SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rhotard Morphine SR 60 mg Tablets
Morphgesic SR 60 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rhotard Morphine SR 60 mg Tablets/ Morphgesic SR 60 mg Tablets
Each tablet contains 60 mg of morphine sulfate.

Excipients with known effect:
Lactose (33.000 mg per tablet).
Fd & C Yellow #6/Sunset Yellow FCF Lake (E110)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Controlled release tablets
Each 60 mg tablet is an orange coloured biconvex round film coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rhotard Morphine SR/ Morphgesic SR Tablets are indicated in adults for the prolonged relief of severe pain.

4.2 Posology and method of administration

Posology

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

Adults
The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. The tablets should normally be administered twice daily at 12 hourly intervals. One or two 10 mg tablets (10 mg) twice daily is the recommended starting dosage for a patient presenting with severe pain. With increasing severity of pain it is recommended that the dosage of morphine be increased to achieve the desired relief. The dosage may be varied by choosing combinations of available strengths (10, 30, 60, and 100 mg) or by using higher strength tablets alone.

It is recommended that a patient transferred from another oral morphine preparation, having similar bioavailability to oral morphine liquid, should receive the same total morphine dose in one 24-hour period. This total dose should be divided between the morning and evening administration. Dosage titration and clinical assessment may be appropriate.

Where a patient had previously received parenteral morphine prior to being transferred to Rhotard Morphine SR/ Morphgesic SR Tablets, a higher dosage of morphine may be required. Individual dosage adjustment will be necessary to compensate for any reduction in analgesic effect associated with oral administration.

Some patients may require supplemental parenteral morphine which is perfectly acceptable. Careful attention should be paid to the total morphine dosage however, and the prolonged effects of morphine in the Rhotard Morphine SR/ Morphgesic SR formulation should also be borne in mind.

Paediatric population
Rhotard Morphine SR/ Morphgesic SR Tablets are not recommended for paediatric use.

Method of administration

Treatment goals and discontinuation
Before initiating treatment with Rhotard Morphine SR/ Morphgesic SR Tablets, 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 Rhotard Morphine SR/ Morphgesic SR Tablets, 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
Rhotard Morphine SR/ Morphgesic SR Tablets should not be used longer than necessary.

Oral

Rhotard Morphine SR / Morphgesic SR Tablets should be swallowed whole and not chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Respiratory depression, paralytic ileus, acute abdomen, delayed gastric emptying, obstructive airways disease, or acute hepatic disease. It is also contra-indicated in the presence of acute alcoholism, head injuries and conditions in which intracranial pressure is raised. Neither should it be given during an attack of bronchial asthma nor heart failure secondary to chronic lung disease.

Patients with excessive bronchial secretions should not be given Rhotard Morphine SR/ Morphgesic SR Tablets as morphine diminishes the cough response.

Not recommended for pre-operative use or for acute post operative use.

Not recommended during pregnancy and lactation (see section 4.6).

Concurrent administration of monoamine oxidase inhibitors (MAOIs) or within two weeks of discontinuation of their use.

Renal impairment
Severe and prolonged respiratory depression may occur in patients with renal impairment given morphine; this is attributed to the accumulation of the active metabolite morphine-6-glucuronide. Therefore Rhotard Morphine SR/ Morphgesic SR Tablets should not be administered to patients with moderate or severe renal impairment (glomerular filtration rate <20 ml/min).

Hepatic impairment
As with other opioid analgesic containing preparations Rhotard Morphine SR/ Morphgesic SR Tablets should not be administered to patients with severe hepatic impairment as it may precipitate coma.

Rhotard Morphine SR/ Morphgesic SR Tablets, as with other opioid containing preparations, is contraindicated in patients with ulcerative colitis, since such preparations may precipitate toxic dilation or spasm of the colon.

