SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cyclimorph-15 Injection

Cyclizine Tartrate 50mg/ml and Morphine Tartrate 15mg/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicine contains morphine tartrate 15 mg and cyclizine tartrate 50 mg (equivalent to 39.01 mg cyclizine) in each 1 ml ampoule.

Excipient with known effect:

Each 1 ml contains 1 mg sodium metabisulphite (E223).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection.

A clear very slightly coloured solution. pH 4.3 to 5.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine is indicated for the relief of moderate to severe pain in all suitable medical and surgical conditions (see Contraindications and Precautions & Warnings) in which reduction of the nausea and vomiting associated with the administration of morphine is required.

4.2 Posology and method of administration

Posology

Adults

The usual dose is 10-20 mg morphine tartrate, given subcutaneously, intramuscularly or intravenously.

Additional doses may not be given more frequently than 4 hourly.

Not more than 3 doses (representing 150 mg cyclizine tartrate: i.e. 3 ml of Cyclimorph 15 Injection) should be given in any 24-hour period.

Elderly

Morphine doses should be reduced in elderly patients and titrated to provide optimal pain relief with minimal side effects since:

- Increased duration of pain relief from a standard dose of morphine has been reported in elderly patients.

- A review of pharmacokinetic studies has suggested that morphine clearance decreases and half-life increases in older patients.

- The elderly may be particularly sensitive to the adverse effects of morphine.

Paediatric population

This medicine should not be used in children under 12 years of age.

Method of administration

Treatment goals and discontinuation

Before initiating treatment with Cyclimorph, 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 Cyclimorph, 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

Cyclimorph should not be used longer than necessary.

By subcutaneous, intramuscular or intravenous injection.

4.3 Contraindications

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

This medicine, like other opioid-containing preparations, is contraindicated in patients with respiratory depression. Patients with excessive bronchial secretions should not be given this medicine as morphine diminishes the cough response.

This medicine should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.

This medicine is contraindicated in patients with head injury or raised intra-cranial pressure.

This medicine, as with other opioid-containing preparations, is contraindicated for children less than one year of age. It is also contraindicated for pre-operative use or during the first 24 hours post-operatively.

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, this medicine 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 this medicine should not be administered to patients with severe hepatic impairment as it may precipitate coma.

This medicine is contra-indicated in the presence of acute alcohol intoxication. The antiemetic properties of cyclizine may increase the toxicity of alcohol.

This medicine is contraindicated in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment.

This medicine, 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. This medicine is contraindicated in patients with paralytic ileus and delayed gastric emptying.

This medicine is contraindicated in biliary and renal tract spasm and in patients immediately after operative interventions in the biliary tract.

4.4 Special warnings and precautions for use

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.

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.

This medicine should be used with caution in the debilitated since they may be more sensitive to the respiratory depressant effects.

This medicine should be used with caution (including consideration of dose administered) in the presence of the following:

convulsive disorders

delerium tremens

severe cor pulmonale

hypothyroidism

adrenocortical insufficiency

hypopituitarism

prostatic hypertrophy

shock

diabetes mellitus

myasthenia gravis

hypotension and hypovolaemia

pancreatitis

obstructive bowel disorders

inflammatory bowel disorders

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

Cyclizine may cause a fall in cardiac output associated with increase in heart rate, mean arterial pressure and pulmonary wedge pressure. This medicine should therefore be used with caution in patients with severe heart failure.

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.

Cyclizine should be avoided in patients with porphyria. Therefore use of this medicine should also be avoided in these patients.

Case reports of paralysis have been received in patients using intravenous cyclizine. Some of the patients mentioned in these case reports had an underlying neuromuscular disorder. Thus, intravenous cyclizine should be used with caution in all patients in general, and in patients with underlying neuromuscular disorders in particular.

Because cyclizine has anticholinergic activity it may precipitate incipient glaucoma. It should be used with caution and appropriate monitoring in patients with glaucoma and also in obstructive disease of the gastrointestinal tract.

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

Concomitant use of Cyclizine Tartrate 50mg/ml and Morphine Tartrate 10mg/ml Injection 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 Cyclizine Tartrate 50mg/ml and Morphine Tartrate 10mg/ml Injection 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).

