1.4.1. PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

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

2. Qualitative and Quantitative composition

2.1 Qualitative composition

Each ml contains

Morphine Sulphate BP

Water for Injection BP

2.2 Quantitative composition

Each ml contains

Morphine Sulphate BP	10mg
Water for Injection BP	qs

2.3 Salts and hydrates

Morphine Sulphate is equivalent to 10mg of Morphine

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable

2.6 Parenterals excluding powders for reconstitution

Each ml contains

Morphine Sulphate BP 10mg

2.7 Powders for reconstitution prior to parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multi dose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

2.11.1 Expression of strength

Not Applicable

2.11.2 The biological origin of the active substance

Not Applicable

2.11.3 Special provisions for normal immunoglobulins

Not Applicable

2.11.4 Herbal pharmaceutical products

Not Applicable

3. Pharmaceutical form

Solution for Injection

A colourless or almost colourless solution filled in 1ml amber USP Type-1 glass ampoule.

4. Clinical particulars

4.1 Therapeutic indications

Morphine is used for the symptomatic relief of severe pain; relief of dyspnoea of left ventricular failure and pulmonary oedema; pre-operative use.

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 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	2.5-10mg
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.

Discontinuation of therapy

Withdrawal (abstinence) syndrome may be precipitated if opioid administration is suddenly discontinued (See Section 4.4). Therefore the dose should be gradually reduced prior to discontinuation.

Children under 12 years

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

In the Elderly

The dose of morphine should be reduced in elderly patients and titrated to provide optimal pain relief with minimal side effects. Morphine clearance decreases and half-life increase in older patients.

In patients with disturbed Renal Function

Caution should be exercised in the use of Morphine in patients with renal dysfunction i.e. renal failure, because such patients can show signs of overdose following conservative dosage regimens.

In patients with impaired Liver Function

Caution should be exercised in the use of Morphine in patients with impaired liver function e.g. cirrhosis as this condition is likely to affect elimination. The dose therefore should be carefully titrated to provide optimal pain relief.

4.3 Method of administration

By intramuscular, subcutaneous or intravenous injection.

The subcutaneous route is not suitable for oedematous patients.

The epidural or intrathecal routes must not be used as the product contains a preservative.

4.4 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
• Respiratory depression or insufficiency
• Obstructive airways disease
• Cerebral trauma
• Increased intracranial pressure
• Coma
• Convulsive disorders
• Acute alcoholism
• Renal failure
• Ureteral stenosis
• Pancreatitis
• Liver failure
• Gall-bladder dysfunction
• Ileus
• Inflammatory bowel disease
• Hypotension with hypovolaemia
• Prostatic hypertrophy
• Myxoedema
• Phaeochromocytoma
• Concurrent administration of MAO inhibitors or within two weeks of discontinuation of their use.

4.5 Special warnings and precautions for use

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of morphine and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom

alternative treatment options are not possible. If a decision is made to prescribe morphine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over- the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with morphine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain.

This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia 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 treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency

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

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics 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 of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin (see section 4.5).

Other conditions/situations in which morphine should be used with caution

Hypotension, hypothyroidism, asthma (avoid during attack), and decreased respiratory reserve; pregnancy and breast-feeding (see section 4.6); treatment may precipitate coma in hepatic

impairment (reduce dose but many such patients tolerate morphine well – see section 4.2); reduce dose in renal impairment, elderly and debilitated patients (see section 4.2).

Oral P2Y12 inhibitor antiplatelet therapy

Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

Sodium content

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

4.6 Paediatric population

The safety and effectiveness of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established.

4.7 Interaction with other medicinal products and other forms of interaction

• Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

• Other CNS depressants: In patients concurrently receiving other central nervous system depressants (including sedatives, hypnotics, general anaesthetics, phenothiazines, 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: Mixed agonist/antagonist opioid analgesics (e.g. pentazocine, nalbuphine, and buprenorphine) can reduce the analgesic effect of morphine by competitive blocking of the receptor. Therefore these drugs should not be administered to patients who have received or are 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 (e.g. anxiety, confusion and significant depression of respiration, sometimes leading to coma) have been observed with co-administration of both drugs. 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 of morphine have been observed with co-administration of cimetidine. Confusion and severe respiratory depression were reported after a haemodialysis patient had received both morphine and cimetidine.

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

• Alcohol: enhanced sedative and hypotensive effect.

• Anti-Arrhythmtics: delayed absorption of mexiletine.

