, the volume of distribution is considerable smaller and initial concentrations of morphine are correspondingly higher (see Other special risk patients).

Paediatric use

Safety and effectiveness in neonates have not been established. However, neonates have an enhanced susceptibility to the respiratory depressant effects of ORAMORPH. ORAMORPH should not be administered to premature infants (see Section 4.3 Contraindications).

Effects on laboratory tests

ORAMORPH delays gastric emptying, thereby invalidating test results in gastric emptying studies. ORAMORPH may interfere with hepatobiliary imaging using technetium Tc99m diosfenin. ORAMORPH 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.

Cordotomy

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly manifest. Patients who are scheduled for cordotomy or other pain-relieving surgical procedures should not receive ORAMORPH oral solution within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with ORAMORPH oral solution is then indicated, the dosage should be adjusted to the new post-operative requirement.

4.5 **Interaction with other medicines and other forms of interaction**

Acidifying/Alkalising Agents

The clearance of morphine may be increased by acidifying agents and decreased by alkalising agents. Morphine's actions on gastrointestinal motility may influence absorption of other drugs (either increase, or decrease, or increase the onset time).

CNS Depressants

ORAMORPH should be used with great caution and in reduced dosage in patients concurrently receiving other CNS depressants, such as other opioid analgesics, general anaesthetics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, chloral hydrate, glutethimide, barbiturates, tricyclic antidepressants, monoamine oxidase inhibitors (including procarbazine hydrochloride), pyrazolidone antihistamines, cimetidine, centrally-active antiemetics, antihypertensives, beta blockers, muscle relaxants, antipsychotics, phenothiazines, tranquilisers and other CNS depressants, including alcohol because of the risk of respiratory depression, hypotension, profound sedation and coma. When considering concurrent use, the dose of one or both agents should be reduced. Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of morphine with CNS depressant medicines increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4 Special warnings and precautions for use).
Examples	CNS depressant medicines such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, beta blockers, alcohol.

Diazepam

When used following high doses of ORAMORPH, diazepam exacerbates the hypotensive effects produced by ORAMORPH, and is associated with reduced plasma catecholamine levels.

Antihypertensive Agents

Concurrent administration of ORAMORPH may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

Muscle Relaxants

ORAMORPH 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.

Anticoagulants

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, and monoamine oxidase inhibitors (MAOIs).

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment (see section 4.3 Contraindications). It is not known whether there is an interaction between the selective MAOIs (e.g., moclobemide, selegiline) and morphine, therefore caution is advised with this drug combination.

Cimetidine and other H2 Receptor Antagonists

There is a report of confusion and severe respiratory depression when a patient receiving haemodialysis 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. Therefore, caution is advised when administering morphine with cimetidine or ranitidine.

Diuretics

Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also induce acute urinary retention by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

Phenothiazines

The analgesic effect of ORAMORPH is potentiated by chlorpromazine.

Amphetamines

Dexamphetamine and other amphetamines may enhance the analgesic effects and decrease sedation and lack of alertness caused by ORAMORPH.

Metoclopramide and Domperidone

ORAMORPH may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of ORAMORPH on gastric emptying.

Zidovudine

Morphine may competitively inhibit glucuronidation or directly inhibit hepatic microsomal metabolism of zidovudine thus reducing its clearance. Concurrent use of morphine and zidovudine should be avoided 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 efficacy.

Rifampicin

Plasma concentrations of ORAMORPH may be reduced by rifampicin. The analgesic effect of ORAMORPH should be monitored, and doses of morphine adjusted during and after treatment with rifampicin.

Antibacterials

The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The ciprofloxacin manufacturer advises that premedication with opioid analgesics be avoided.

Anticholinergic Agents

Concurrent administration of ORAMORPH and anticholinergic agents (such as atropine) or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

Antidiarrhoeal and Antiperistaltic Agents

Concurrent administration of ORAMORPH 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 ORAMORPH, 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 ORAMORPH will precipitate withdrawal symptoms.

Other Drugs

ORAMORPH delays gastric emptying, so may affect the absorption of orally administered drugs. For example, ORAMORPH delays the absorption of paracetamol.

P-glycoprotein (P-gp) Inhibitors/Inducers

Morphine is a substrate of P-gp. P-gp inhibitors (e.g., quinidine) may increase the oral absorption/exposure of morphine by about two-fold. Conversely, P-gp inducers (e.g., rifampin) may decrease the oral absorption/exposure of morphine. Therefore, exercise caution when morphine is co-administered with P-gp inhibitors or inducers.

$P2Y_{12}$ Inhibitors

Clinical Impact: The co-administration of oral $P2Y_{12}$ inhibitors and morphine can decrease the absorption and peak concentration of oral $P2Y_{12}$ inhibitors and delay the onset of the antiplatelet effect, due to morphine's effect on delay of gastric emptying.

Intervention: Consider the use of a parenteral antiplatelet agent in the setting of acute coronary syndrome requiring co-administration of morphine.

Examples of $P2Y_{12}$ inhibitors include but are not limited to: clopidogrel, prasugrel, ticagrelor.