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.

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

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.

Morphine has an abuse potential similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol or drug abuse.

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.

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

This medicine contains sodium metabisulphate which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

The action of morphine may in turn affect the activities of other compounds, for example its gastrointestinal effects may delay absorption as with mexilitine or may be counteractive as with metoclopramide.

Monoamine oxidase inhibitors (MAOI's) may prolong and enhance the respiratory depressant effects of morphine. Opioids and MAOI's used together may cause fatal hypotension and coma (see Contra-indications).

Cimetidine inhibits the metabolism of morphine.

Because of its anticholinergic activity cyclizine may enhance the side effects of other anticholinergic drugs.

The analgesic effect of opioids tends to be enhanced by co-administration of [1]dexamfetamine, hydroxyzine, and some phenothiazines although respiratory depression may also be enhanced by the latter combination.

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

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.

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.

In vitro data suggest that St. John's Wort (Hypericum perforatum) may induce cytochrome P450 3A4. There is a theoretical possibility therefore, that plasma levels of morphine tartrate may be decreased during concomitant administration and increased upon withdrawal of St. John's Wort.

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

Interference with laboratory tests

Morphine can react with Folin-Ciocalteau reagent in the Lowry method of protein estimation.

Morphine can also interfere with the determination of urinary 17-ketosteroids due to chemical structure effects in the Zimmerman procedure.

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).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence on the safety of the combination in human pregnancy nor is there evidence from animal work that the constituents are free from hazard. However, limited data from epidemiological studies of cyclizine and morphine in human pregnancies have found no evidence of teratogenicity. In the absence of definitive human data with the combination the use of this medicine in pregnancy is not advised.

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 of morphine during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding
Cyclizine is excreted in human milk, however, the amount has not been quantified.

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

Morphine can significantly suppress lactation. Morphine is excreted in human milk, but the amount is generally considered to be less than 1% of any dose.

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

In common with other opioids, morphine may produce orthostatic hypotension and drowsiness in ambulatory patients. Sedation of short duration has been reported in patients receiving intravenous cyclizine. The CNS depressant effects of this medicine may be enhanced by combination with other centrally acting agents (see *Interaction with Other Medicaments and Other Forms of Interactions*). Patients should therefore be cautioned against activities requiring vigilance including driving vehicles and 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:
  - 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

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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)

The following undesirable effects have been reported with a frequency of Not known:

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system	Not known	Agranulocytosis, morphine-induced

System Organ Class	Frequency	Adverse reactions
disorder		thrombocytopenia
Immune system disorders	Not known	Hypersensitivity reactions, including anaphylaxis, angioedema, allergic skin reactions, hypersensitivity hepatitis, anaphylactoid reactions, anaphylactic shock
Psychiatric disorders	Not known	Dysphoria, drug dependence (see section 4.4)
Nervous system disorders	Not known	Somnolence, raised intra-cranial pressure, confusion, restlessness, restless leg syndrome, vertigo, sedation, headache, nervousness, insomnia, auditory and visual hallucinations, dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, twitching, muscle spasms, convulsions, disorientation, dizziness, decreased consciousness, transient speech disorders, paraesthesia, generalised chorea, allodynia, hyperalgesia (see section 4.4), hyperhidrosis
Eye disorders	Not known	Miosis, blurred vision, oculogyric crisis
Cardiac disorders	Not known	Tachycardia
Vascular disorders	Not known	Orthostatic hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression, bronchospasm, apnoea This medicine has demonstrated significant incidence of single cough or paroxysm of coughing immediately after its administration. Central sleep apnoea syndrome
Gastrointestinal disorders	Not known	Constipation, nausea, vomiting, dryness of the mouth, nose and throat, pancreatitis
Hepatobiliary disorders	Not known	Biliary tract spasm, cholestatic jaundice has occurred in association with cyclizine, cholestatic hepatitis, hepatic dysfunction, spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders	Not known	Skin reactions (e.g. urticaria) drug rash, fixed drug eruption (rash), acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Not known	Renal spasm, difficulty with micturition, urinary retention
Reproductive system and breast disorders	Not known	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.
General disorders and administration site conditions	Uncommon Not known	Drug withdrawal syndrome Injection site reactions including vein tracking, erythema, pain and thrombophlebitis, dysphoric mood, anxiety

A case of psychomotor hyperactivity following intravenous administration of morphine during the induction of anaesthesia has been reported.

