VERMOR-10 (Morphine Sulphate Injection BP 10 mg/ml, 1ml)

Summary of Product Characteristics (SPC)

1. Name of the Finished Pharmaceutical Product

Morphine Sulphate Injection BP 10 mg/ml, 1 ml

2. Qualitative and Quantitative Composition

Each ml contains:

Morphine Sulphate BP 10 mg

Water for Injection BP q.s.

3. Pharmaceutical Form

Solution for injection. A colourless or almost colourless solution filled in 1 ml amber glass ampoules.

4. Clinical Particulars

4.1 Therapeutic indications

Analgesic for severe and very severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with morphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Morphine Sulfate 10 mg/ml solution for injection may be administered subcutaneously, intramuscularly or intravenously.

Dosage should be adjusted according to the severity of the pain and the response of the patient. Appropriate starting doses are as follows:

Administration	Adults and adolescents over 12 years
Intravenously	2.5–10 mg
Subcutaneously, intramuscularly	5–20 mg

Individuals might require considerably higher doses for sufficient relief of pain. In general, the minimum effective dose should be administered. For intravenous administration it is important to inject morphine slowly over a period of 4 to 5 minutes with the patient in the recumbent position.

For continuous intravenous infusion of morphine, appropriate starting doses are 1–2 mg per hour in adults and adolescents over 12 years. Daily doses will not

usually exceed 100 mg per day in adults and adolescents over 12 years, however, in cancer patients chronic administration of higher doses up to 4 g per day may occasionally be required.

Treatment goals and discontinuation: Before initiating treatment, a treatment strategy including treatment duration and goals, and a plan for end of treatment, should be agreed with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between physician and patient to evaluate the need for continued treatment, consider discontinuation and adjust dosages if needed. When a patient no longer requires therapy, it may be advisable to taper the dose gradually to prevent withdrawal symptoms. In the absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment: Should not be used longer than necessary.

Children under 12 years: This formulation is not recommended for use in children under 12 years.

In the Elderly: The dose should be reduced and titrated to provide optimal pain relief with minimal side effects; morphine clearance decreases and half-life increases in older patients.

In patients with disturbed renal function: Caution should be exercised, as such patients can show signs of overdose following conservative dosage regimens.

In patients with impaired liver function: Caution should be exercised, e.g. cirrhosis, as this condition is likely to affect elimination; the dose should be carefully titrated to provide optimal pain relief.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Respiratory depression or insufficiency
- Obstructive airways disease
- Acute alcoholism
- Concurrent administration of MAO inhibitors or within two weeks of discontinuation of their use

4.4 Special warnings and precautions for use

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: may result in sedation, respiratory depression, coma and death. Concomitant prescribing should be reserved for patients for whom alternative treatment options are not possible, using the lowest effective dose and shortest duration. Patients should be followed closely for signs and symptoms of respiratory depression and sedation.

Sleep-related breathing disorders: Opioids can cause central sleep apnoea (CSA) and sleep-related hypoxemia in a dose-dependent fashion; consider decreasing total opioid dosage in patients presenting with CSA.

Opioid Use Disorder (abuse and dependence): Tolerance and physical and/or psychological dependence may develop upon repeated administration; a higher dose and longer duration of treatment increase the risk of developing Opioid Use Disorder (OUD). Abuse or intentional misuse may result in overdose and/or death. Risk of OUD is increased with a personal or family history of substance use disorders (including alcohol), current tobacco use, or personal history of other mental health disorders. Treatment goals and a discontinuation plan should be agreed before and during treatment; patients should be informed about the risks and signs of OUD and monitored for signs of drug-seeking behaviour. A comprehensive patient history should document concomitant medications and past/present medical and psychiatric conditions. Patients may develop tolerance and should be closely monitored for signs of misuse, abuse or addiction; the clinical need for treatment should be reviewed regularly.

Drug withdrawal syndrome: A withdrawal strategy should be discussed prior to starting treatment. Withdrawal syndrome may occur upon abrupt cessation or dose reduction; the dose should be tapered gradually when no longer required (which may take weeks to months). It is characterised by restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations, and may include irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate. Use during pregnancy risks neonatal withdrawal syndrome.