4.4 Special warnings and precautions for use

Concomitant use of alcohol and Rhotard Morphine SR/ Morphgesic SR Tablets may increase the undesirable effects of Rhotard Morphine SR/ Morphgesic SR Tablets, concomitant use should be avoided.

Rhotard Morphine SR/ Morphgesic SR Tablets should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, or shock.

It should be used with caution in patients with either obstructive bowel disorders or myasthenia gravis.

Caution in patients with convulsive disorders, hypotension with hypovolaemia, the elderly, opioid dependent patients, diseases of the biliary tract, pancreatitis and inflammatory bowel disorders. Use with caution in patients with impaired respiratory function, delirium tremens, severe cor pulmonale and patients with a history of substance abuse. Morphine may lower the seizure threshold in patients with a history of epilepsy.

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.

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.

Should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected to occur during use, treatment should be discontinued immediately.

Extreme caution should be exercised when administering morphine to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.

As with all morphine sulfate preparations, patients about to undergo additional pain relieving procedures (e.g. cordotomy, surgery, plexus blockade) should not receive Rhotard Morphine SR/ Morphgesic SR Tablets for 24 hours prior to the intervention. If further treatment with Rhotard Morphine SR/ Morphgesic SR Tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

Persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)

Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)

The major risk of opioid excess is respiratory depression.

Opioid Use Disorder (abuse and dependence)

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

Repeated use of Rhotard Morphine SR/ Morphgesic SR Tablets 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 Rhotard Morphine SR/ Morphgesic SR Tablets 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 (eg. major depression, anxiety and personality disorders).

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.

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.

The clinical need for analgesic treatment should be reviewed regularly. Before initiating treatment with Rhotard Morphine SR/ Morphgesic SR Tablets 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 behavior (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

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.

The prolonged release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine sulfate (see section 4.9).

Abuse of Rhotard Morphine SR/ Morphgesic SR Tablets by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Urinary retention may occur in patients with urethral disease or prostatic hypertrophy.

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.

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

It is not possible to ensure bio-equivalence between different brands of controlled release morphine products. Therefore, it should be emphasised that patients, once titrated to an effective dose should not be changed from Rhotard Morphine SR/ Morphgesic SR Tablets to other slow, sustained or controlled release morphine or other potent narcotic analgesic preparations without retitration and clinical assessment.

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

Concomitant use of Rhotard Morphine SR/ Morphgesic SR Tablets 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 Rhotard Morphine SR/ Morphgesic SR Tablets 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).

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).

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

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.

Rhotard Morphine SR/ Morphgesic SR Tablets contains:

- Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Sunset yellow (E 110): May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol may enhance the pharmacodynamic effects of Rhotard Morphine SR/ Morphgesic SR Tablets; concomitant use should be avoided.

Rhotard Morphine SR/ Morphgesic SR Tablets should not be concurrently administered with monoamine oxidase inhibitors (MAOI's) or used within two weeks of discontinuation of MAOI use (see section 4.3). The depressant effects of morphine may be enhanced, or the effects of other compounds potentiated, by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants and phenothiazines, as well as muscle relaxants, gabapentin or pregabalin and antihypertensives. 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 sulfate. The action of morphine may in turn affect the activities of other compounds, for example its gastro-intestinal effects may delay absorption as with mexilitine or may be counteractive as with metoclopramide.

Cimetidine inhibits the metabolism of morphine.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

The analgesic effect of opioids tends to be enhanced by co-administration of dexamfetamine and hydroxyzine.

Medicinal products that block the action of acetylcholine, for example anti-histamines, anti-parkinsonian agents and anti-emetics, may interact with morphine sulfate to potentiate anti-cholinergic adverse events.

Plasma concentrations of morphine sulfate may be reduced by rifampicin.

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.

Morphine may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals, although the significance of this finding is not known for man. Caution should be exercised when these drugs are administered concurrently.

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine sulfate, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine sulfate and may possibly decrease plasma concentrations of morphine sulfate.

