SUMMARY OF PRODUCT CHARACTERISTICS

MORPHIA – Morphine Sulfate 10mg in 1ml solution for injection

Active Ingredient
Morphine Sulfate

1. Name of the medicinal product

MORPHIA – Morphine Sulfate 10mg in 1ml solution for injection

2. Qualitative and quantitative composition

Each ml of solution for injection contains 10mg Morphine Sulfate

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

4. Clinical particulars

4.1 Therapeutic indications

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

Morphine Sulfate may be given by the subcutaneous, intramuscular or intravenous route. The subcutaneous route is not suitable for oedematous patients. The dosage should be based on the severity of the pain and the response and tolerance of the individual patient. The epidural or intrathecal routes must not be used as the product contains a preservative.

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

Adults:
Subcutaneous or intramuscular injection:
10mg every four hours if necessary (the dose may vary from 5mg-20mg depending on the individual patient).

Slow intravenous injection (2mg/minute):
Quarter to half of corresponding intramuscular dose not more than every four hours.

Elderly and debilitated patients: The dose should be reduced because of the depressant effect on respiration. Caution is required.

Children: Use in children is not recommended.

Hepatic impairment:
A reduction in dosage should be considered in hepatic impairment.

Renal impairment:
The dosage should be reduced in moderate to severe renal impairment.

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use.

Discontinuation of therapy
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to discontinuation.

4.3 Contraindications

Acute respiratory depression, known morphine sensitivity, biliary colic (see also biliary tract disorders 4.4 Special Warnings and Precautions), acute alcoholism. Conditions in which intracranial pressure is raised, comatose patients, head injuries, as there is an increased risk of respiratory depression that may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient. Morphine is also contraindicated where there is a risk of paralytic ileus, or in acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated).

Phaeochromocytoma (due to the risk of pressor response to histamine release).

4.4 Special warnings and precautions for use

Morphine should be given in reduced doses or with caution to patients with asthma or decreased respiratory reserve (including cor pulmonale, kyphoscoliosis, emphysema, severe obesity). Avoid use during an acute asthma attack (see 4.3 Contraindications). Opioid analgesics in general should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, or convulsive disorders.

Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.

Morphine can cause an increase in intra-biliary pressure as a result of effects on the sphincter of Oddi. Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see 4.3). In patients given morphine after cholecystectomy, biliary pain has been induced.
Caution is advised when giving morphine to patients with impaired liver function due to its hepatic metabolism (see 4.2 Posology).

Severe and prolonged respiratory depression has occurred in patients with renal impairment who have been given morphine (see 4.2 Posology).

Dosage should be reduced in elderly and debilitated patients (see 4.2 Posology).

Palliative care - in the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

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.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: Concomitant use of morphine sulfate 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 sulfate 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).

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.

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 sulfate.

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 new-born 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: enhanced sedative and hypotensive effects.

Anti-arrhythmics: There may be delayed absorption of mexiletine.

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

Antidepressants, anxiolytics, hypnotics: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs.

The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

Antipsychotics: possible enhanced sedative and hypotensive effect.

Anti-diarrhoeal and anti-peristaltic agents (such as loperamide and kaolin): concurrent use may increase the risk of severe constipation.

Antimuscarinics: agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects.
Consequently, severe constipation and urinary retention may occur during intensive antimuscarinic-analgesic therapy.

Metoclopramide and domperidone: There may be antagonism of the gastrointestinal effects of metoclopramide and domperidone.

Oral P2Y12 inhibitor antiplatelet therapy: 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.

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).

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 in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast feeding
Administration to nursing women is not recommended as morphine sulphate may be secreted in breast milk and may cause respiratory depression in the infant.

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 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions
Adverse reactions reported in the following table by MedDRA System Organ Class (SOC), Preferred Term and frequency. The following frequency categories are used:

Term	Frequency of occurrence
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)
Not known	(Cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Gastro-intestinal disorders	Very Common	Nausea, vomiting, constipation.
System Organ Class	Frequency	Undesirable effects
	Common	Dryness of mouth, pyloro-spasm, singultus, diarrhoea, abdominal cramps, biliary colic.
Immune System Disorders	Uncommon	Anaphylactic / anaphylactoid reaction after i.v. injection.
Psychiatric Disorders	Very Common	Disorientation, hallucinations, dysphoria, euphoria, tolerance.
	Not Known	Drug dependence (see section 4.4)
CNS and Nervous system disorders	Very Common	Sedation, drowsiness.
	Common	Headache, vertigo, agitation, convulsions, impairment of taste, mood changes, changes of cognitive and sensory abilities, insomnia, intracranial hypertension, tremor.
	Not Known	Allodynia, hyperalgesia, hyperhidrosis (see section 4.4)
Eye Disorders	Common	Miosis, visual disturbances (blurred vision, nystagmus, diplopia).
Urogenital Disorders	Common	Urinary retention or hesitancy, oliguria, loss of libido, impotence.
Cardiac Disorders	Common	Flushing, chills, orthostatic hypotension, bradycardia, hypertension, tachycardia, heart failure, pulmonary oedema.
Endocrine Disorders	Common	Inappropriate antidiuretic hormone (ADH) secretion characterised by hyponatraemia secondary to decreased free water excretion.
Respiratory Disorders	Very Common	Respiratory depression.
	Common	Laryngeal spasm, bronchospasm, cough attenuation.
Skin and Subcutaneous Tissue	Very Common	Itching.

Disorders	Common	Urticaria, skin rash, pain at injection site, contact dermatitis
Musculoskeletal and Connective Tissue Disorders	Common	Muscle spasms.
General Disorders and Administration Site Condition	Common	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	Drug withdrawal 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 section 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. The euphoric activity of morphine has led to its abuse.

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 asked to report any suspected adverse reactions via Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org/

4.9 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.

Toxic doses vary considerably with the individual, and regular users may tolerate large doses.
The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Death may occur from respiratory failure

Other opioid overdose symptoms include hypothermia, pneumonia aspiration, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure pulmonary oedema, severe nervousness or restlessness, hallucinations, convulsions (especially in infants and children).
Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

Treatment
The medical management of overdose involves prompt administration of the specific opioid antagonist naloxone if coma or bradypnea are present using one of the recommended dosage regimens. Both respiratory and cardiovascular support should be given where necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, natural opium

alkaloids ATC code N02AA01

Morphine is obtained from opium, which acts mainly on the CNS and smooth muscle.

Morphine is a potent analgesic with competitive agonist actions at the μ-receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a μ-1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a μ-2 receptor subtype. Morphine is also a competitive agonist at the κ-receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the δ- and the σ-receptors.

Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine.

5.2 Pharmacokinetic properties

Absorption:	Rapidly absorbed after subcutaneous or intramuscular administration.
Blood concentration:	After an intramuscular dose of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes. After an intravenous dose of 10mg, serum concentrations of about 60ng/ml are obtained in 15 minutes falling to 30ng/ml after 30 minutes and to 10ng/ml after three hours. Subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following three hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the elderly.
Half-life	Serum half-life in the period ten minutes to six hours following intravenous administration-two to three hours; serum half-life in the period six hours onwards-10 to 44 hours.
Distribution:	Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles. Morphine crosses the placenta and traces are secreted in sweat and milk. Protein binding-about 35% bound to albumin and to immunoglobulins at concentrations within the therapeutic range.

Metabolic reactions:	Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides. N-demethylation, O-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parental administration; the O-methylation pathway to form codeine has been challenged and codeine and nor-codeine metabolites in urine may be formed from codeine impurities in the morphine sample studied.
Excretion:	After a parental dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide. After administration of large doses to addicts about 0.1% of a dose is excreted as nor-codeine. Urinary excretion of morphine appears to be pH dependent to some extent; as the urine becomes more acidic more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted.
	Up to 10% of a dose may be excreted in the bile.

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
Sodium metabisulfite
Hydrochloric acid (for pH
adjustment) Sodium hydroxide (for
pH adjustment) Water for injections

6.2 Incompatibilities
Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities (sometimes attributed to particular formulations) have included aciclovir sodium, doxorubicin, fluorouracil, frusemide, heparin sodium, pethidine hydrochloride, promethazine hydrochloride and tetracyclines. Specialised references should be consulted for specific compatibility information.
Physiochemical 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
Do not store above 30°C. Keep the ampoules in the outer carton to protect from light. Do not use if particulate matter is present.

6.5 Nature and contents of container

Clear glass ampoules, glass type I,
Ph. Eur. Pack sizes: 10 x 1 ml

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Tasa Pharma
Limited Unit C1-C3
Kay
complex
Nairobi
Kenya

8. Marketing Authorization Numbers

H2024/CTD10126/22973

9. Date of first authorization/renewal of the authorization

2024 March 06

10. Date of revision of the text

21/08/2026