Hyperalgesia: May be diagnosed if the patient on long-term opioid therapy presents with increased pain, qualitatively and anatomically distinct from disease-related or tolerance-related breakthrough pain, more diffuse and less defined than pre-existing pain; symptoms may resolve with a reduction of opioid dose.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD): Due to a possible association between ACS and morphine use in SCD patients during vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Severe cutaneous adverse reactions (SCARs): Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported, mostly within the first 10 days of treatment. Patients should be informed of the signs and symptoms and advised to seek medical care; if signs and symptoms appear, morphine should be withdrawn and an alternative treatment considered.

Hepatobiliary disorders: Morphine may cause dysfunction and spasm of the sphincter of Oddi, raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

Adrenal insufficiency: Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy; symptoms include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased sex hormones and increased prolactin: Long-term use may be associated with decreased sex hormone levels and increased prolactin; symptoms include decreased libido, impotence or amenorrhea.

Rifampicin: Plasma concentrations of morphine may be reduced by rifampicin; the analgesic effect should be monitored and morphine doses adjusted during and after rifampicin treatment.

Other conditions/situations in which morphine should be used with caution: Hypotension, hypothyroidism, asthma (avoid during attack), decreased respiratory reserve; pregnancy and breast-feeding (see section 4.6); treatment may precipitate coma in hepatic impairment (reduce dose, though many patients tolerate morphine well); reduce dose in renal impairment, elderly and debilitated patients.

Oral P2Y12 inhibitor antiplatelet therapy: Within the first day of concomitant use, reduced efficacy of P2Y12 inhibitor treatment has been observed.

Sodium content: This medicine contains less than 1 mmol sodium (23 mg) per 1 ml ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs: Concomitant use increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect; dose and duration of concomitant use should be limited.

Other CNS depressants: In patients concurrently receiving other central nervous system depressants (sedatives, hypnotics, general anaesthetics, phenothiazines, gabapentin or pregabalin, other tranquillisers and alcohol), morphine should be used with caution and in reduced dosage because of the risk of respiratory depression, hypotension and profound sedation or coma.

Muscle relaxants: Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants.

Mixed agonist/antagonist opioid analgesics: (e.g. pentazocine, nalbuphine, and buprenorphine) can reduce the analgesic effect of morphine by competitive blocking of the receptor and should not be administered to patients receiving a course of therapy with a pure opioid agonist analgesic.

Monoamine oxidase inhibitors (MAOIs): MAOIs intensify the effect of morphine and other opioid drugs; severe and even fatal events (anxiety, confusion and significant depression of respiration, sometimes leading to coma) have been observed. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment.

Cimetidine: Higher plasma concentrations of morphine due to decreased metabolism have been observed with co-administration; confusion and severe respiratory depression were reported in a haemodialysis patient receiving both drugs.

Diuretics: Morphine reduces the efficacy of diuretics by inducing release of antidiuretic hormone, and may lead to acute urinary retention by causing spasm of the bladder sphincter, particularly in men with prostatism.

Alcohol: Enhanced sedative and hypotensive effect.

Anti-Arrhythmics: Delayed absorption of mexiletine.

Antidepressants: CNS excitation or depression (hypertension or hypotension) if pethidine and possibly other opioid analgesics are given to patients receiving MAOIs (including moclobemide).

Anxiolytics and Hypnotics: Enhanced sedative effect.

Cisapride: Possible antagonism of gastro-intestinal effect.

Domperidone and metoclopramide: Antagonism of gastro-intestinal effects.

Dopaminergics: Hyperpyrexia and CNS toxicity reported with selegiline.

Rifampicin: Plasma concentrations of morphine may be reduced; the analgesic effect should be monitored and doses adjusted during and after treatment.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine, possibly related to reduced gastrointestinal motility, and may apply to other opioids; clinical relevance is unknown. In patients with acute coronary syndrome in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, use of a parenteral P2Y12 inhibitor may be considered.

4.6 Fertility, pregnancy and Lactation

Pregnancy: Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure appropriate treatment will be available. Animal reproduction studies have shown that morphine can cause foetal damage when administered throughout pregnancy; an association with increased frequency of inguinal hernias in infants has been postulated in man. Pregnant patients

should only be given morphine when benefits clearly outweigh potential risks to the foetus. Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome; treatment may include an opioid and supportive care.