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 sulfate may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

Effects of morphine exposure on sexual maturation of male rats, their reproductive capacity and the development of their progeny have been examined. Results indicated that exposure during adolescence led to pronounced inhibition of several indices of sexual maturation (e.g. hormone levels, reduced gonad weights), smaller litters and selective gender specific effects on endocrine function in the offspring.

Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

A disruption in ovulation and amenorrhoea can occur in women given morphine.

4.7 Effects on ability to drive and use machines

Rhotard Morphine SR/ Morphgesic SR Tablets may modify the patient's reactions to a varying extent depending on the dosage and susceptibility. If affected, 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. 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:
  - The medicine has been prescribed to treat a medical or dental problem and

- 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

4.8 Undesirable effects

In normal doses, the most common side effects of morphine are nausea, vomiting, constipation, difficulty in micturition and drowsiness. With chronic therapy, nausea and vomiting are unusual with Rhotard Morphine SR/ Morphgesic SR Tablets but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

A case of morphine induced thrombocytopenia has been reported.

Morphine has a depressant effect on gonadal hormone secretion which can result in a reduction of testosterone leading to regression of secondary sexual characteristics in men on long-term therapy.

Very Common (≥ 1/10), Common (≥1/100 to <1/10),Uncommon (≥1/1,000 to <1/100) and Not known (cannot be estimated from the available data); adverse drug reactions are listed in the table below:

Undesirable Effects	**Very Common**	**Common**	**Uncommon**	**Not known**
Immune system disorders			Allergic reaction	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Drug dependence (see section 4.4)*, Dysphoria Thinking disturbances restlessness
Nervous system disorders		Headache Involuntary muscle contractions Somnolence Dizziness	Convulsions Hypertonia Myoclonus Paraesthesia Syncope	Raised intracranial pressure Coma Hyperalgesia (see section 4.4) hyperaesthesia/allodynia

				Hyperhidrosis
Eye disorders			Visual disturbance	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Circulatory failure Hypertension
Respiratory, thoracic and mediastinal disorders			Bronchospasm Pulmonary oedema Respiratory depression	Cough decreased Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Vomiting	Dyspepsia Ileus Taste perversion	Narcotic bowel syndrome Dry mouth Pancreatitis
Hepatobiliary disorders			Increased hepatic enzymes	Exacerbation of pancreatitis Biliary pain Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders		Hyperhidrosis Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders			Urinary retention	Ureteric spasm Dysuria
Reproductive system and breast disorders				Amenorrhea Decreased libido Erectile dysfunction
General disorders and administration		Asthenic conditions	Peripheral oedema, drug withdrawal	Drug tolerance Hypothermia

site conditions		Pruritus	syndrome†	Anxiety Dysphoric mood

*Physical and psychological dependence may appear after administration of therapeutic doses for periods of 1 to 2 weeks. Some cases of dependence have been observed after only 2 to 3 days.

†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 Rhotard Morphine SR/ Morphgesic SR Tablets 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).

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 asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Signs & symptoms:

Signs of morphine toxicity and overdosage are pin-point pupils, skeletal muscle flaccidity, bradycardia respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. Overdosage can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage. Death may occur from respiratory failure. Pneumonia aspiration.

Crushing and taking the contents of a prolonged release dosage form may lead to the release of morphine in an immediate fashion; this might result in a fatal overdose.

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.

Management

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Rhotard Morphine SR/ Morphgesic SR Tablets remaining in the intestine will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdosage should be modified accordingly.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

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

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, ATC code: N02A

Mechanism of action

Morphine acts as an agonist at opiate receptors in the CNS particularly Mu and to a lesser extent Kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression and euphoria, and Kappa receptors, spinal analgesia, miosis and sedation.

Central Nervous System:

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). Morphine produces respiratory depression by direct action on brain stem respiratory centres. Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of

haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Morphine and related analgesics may produce both physical and psychological dependence and should therefore be used with discrimination. Tolerance may also develop.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts. Morphine may produce spasm of the sphincter of Oddi, thus raising intrabiliary pressure.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Some premenopausal women may have low oestrogen levels. Clinical symptoms may be manifest from these hormonal changes.

