

## **1. NAME OF THE MEDICINAL PRODUCT**

RUMORF 10mg/ml solution for injection.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 ml contains 10 mg morphine sulphate.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for injection.

Clear colourless to pale yellow solution.

pH 2.5 to 6.0.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Morphine is indicated for the management of severe post-operative and post-traumatic pain as well as severe opioid sensitive pain such as cancer pain.

### **4.2 Posology and method of administration**

#### Posology

Administration and dosage should be individualized taking into account the nature and severity of pain and the patient's general condition.

Individual criteria for the dose depend on the patient's age, weight, pain severity, and medical and analgesic history.

#### **Adults:**

Intravenous: 2.5 – 15 mg administered during 4-5 minutes.

Epidural: Initially up to 5 mg, if necessary 1-2 mg after one hour. To be repeated as

needed. Epidural infusion: Initially 3.5-7.5 mg daily, if necessary increased by 1-2

mg daily.

#### **Children and youth:**

Intravenous: Only when a particularly fast response is required: 0.05-0.1 mg/kg body weight administered very slowly (dilution with isotonic sodium chloride solution is recommended).

Epidural: 0.03-0.05 mg/kg 1-2 times daily.

Subcutaneous, intramuscular: 0.05-0.2 mg/kg body weight, up to every 4 hours if needed.

### **New born**

Intravenous: Only when a particularly fast response is required: 0.025-0.05 mg/kg body weight, administered very slowly (dilution with isotonic sodium chloride solution is recommended).

Epidural: 0.03-0.05 mg/kg 1-2 times daily.

Subcutaneous, intramuscular: 0.025-0.05 mg/kg body weight, up to every 4 hours if needed. For doses corresponding to very small volumes Morphine is recommended to be diluted with isotonic sodium chloride solution to ensure correct dosing.

In severe cancer related pain dose adjustments can be made as long as the effect of the morphine gives a true pharmacological analgesia, i.e. it does not give a sedative effect.

Respiratory depression is uncommon with repeated dosing of epidural morphine to treat pain in cancer patients.

The equianalgesic dose of intrathecal morphine is about 5 times lower than that of epidural morphine, but data from clinical trials are lacking.

### *Treatment control.*

Respiratory supportive therapy and naloxone may be required at respiratory depression. As the respiratory depressant effect may be sustained, repeat doses of naloxone may be required in some cases.

Due to the risk of respiratory depression, patients given epidural morphine for the treatment of postoperative or traumatic pain should be carefully monitored for 8-12 hours after the last injection. The need for monitoring must be assessed for each individual case. Urinary retention caused by morphine could if necessary be reversed by naloxone.

### *Special populations*

Caution should be exercised and the dosage initially reduced in morphine treatment of elderly patients and in patients with hepatic and renal impairment. See also section 4.3 and 4.4.

### *Paediatric population*

Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.

### Method of administration

Before subcutaneous and intramuscular doses corresponding to very small volumes are administered to a new born child Morphine should be diluted to avoid dosing errors. Isotonic sodium chloride solution should be used. Dilution corresponding to an administration volume above 2 ml should be avoided.

*For epidural use* it is appropriate, with customary techniques, to ensure that the administration of morphine occurs in the epidural space. Both the effect and the risk of undesirable effects are significantly strengthened if Morphine accidentally is administered intrathecally.

### *Treatment goals and discontinuation*

Before initiating treatment with Morphine, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the

patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In 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*

Morphine should not be used longer than necessary.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Secretion stagnation
- Respiratory depression
- Acute liver disease
- Agitation states during effect of alcohol or hypnotics
- General contraindications related to epidural administration shall be taken into consideration.

### **4.4 Special warnings and precautions for use**

Addictive agent. Take extreme caution when prescribing this drug.

The patient may develop tolerance to morphine with prolonged use and require progressively higher doses to achieve the desired analgesic effect. There may also be cross-tolerance with other opioids.

The dose may need to be reduced in bronchial asthma, head injuries, hypotension associated with hypovolaemia, hypothyroidism, impaired hepatic and renal function, inflammatory bowel diseases, pancreatitis, bile duct spasm, urinary tract spasm and in the treatment of elderly patients.

Morphine should not be used in idiopathic or psychopathological pain conditions.

Treatment with MAO inhibitors, see 4.5 Interaction with other medicinal products and other forms of interaction.

There is an increased risk for respiratory depression in the treatment of elderly patients.

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

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.

#### *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).

### *Constipation*

Constipation is a common side effect of morphine. The use of laxatives should be considered during the use of Morphine.