4.6 **Fertility, pregnancy and lactation**

Pregnancy

Morphine crosses the placenta and can produce respiratory depression if it is administrated during labour. Infants born to mothers receiving opioid analgesics during labour should be observed closely for signs of respiratory depression. Morphine should therefore only be used during the last 2-3 hours before expected delivery after weighing the expected benefits for the mother against the potential risk to the fetus. In such infant a specific opioid antagonist, naloxone hydrochloride, should be available for reversal of opioid induced respiratory depression.

Morphine has been associated with fetal CNS defects in rodent studies. Use of ORAMORPH should be avoided to the extent possible in patients who are pregnant. It is not known whether morphine can cause fetal harm in humans when administered during pregnancy. Pregnant patients should only be given ORAMORPH when the benefits clearly outweigh potential risks to the fetus.

Safe use in pregnancy prior to labour has not been established in respect to possible adverse effects on fetal development. Morphine may prolong labour by reducing the strength and frequency of uterine contractions. Prolonged use of ORAMORPH during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognised and treated. Babies born to mothers who are physically dependent on ORAMORPH may also be physically dependent on the drug. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Breast-feeding

Morphine appears in breast milk. Published studies report variable concentrations of morphine in breast milk with intravenous/intramuscular administration of morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio ranging from 1.1 to 3.6 in one lactation study. Morphine administration to nursing mothers is 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.

Reduced fertility has been shown in male rats administered repeat doses of morphine subcutaneously.

4.7 Effects on ability to drive and use machines

ORAMORPH may cause drowsiness and may impair co-ordination, the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating dangerous machinery. Patients should be cautioned accordingly.

Patients should also be cautioned about the combined effects of ORAMORPH with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

4.8 Undesirable effects

The major hazards associated with morphine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following use of morphine.

Most Common Adverse Effects Requiring Medical Attention

The most frequently observed side effects of narcotic analgesics such as morphine are sedation, nausea and vomiting, constipation and sweating.

Sedation

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realised. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting

Nausea and vomiting occur frequently after single doses of narcotics or as an early unwanted effect of regular narcotic therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to narcotic-induced gastric stasis. In such patients, metoclopramide is often useful.

Constipation

Practically all patients become constipated while taking narcotics on a persistent basis. Elderly or bedridden patients may become impacted. It is essential to caution patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged narcotic therapy. Dietary modification, suitable exercise and softeners, laxatives and other appropriate measures should be used as required.

Other Adverse Reactions Include

Endocrine Disorders

Uncommonly: peripheral oedema, pulmonary oedema, syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary). Morphine stimulates prolactin release, and may also cause hyperglycaemia.

Frequency not known: adrenal insufficiency.

Nervous System Disorders
Euphoria, dysphoria, weakness, insomnia, dizziness, confusional symptoms, vertigo, restlessness, anxiety, irritability, tremor, delirium, drowsiness, excessive or persistent sedation.

Occasionally: hallucinations, visual disturbances, headache, involuntary muscle contraction, asthenia, somnolence, thought abnormalities.

Uncommonly: malaise, mood changes, seizures, miosis, paraesthesia, agitation.

Frequency not known: allodynia, hyperalgesia.

Cardiac Disorders
Supra-ventricular tachycardia, hypotension, circulatory depression, shock and cardiac arrest, postural hypotension, bradycardia, palpitations, faintness, syncope, hypertension.

Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression, apnoea, respiratory arrest, laryngospasm, bronchospasm, cough decreased.

Gastrointestinal Disorders
Dry mouth, anorexia, dyspepsia, ileus, constipation, abdominal pain and cramps, taste alterations, gastrointestinal disorders, biliary tract cramps, biliary pain, biliary spasm, nausea, vomiting and gastric status.
Uncommonly: elevated hepatic enzymes

Genitourinary
Urinary retention or hesitancy, uretic spasm, ureteric spasm, oliguria.

Reproductive System and Breast Disorders
Amenorrhoea, erectile dysfunction, reduced libido or potency, hypogonadism.

Visual disturbances
Blurred vision, nystagmus, diplopia and miosis.

General Disorders
Facial flushing, hyperhidrosis, hypertonia, oedema, chills.

Allergic
Allergic reaction, anaphylactic and anaphylactoid reactions, pruritis, urticaria and other skin rashes including contact dermatitis.

Dependence/tolerance
Drug dependence, physical dependence and tolerance may develop with long term use of ORAMORPH. In drug dependence, “drug craving” is often involved.

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, restless legs syndrome, abdominal colic, nausea, flu-like symptoms, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia, mydriasis and unexplained fever. 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 and Signs

Serious morphine overdosage is characterised by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia, and pinpoint pupils (dilated if hypoxia is severe). Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death.

Treatment

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. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous (I.V.) adult dose of naloxone is 0.4 mg or higher (please refer to Naloxone Data Sheet for specific directions). Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonists should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated to manage circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary and fluid and electrolyte metabolism maintained.

In an individual physically depended on narcotics, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10% to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug.

Toxicity

Morphine toxicity may be a result of overdosage but because of the large interindividual 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. Published data suggest that in a morphine naïve, pain-free individual, the lethal dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 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).