Other Pharmacological Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

Routes of administration include the oral, subcutaneous, intramuscular, intravenous, intraspinal and rectal routes. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

5.2 Pharmacokinetic properties

Absorption

Morphine is immediately absorbed from the digestive tract following oral administration. Morphine has a plasma half life of about 2 to 3 hours and if given IV must be administered frequently. Rhotard Morphine SR/ Morphgesic SR Tablets, being a sustained release preparation of morphine, has the advantage that it is only administered twice daily.

Distribution

The percentage of binding to plasma proteins after absorption is low. There is no clearly defined correlation between the plasma concentration of morphine and the analgesic effect.

Biotransformation

A considerable quantity of morphine is metabolised by the liver to glucuronides, which undergo enterohepatic recirculation.

Elimination

The product is eliminated essentially in the urine, by glomerular filtration, mainly as glucuronides. A small amount (less than 10%) is eliminated in the faeces.

A summary of the morphine pharmacokinetic parameters is given below:

(a) Half life; plasma half life; about 2-3 hours
(b) Volume of distribution; about 3-5 litres/KG
(c) Clearance; plasma clearance; about 15 to 20 ml/min/kg
(d) Protein binding; in plasma 20-35%

Pharmacokinetic parameters pertinent to Rhotard Morphine SR/ Morphgesic SR Tablets are summarised in the following table:

Parameters	**Rhotard Morphine SR/ Morphgesic SR Tablets** **Fasting (A)**	**Rhotard Morphine SR/ Morphgesic SR Tablets** **Food (B)**
$AUC_{(0-t)}$ (ng.h/ml)	46.02 ± 18.85	59.88 ± 20.52
C_{max} (ng/ml)	9.2 ± 3.6	13.6 ± 4.6
T_{max} hours	2.5 ± 1.7	3.9 ± 1.6

5.3 Preclinical safety data

A. Mutagenicity

No bacterial mutagenicity studies with morphine have been reported. A review of the literature has indicated that morphine was negative in gene mutation assays in Drosophila

melanogaster but was positive in a mammalian spermatocyte test. The results of another study has indicated that morphine causes chromosomal aberrations, in germ cells of male mice when given at dose levels of 10, 20, 40 or 60 mg/kg bodyweight for 3 consecutive days.

B. Carcinogenicity

No long term studies have been conducted in animals to determine whether morphine is potentially carcinogenic.

C. Teratogenicity

Morphine was not teratogenic in rats when dosed for up to 15 days at 70mg/kg/day. Morphine given subcutaneously to mice at very high doses (200, 300 or 400 mg/kg/day) on days 8 or 9 of gestation, resulted in a few cases of exencephaly and axial skeletal fusions. The hypoxic effects of such high doses could account for the defects seen.

Lower doses of morphine (40, 4.0 or 0.4 mg/ml) given to mice as a continuous i.v. infusion (at a dose volume of 0.3 ml/kg) between days 7 and 10 of gestation, caused soft tissue and skeletal malformations as shown in previous studies.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose,
Hydroxyethylcellulose,
Hypromellose (E464),
Povidone,
Talc,
Magnesium Stearate,
Macrogol
Industrial Methylated Spirits 99%

Rhotard Morphine SR 60 mg Tablets/ Morphgesic SR 60 mg Tablets contain the colourants listed below:
Titanium Dioxide (E171)
FD&C Yellow #6/Sunset Yellow FCF Lake (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Each pack contains either 10 or 60 tablets in PVC blister packs with aluminium foil lidding.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

Amdipharm UK Limited
Dashwood House, 69 Old Broad Street, London,
EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0233

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 28 June 2002

10 DATE OF REVISION OF THE TEXT

17/02/2025