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

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

### *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.

### *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).

### *Sleep-related breathing disorders*

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

### *Severe cutaneous adverse reactions (SCARs)*

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

### *Hepatobiliary disorders*

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

### *Opioid Use Disorder (abuse and dependence)*

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

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

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

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

#### *Withdrawal (abstinence)*

The risk of withdrawal (abstinence) increases with the time the drug is used, and with higher doses. Symptoms can be minimized with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

#### *Paediatric population*

Respiratory depression poses a risk to all children. Neonates (especially if they breathe spontaneously) may have an increased sensitivity. Use intravenous morphine with special care in children below 1 year of age.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *The combination should be avoided*

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, gabapentin or pregabalin.

Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

#### *Small amounts of alcohol*

Small amounts of alcohol can dramatically potentiate the weak respiratory depressant effect of morphine. The combination should therefore be avoided.

#### *MAO-inhibitors*

MAO inhibitors may potentiate the effect of morphine (respiratory depression and hypotension). Serotonergic syndrome has been reported with concomitant use of pethidine and MAO inhibitors, and can therefore not be excluded in the combination of morphine and MAO inhibitors.

#### *P2Y12 inhibitor*

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 P2Y<sub>12</sub> inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y<sub>12</sub> inhibition is deemed crucial, the use of a parenteral P2Y<sub>12</sub> inhibitor may be considered.

*The following combinations may require dose adjustment*

*Rifampicin*

Rifampicin decreases the plasma concentration of orally administered morphine to such an extent, that higher doses than normal are required for analgesic effect.

*Diclofenac*

Diclofenac may increase the analgesic effect of morphine, shown in a study of 120 women who received epidural morphine.

*Amitriptyline, clomipramine and nortriptyline*

Amitriptyline, clomipramine and nortriptyline enhance the analgesic effect of morphine. Dose adjustment may be required.

*Combined morphine agonists/antagonists*

Combined morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) reduce the analgesic effect by competitive blocking of receptors, thereby increasing the risk of withdrawal symptoms.

*For the following combinations, the clinical significance is unclear.*

*Baclofen*

The combination of morphine and intrathecal baclofen caused decreased blood pressure in a patient. The risk that this combination can cause apnoea or other CNS symptoms cannot be excluded.

*Hydroxyzine*

Due to an additive effect, concomitant administration of hydroxyzine and morphine may increase CNS depression and drowsiness. Consider changing to non-sedating antihistamine.

*Methylphenidate*

Methylphenidate may increase the analgesic effect of morphine. Consider reducing the dose of morphine when used concomitantly.

*Nimodipine*

Nimodipine may increase the analgesic effect of morphine. Consider reducing the dose of morphine when used concomitantly.

*Ritonavir*

Morphine levels may be decreased due to induction of glucuronidation by concomitant administration of ritonavir, when used as an antiretroviral agent or as a pharmacokinetic enhancer (boost) of other protease inhibitors.

## **4.6 Fertility, pregnancy and lactation**

*Men and women of childbearing potential*

Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is

assured (see section 5.3).

#### *Pregnancy*

There are limited amounts of data from the use of morphine in pregnant women. Morphine crosses the placenta. Studies in animals have shown reproductive toxicity (see section 5.3). For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Morphine can prolong or shorten the duration of labour. Morphine can produce respiratory depression in the neonate, if it is administered during labour. Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome and respiratory depression. Treatment may include an opioid (withdrawal), an opioid antagonist (respiratory depression) and supportive care.

Especially during the 2 to 3 hours before expected partum morphine should only be administered on strict indication and following a mother benefit versus baby risk analysis.

#### *Breast-feeding:*

Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma. Since clinically relevant concentrations of morphine may be reached in nursing infants, breast-feeding is not recommended (see section 5.2).

#### *Fertility*

There are no clinical data on the effects of morphine on male or female fertility. Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

### **4.7 Effects on ability to drive and use machines**

Morphine has major influence on the ability to drive and use machines. Treatment with Morphine may impair reaction ability.

### **4.8 Undesirable effects**

Approximately 20% of the patients experience nausea and vomiting. Most side effects are dose dependent.

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10000$  to  $< 1/1000$ ), very rare ( $< 1/10000$ ), not known (cannot be estimated from the available data).

#### *Immune system disorders:*

Not known: anaphylactoid reactions

#### *Endocrine disorders:*

Common: increased ADH release.

#### *Psychiatric disorders:*

Uncommon: dysphoria.

Not known: euphoria, sleep, memory and concentration difficulties, hallucinations,

confusion, dependence

*Nervous system disorders:*

*Common:* increased PaCO<sub>2</sub> levels, sedation.

*Uncommon:* respiratory depression, disorientation, drowsiness, dizziness, headache, dazed, dysphoria

*Not known:* convulsions, allodynia, hyperalgesia (see section 4.4), hyperhidrosis

*Eye disorders:*

*Common:* miosis.