Use in labour/delivery: Infants born to mothers receiving opioid analgesics during labour should be observed closely for signs of respiratory depression; naloxone hydrochloride should be readily available for reversal of narcotic-induced respiratory depression. After chronic maternal morphine use, newborns may develop withdrawal symptoms. Morphine may prolong labour by temporarily reducing the strength, duration and frequency of uterine contractions, or may tend to shorten labour by increasing the rate of cervical dilatation.

Breast-feeding: Administration to nursing women is not recommended, as morphine may be secreted in breast milk and may cause respiratory depression in the infant. Withdrawal syndrome was observed in breast-fed infants after maternal administration of morphine had been stopped.

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

4.7 Effects on ability to drive and use machines

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 narcotic analgesics, phenothiazines, sedative-hypnotics, and alcohol have additive depressant effects. Patients should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. Patients should be told: the medicine is likely to affect their ability to drive; not to drive until they know how the medicine affects them; and it is an offence to drive while under the influence of this medicine. However, they would not be committing an offence (a 'statutory defence') if it has been prescribed to treat a medical or dental problem, taken according to the prescriber's instructions, and was not affecting their ability to drive safely.

4.8 Undesirable effects

Frequency categories: Very common ≥1/10; Common ≥1/100 to <1/10; Uncommon ≥1/1,000 to <1/100; Rare ≥1/10,000 to <1/1,000; Very rare <1/10,000; Frequency not known: cannot be estimated from the available data.

System Organ Class	Frequency	Reactions
Gastrointestinal disorders	Very common	Nausea, vomiting, constipation

System Organ Class	Frequency	Reactions
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory depression
Nervous system disorders	Very common	Sedation, drowsiness
Skin and subcutaneous tissue disorders	Very common	Itching
Psychiatric disorders	Very common	Disorientation, hallucinations, dysphoria, euphoria, tolerance
Skin and subcutaneous tissue disorders	Common	Urticaria, skin rash, pain at injection site, contact dermatitis, acute generalised exanthematous pustulosis (AGEP)
Nervous system disorders	Common	Headache, vertigo, agitation, convulsions, impairment of taste, mood changes, changes of cognitive and sensory abilities, insomnia, intracranial hypertension, tremor
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
Eye disorders	Common	Miosis, visual disturbances (blurred vision, nystagmus, diplopia)
Gastrointestinal disorders	Common	Dryness of mouth, pylorospasm, singultus, diarrhoea, abdominal cramps, biliary colic, pancreatitis
Hepatobiliary disorders	Common	Spasm of sphincter of Oddi
Cardiac disorders	Common	Orthostatic hypotension, bradycardia, hypertension, tachycardia, heart failure, pulmonary oedema
Vascular disorders	Common	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Laryngeal spasm, bronchospasm, cough attenuation, central sleep apnoea syndrome
Renal and urinary disorders	Common	Urinary retention or hesitancy, oliguria
Reproductive system and breast disorders	Common	Loss of libido, impotence
Endocrine disorders	Common	Inappropriate antidiuretic hormone (ADH) secretion characterised by hyponatraemia secondary to

System Organ Class	Frequency	Reactions
		decreased free water excretion
General disorders and administration site conditions	Common	Oedema, chills, hypothermia, hyperthermia
Immune system disorders	Uncommon	Anaphylactic/anaphylactoid reaction after i.v. injection
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome
Nervous system disorders	Not known	Allodynia, hyperalgesia, hyperhidrosis
Psychiatric disorders	Not known	Drug dependence

Pulmonary oedema after overdose is a common cause of fatalities among opioid addicts. Morphine and some other opioids have a dose-related histamine effect, which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Contact dermatitis has been reported and pain and irritation may occur on injection; anaphylactic reactions following intravenous injection have been reported rarely.