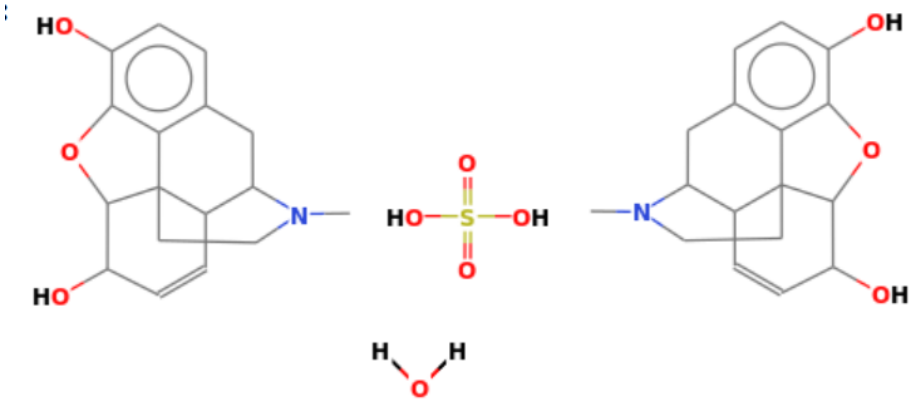
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Nervous system, Analgesics, Opiods, Natural opium alkaloids

ATC code: N022AA01

Chemical Structure:



Chemical name: 3-methyl-2,4,4*a*,7,7*a*,13-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol;sulfuric acid;pentahydrate

Molecular Formula: $C_{34}H_{50}N_2O_{15}S$

CAS number: 6211-15-0

Molecular weight: 758.8g/mol.

Morphine sulfate pentahydrate is an odourless white crystalline powder or needle like crystals with a bitter taste.

Mechanism of Action

Morphine, like other opioids, acts as an agonist interacting with stereo-specific and saturable binding sites/receptors in the brain, spinal cord and other tissues. These sites have been classified as μ receptors and are widely distributed throughout the central nervous system being present in highest concentration in the limbic system (frontal and temporal cortex, amygdala and hippocampus), thalamus, striatum, hypothalamus, midbrain and laminae I, II, IV and V of the dorsal horn in the spinal cord. It has been postulated that exogenously administered morphine exerts its analgesic effect, in part, by altering the central release of neurotransmitter from afferent nerves sensitive to noxious stimuli.

Peripheral threshold or responsiveness to noxious stimuli is unaffected leaving monosynaptic reflexes such as the patella or the Achilles tendon reflex intact.

Morphine exerts its primary effects on the central nervous system and organs containing smooth muscle. Pharmacological effects include analgesia, drowsiness, alteration in mood (euphoria), reduction in body temperature, dose-related depression of respiration, interference with

adrenocortical response to stress (at high doses), reduction in peripheral resistance with little or no effect on cardiac index, cough suppressions mediated through a direct effect on the medullary centre and miosis.

Direct stimulation of the chemoreceptor trigger zone may cause emesis and spasmogenic effects on the gastrointestinal tract resulting in decreased peristaltic activity. Urinary retention may occur due to increased bladder sphincter tone.

5.2 Pharmacokinetic properties

Absorption

Morphine is readily absorbed from the gastrointestinal tract. Significant first-pass metabolism occurs in the liver following oral administration; hence, the bioavailability of oral morphine is low and variable.

With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection.

Distribution, Metabolism and Elimination

Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as kidney, lung, liver and spleen. Lower concentrations are found in skeletal muscle and brain tissue. Morphine diffuses across the placenta and trace amounts are found in sweat. Morphine is excreted in breast milk (see section 4.6). About 35% is protein bound, mainly to albumin. Morphine is metabolised principally in the liver by conjunction with glucuronic acid at the 3-hydroxyl group, and to a much lesser extent to the 3,6-diglucuronide. Elimination half-life is approximately 1.5-2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours. Approximately 7-10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.

Specific Populations

Hepatic Impairment

Morphine pharmacokinetics are altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients, indicating diminished metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. The AUC is increased, and clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

5.3 **Preclinical safety data**

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the datasheet.

6 PHARMACEUTICAL PARTICULARS

6.1 **List of excipients**

ORAMORPH 2mg/mL oral solution contains the following inactive ingredients:

- Sucrose
- Corn syrup
- Methyl parahydroxybenzoate
- Propyl parahydroxybenzoate
- Ethanol (96%)
- Water

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf life**

36 months from the date of manufacture

Discard ORAMORPH oral solution 3 months after first opening

6.4 Special Precautions

Store at or below 25°C

Store in the original container protected from light.

For storage conditions after opening of the medicine, see section 6.3

6.5 Nature and contents of container

ORAMORPH 2mg/mL comes in an amber glass bottle with a tamper-evident child resistant polypropylene closure with expanded PE liner and is available in packs of 100mL

6.6 Special precautions for disposal

If only part used, discard the remaining solution.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Class B1 Controlled Drug

8 SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

New Zealand

9 DATE OF FIRST APPROVAL

24 April 2024

10 DATE OF REVISION OF THE TEXT

02 April 2024

Summary Table of Changes

Section changed	Summary of new information