*Cardiac disorders*

*Rare:* palpitations, tachycardia

*Vascular disorders:*

*Rare:* orthostatic hypotension., hypertension, hypotension, peripheral oedema, syncope

*Respiratory, thoracic and mediastinal disorders:*

*Uncommon:* bronchoconstriction

*Not known:* central sleep apnoea syndrome

*Gastrointestinal disorders:*

*Common:* nausea, vomiting, constipation

*Not known:* dry mouth, pancreatitis

*Hepatobiliary disorders:*

*Uncommon:* bile duct spasm

*Not known:* spasm of sphincter of Oddi

*Skin and subcutaneous tissue disorders:*

*Common:* pruritus

*Not known:* acute generalised exanthematous pustulosis (AGEP), urticaria

*Musculoskeletal, connective tissue and bone disorder*

*Not known:* myoclonus

*Renal and urinary disorders:*

*Common:* urinary retention.

*Uncommon:* urinary tract spasm

*General disorders and administration site conditions:*

*Uncommon:* light-headedness.

*Not known:* drug withdrawal (abstinence) syndrome

*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 4.4.

Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis.

Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence,



“drug craving” is often involved.

#### *Drug dependence*

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

Respiratory depression has a slow onset and is most evident 5-8 hours after injection. Co-administration of parenteral narcotics may increase the frequency of side effects and can enhance the depressant effects. The risk of late respiratory depression should be specially monitored at post-operative use. The risk of respiratory depression is very small in the treatment of cancer patients previously treated with morphine.

With regards to undesirable effects, in epidural morphine treatment the occurrence of pruritus is observed, whereas epidurally administered morphine does not appear to give the same tendency to nausea and vomiting, bile duct and urinary tract spasm and sedation, as when given intramuscularly with equianalgesic doses. However, epidural morphine gives an increased frequency of urinary retention by relaxing the detrusor muscle with subsequent increased bladder capacity.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

## **4.9 Overdose**

#### *Symptoms of overdose:*

Signs of overdose include pin-point pupils, respiratory depression and hypotension. Circulatory disorders and coma may occur in severe cases. Death may occur from respiratory failure. Pneumonia aspiration.

Typical triad symptoms: low level of consciousness, severe respiratory depression, maximum miosis pupils. Hypotension. Pale, clammy skin. At high doses, cyanosis, areflexia, respiratory arrest, unconsciousness, circulatory failure, pulmonary oedema. Acidosis, convulsions (especially in children), possibly hypokalaemia and hypocalcaemia. Nausea, vomiting, constipation. Risk of myocardial injury, rhabdomyolysis and renal failure in severe intoxication.

#### *Treatment of overdose:*

Respiratory depression at morphine intoxication can be reversed with naloxone, initially 0.4 mg for adults (children 0.01 mg/kg) slowly intravenously, the dose is gradually increased if necessary.

Continuous infusion of naloxone can sometimes be a practical option.

Respiratory treatment on the indication (with PEEP in pulmonary oedema). Naloxone cannot replace respiratory therapy in serious intoxication. Intravenous fluids (electrolyte, glucose), blood gas control, acidosis correction. Symptomatic therapy.

### *Toxicity:*

Toxic dose for adults (no onset of tolerance) is usually in the range of 40-60 mg orally and 30 mg parenterally. Scopolamine, hypnotics and alcohol potentiate toxic effects.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Natural opium alkaloids, ATC code: N02AA01

#### *Latency and duration*

The latency to achieve analgesic effect is about 10 minutes and the time for full effect is about 45-60 minutes after injection. Epidural administration of morphine is a long-acting analgesic method intended for epidural, lumbar or thoracic, administration. A more effective pain relief with longer duration on pain from the thorax, abdomen and lower extremities is obtained compared with morphine administered parenterally. The mean duration of effect at a dose of 4 mg epidural morphine is about 10-12 hours in post-operative pain. The treatment effect and analgesic duration varies with type of surgery. In the treatment of severe opioid sensitive pain, e.g., in cancer, the analgesic effect of the above dose may be lower and of shorter duration.

#### *Mode of action*

Morphine has an agonistic effect on opioid receptors. The strong analgesic effect is due to an altered pain perception and partly to an increase in pain threshold.

Epidurally administered morphine probably exerts its main effect directly on the opiate receptors in the spinal cord and causes a selective inhibition of the pain impulse to the central nervous system (CNS). The analgesic effect is segmental, however, not completely, and free of motor, sensory or sympathetic blockade.

#### *Metabolites*

Morphine is metabolised by conjugation to the 2 major metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Small amounts of morphine-3,6-diglucuronide may also be formed. M3G has low affinity for opioid receptors, i.e. no documented analgesic effect, but can contribute to excitatory effect. M6G is twice as potent as morphine in systemic administration, and the pharmacological effects of M6G cannot be distinguished from morphine. In chronic administration, it stands for a significant proportion of morphine analgesic effects.