Drug dependence and withdrawal (abstinence) syndrome: Repeated use can lead to drug dependence, even at therapeutic doses; risk varies with individual risk factors, dosage and duration of treatment. Use of opioid analgesics may be associated with physical and/or psychological dependence or tolerance; an abstinence syndrome may be precipitated by sudden discontinuation or opioid antagonists, or experienced between doses. Physiological withdrawal symptoms include restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations, and may include irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

4.9 Overdose

Symptoms: Patients and their family/friends should be informed of the signs and symptoms of overdose and to seek immediate medical help if they occur. Overdosage is characterised by respiratory depression (decrease in respiratory rate, potentially leading to fatal respiratory failure, and/or tidal volume, Cheyne-Stokes respiration, cyanosis), pneumonia aspiration, pinpoint pupils, extreme somnolence progressing to stupor and coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdosage, apnoea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Immediate attention should be given to re-establishing adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluid, vasopressors and other supportive measures should be employed as indicated.

The narcotic antagonist naloxone is a specific antidote for morphine. The recommended adult dose of naloxone is 0.4 to 2.0 mg IV every 2 to 3 minutes as necessary, simultaneously with assisted respiration; for children, the initial recommended dose is 0.01 mg/kg. A response should be seen after 2–3 doses. As naloxone's duration of action is usually shorter than that of morphine, patients should be carefully monitored for signs of CNS depression returning. If the response is suboptimal or not sustained, additional naloxone may be administered as needed; an intravenous infusion of naloxone, titrated to response, has been suggested to sustain opioid antagonism.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage, and should be administered cautiously to persons known or suspected to be physically dependent on morphine, as an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome; the antagonist should be administered with extreme care and by titration with smaller than usual doses in such patients.

Morphine toxicity may result from overdosage, but because of large inter-individual variation in sensitivity to opioids it is difficult to assess the exact toxic or lethal dose. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance; patients receiving chronic morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxic effect.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Morphine is pharmacologically the most important alkaloid of opium. It is used primarily as an analgesic for severe pain. The analgesic effect of morphine is primarily due to interaction with the OP3 (μ) receptor, one of three major classes of opioid receptors distinguished in the central nervous system. The metabolite morphine-6-glucuronide also acts as an agonist on opioid receptors and contributes significantly to the pharmacological effects of chronic morphine treatment. Doses of 0.1 mg/kg body-weight of morphine and higher are effective in various animal analgesic tests.

Morphine causes respiratory depression by diminishing the response of the respiratory centres to CO2; this effect is mediated by action on OP3-receptors and can be antagonised by naloxone. Morphine stimulates the chemo-receptor trigger zone by action on dopamine receptors and may cause nausea and vomiting. Other effects: morphine can induce euphoria and miosis; hypotension may occur due to increased histamine release, especially in hypovolaemic patients.

5.2 Pharmacokinetic properties

Approximately 35% of morphine is bound to plasma proteins. Morphine is rapidly metabolized: approximately 50% is converted to the major metabolite, the pharmacologically inactive morphine-3-glucuronide, and 10–15% is converted to the active morphine-6-glucuronide. Further metabolites include a diglucuronide, normorphine and its glucuronides. Approximately 60% of morphine is excreted in the urine in 24 hours, of which less than 10% of the dose is excreted as unchanged drug.

5.3 Preclinical safety data

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6. Pharmaceutical Particulars

6.1 List of excipients

Di Sodium E.D.T.A, Sodium Chloride, Tri sodium citrate Dihydrate, Citric acid & Water for injection.

6.2 Incompatibilities

Morphine sulfate is physically incompatible with aciclovir sodium, aminophylline, amobarbital sodium, cefepime hydrochloride, chlorothiazide sodium, floxacillin sodium, furosemide, gallium nitrate, heparin sodium, meperidine hydrochloride, meperidine sodium, methicillin sodium, minocycline hydrochloride, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sargramostim, sodium bicarbonate, thiopental sodium. Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulfate and 5-fluorouracil.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

1 ml amber glass ampoules.

6.6 Special precautions for disposal and other Handling

None stated.

7. Marketing Authorisation Holder

M/s Verve Human Care Laboratories (a Unit of Venor Pharma), Plot No-15-A, Pharmacity, Selaqui, Dehradun, Uttarakhand, India.

8. Manufacturer Authorization Number(s)

H2017/CTD3905/217

9. Date of First Authorization/Renewal of the Authorization

27th July 2017

10. Date of Revision of the Text

24-07-2025