• Antidepressants: CNS excitation or depression (hypertension or hypotension) if pethidine and possibly other opioid analgesic 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 by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin (see section 4.4)

• A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

4.8 Additional information on special populations

4.9 Paediatric population

The safety and effectiveness of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established.

4.10 Fertility, pregnancy and lactation

4.10.1 General principles

Low levels of Morphine Sulfate Injection BP have been detected in maternal milk. The milk:plasma morphine AUC ratio is about 2:5:1. The amount of Morphine Sulfate Injection BP delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first-pass metabolism.

4.10.2 Women of childbearing potential / Contraception in males and females

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

4.10.3 Pregnancy

Morphine sulfate should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy.

Morphine crosses the placental barrier. Administration during labour may cause respiratory depression in the new born infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour.

Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

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.

4.10.4 Breastfeeding

While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects.

4.10.5 Fertility

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

4.11 Effects on ability to drive and use machines

Morphine causes drowsiness so patients should avoid driving or operating 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. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

It was not affecting your ability to drive safely

4.12 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
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

Very common:

Gastrointestinal system: Nausea, vomiting, constipation.

Respiratory system: Respiratory depression.

Nervous system disorders: Sedation, drowsiness.

Skin: Itching.

Psychiatric disorders: Disorientation, hallucinations, dysphoria, euphoria, tolerance.

Common:

Skin: Urticaria, skin rash, pain at injection site, contact dermatitis.

CNS and nervous system: Headache, vertigo, agitation, convulsions, impairment of taste, mood changes, changes of cognitive and sensory abilities, insomnia, intracranial hypertension, tremor.

Musculoskeletal system: Muscle spasms.

Eye: Miosis, visual disturbances (blurred vision, nystagmus, diplopia).

Gastrointestinal system: Dryness of mouth, pylorospasm, singultus, diarrhoea, abdominal cramps, biliary colic.

Cardiovascular system: Flushing, chills, orthostatic hypotension, bradycardia, hypertension, tachycardia, heart failure, pulmonary oedema.

Respiratory system: Laryngeal spasm, bronchospasm, cough attenuation.

Urogenital system: Urinary retention or hesitancy, oliguria, loss of libido, impotence.

Endocrine: Inappropriate antidiuretic hormone (ADH) secretion characterised by hyponatraemia secondary to decreased free water excretion.

General: Oedema, hypothermia, hyperthermia.

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 pruritis 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.

Uncommon:

Immune system disorders: Anaphylactic / anaphylactoid reaction after i.v. injection.

General: Drug withdrawal syndrome.

Frequency not known:

Nervous system disorders: allodynia, hyperalgesia, hyperhidrosis (see section 4.4)

Psychiatric disorders: Drug dependence (see section 4.4)

Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see section 4.4.

Physiological withdrawal symptoms include: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

4.13 Overdose

Symptoms

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Overdosage with morphine is characterised by respiratory depression (a 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 the re-establishment of 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 naloxone. A response should be seen after 2-3 doses. Note that the duration of action of naloxone is usually shorter than that of morphine and thus patients should be carefully monitored for signs of CNS depression returning.

If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed to maintain alertness and respiratory function. There is no additional information available about the cumulative dose of naloxone that may be safely administered.

To sustain opioid antagonism, an intravenous infusion of naloxone has been suggested. Naloxone may be infused at a rate titrated in accordance with the patient's response both to the infusion and previous bolus injections.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage. It should be administered cautiously to persons who are known or suspected to be physically dependant to morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome 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 the 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 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

Pharmacotherapeutic group: Natural opium alkaloids,

ATC Code: N02AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

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 an interaction with the OP_3(u)-receptor, one of three major classes of opioid receptors that can be 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 CO_2. This effect is mediated by the action on OP_3-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(anhydrous)

Water for injection

6.2 Incompatibilities

None known.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

The product must be stored at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

Primary Packing – USP Type- I amber glass Ampoule

Secondary Packing- Printed Carton & Tray

Tertiary Packing- i. Corrugated Box

- 10x1 ml USP Type I amber glass Ampoules loading on a plastic Tray.
- 10x1 ml Tray loaded amber glass ampoules in an inner Printed canon.
- 10x10x1ml tray loaded amber glass ampoules in an inner carton are packed in outer carton.

This container closure system is suitable for storage, efficacy, transportation and use of the finished product

PACK SIZE:

10x10x1ml.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused product at the end of each operating session.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

Manufacturing Site:

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE) Not Applicable