#### *Respiratory depression*

The respiratory depressant effect of morphine is due to an inhibition of the carbon dioxide stimulating effect on the respiratory centre in the medulla oblongata, but also due to the fact that respiratory response to low oxygen tension is inhibited. The respiratory depressant effects of epidural morphine is conditioned mainly by cranial CSF transportation from the site of injection. The medicinal product can then reach the vital centres in the medulla oblongata. In patients with normal ventilation abilities an epidural dose of 2-5 mg of morphine have little importance in this regard. There is an increased risk of respiratory depression in the treatment of elderly patients, particularly when used with other narcotic analgesics and in repeated epidural doses. Risk of respiratory depression is also present in patients with chronic respiratory disease and patients with high intracranial pressure. The effects of morphine can be enhanced after encephalitis.

If breathing is affected, respiratory supportive therapy and administration of naloxone may be required. As the depressant effects can be prolonged, repeat doses of naloxone is required in some cases.

### *Tolerance*

Repeated dose of epidural morphine in animals noted reduced efficacy in experimental systems for the evaluation of analgesia. Experience from the development of tolerance in human is still limited but tolerance may occur. However, this usually does not cause any problems in the treatment of severe pain associated with cancer.

The equianalgesic dose of intrathecal morphine is about 5 times lower than that of epidural morphine, but clinical trials are not available.

## **5.2 Pharmacokinetic properties**

Morphine does not have dose-dependent

### kinetics. Absorption

Maximum concentration in blood is reached within 10-20 minutes. Epidurally administered morphine is significantly absorbed to the systemic circulation. The bioavailability of morphine may increase in patients with liver cancer.

Neonates have a reduced capacity to metabolise morphine. Older children probably have significantly lower morphine and metabolite concentrations in plasma compared to adults given a comparable dose/kg.

### Distribution

The volume of distribution is about 3 L/kg with a plasma protein binding of approximately 35%. The clearance is approx. 24 ml/min \* kg and half-life in plasma and cerebrospinal fluid (CSF) is 2-4 hours after epidural administration.

### Metabolism, Elimination

Morphine is metabolized in the liver to the two major metabolites morphine-3-glucuronide (lack analgesic effect but can contribute with excitatory effects) and morphine-6-glucuronide (M6G) (more potent than morphine itself). Small amounts of morphine-3,6-diglucuronide may also be formed.

Morphine and its metabolites undergo enterohepatic circulation. The elimination of morphine occurs primarily by glucuronidation and excretion of unchanged morphine in urine is <0.1%. M6G is excreted through the urine, accordingly M6G may accumulate in renal impairment. Hepatic and renal impairment affects the elimination of the substance.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There have been no long-term animal studies on the tumorigenic potential of morphine. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

### Mutagenic and tumorigenic potential

There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans.

## Reproductive toxicity

Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence). In addition, morphine had an effect on male sexual behaviour and fertility in various animal species. In male rats, reduced fertility and chromosomal damage in gametes have been reported.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride  
Sodium hydroxide  
Hydrochloric acid  
Water for injection

### **6.2 Incompatibilities**

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5-fluorouracil.

### **6.3 Shelf life**

36 months.

The product should be used immediately after first opening.

### **6.4 Special precautions for storage**

Store below 30°C.

### **6.5 Nature and contents of container**

Ten ampoules of 1ml packed in a carton.  
Five ampoules of 1ml packed in a carton.

### **6.6 Special precautions for disposal and other handling**

Splashes on the skin and in the eyes can cause pain, redness and itching. Avoid direct contact with the medical product. For method of administration refer to section 4.2. Do not use if particulate matter is present.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

**Marketing Authorisation Holder:**

Rusan Pharma Ltd.  
58/D. Govt. Industrial Estate,  
Kandivli (W), Mumbai,  
India.

**Manufacturing Site Address:**

Rusan Pharma Ltd.  
Khasra no. 122 MI, Central hopetown, Selaqui,  
Dehradun – 248197, Uttarakhand, India.  
Tel no.: +91 135 2698327  
Fax no.: +91 135 2698440  
Email: [pushkar@rusanpharma.com](mailto:pushkar@rusanpharma.com)

**Local Technical Representative:**

Surgilinks Ltd .  
Surgilinks Building Mombasa Road  
P.O. Box 14461 – 00800 Nairobi, Kenya.  
Telephone: +254 720 702 490  
E-Mail: [registration@surgilinksltd.com](mailto:registration@surgilinksltd.com)

**8. MARKETING AUTHORISATION NUMBER**

CTD8618

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

10/02/2024

**10. DATE OF REVISION OF THE TEXT**

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