Case reports of paralysis have been received in patients using intravenous cyclizine. Some of the patients mentioned in these case reports had an underlying neuromuscular disorder.

Rapid IV administration of cyclizine can lead to symptoms similar to overdose.

Case reports of Narcotic bowel syndrome and hyperaesthesia/ allodynia due to Morphine have also been reported.

Drug dependence

Repeated use of Cyclimorph 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

Symptoms

The signs of overdosage with this medicine are those pathognomic of opioid poisoning i.e. respiratory depression, bradycardia, pin point pupils, hypotension, circulatory failure and deepening coma. Mydriasis may replace miosis as asphyxia intervenes. Opioid overdose can result in death from respiratory failure.

Drowsiness, floppiness, miosis and apnoea are signs of opioid overdosage in children as are convulsions.

Rhabdomyolysis progressing to renal failure and Pneumonia aspiration has been reported in opioid overdosage.

Signs and symptoms of acute toxicity from cyclizine arise from peripheral anticholinergic effects and effects on the central nervous system.

Peripheral anticholinergic symptoms include, dry mouth, nose and throat, blurred vision, tachycardia and urinary retention.

Central nervous system effects include drowsiness, dizziness, incoordination, ataxia, weakness, hyperexcitability, disorientation, impaired judgement, hallucinations, hyperkinesia, extrapyramidal motor disturbances, convulsions, hyperpyrexia and respiratory depression.

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

It is imperative to maintain and support respiration and circulation.

The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and restoration of spontaneous respiration. The literature should be consulted for details of appropriate dosage.

The use of a specific opioid antagonist in patients tolerant to morphine may produce withdrawal symptoms.

Convulsions should be controlled with parenteral anticonvulsant therapy.

Patients should be monitored closely for at least 48 hours in case of relapse.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids, Natural opium alkaloids, Morphine combinations; ATC Code: N02AA51

Mechanism of action of cyclizine

Cyclizine is a histamine H_1 receptor antagonist of the piperazine class. It possesses anticholinergic and antiemetic properties. The exact mechanism by which cyclizine can prevent or suppress both nausea and vomiting from various causes is unknown.

Pharmacodynamic effects of cyclizine

Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus.

Mechanism of action of Morphine

Morphine is a competitive agonist at the μ-opioid receptor and is a potent analgesic. It is thought that activity at the μ1-receptor subtype may mediate the analgesic and euphoric actions of morphine whilst activity at the μ2-receptor subtype may mediate respiratory depression and inhibition of gut motility.

Pharmacodynamic effects of Morphine

An action at the K-opioid receptor may mediate spinal analgesia.

5.2. Pharmacokinetic properties

Distribution of cyclizine

In a healthy adult volunteer the administration of a single oral dose of 50 mg cyclizine resulted in a peak plasma concentration of approximately 70ng/ml, occurring at about 2 hours after administration. Urine collected over 24 hours contained less than 1% of the total dose administered.

Biotransformation of cyclizine

Cyclizine is metabolised to its N-dimethylated derivative norcyclizine, which has little antihistaminic (H_1) activity compared to cyclizine.

Elimination of cyclizine

In a separate study in one healthy adult volunteer the plasma elimination half-life of cyclizine was approximately 20 hours.

Distribution of morphine

Morphine is bound to plasma proteins only to the extent of 25-35% and therefore functions that change the extent of protein binding will have only a minor impact on its pharmacodynamic effects.

Biotransformation of morphine

Morphine is extensively metabolised by hepatic biotransformation. In addition, the kidney has been shown to have the capacity to form morphine glucuronides. The major metabolite is morphine-3-glucuronide (approximately 45% of a dose). Morphine-6-glucuronide is a minor metabolite (approx. 5% of the dose) but is highly active. Although renal excretion is a minor route of elimination for unchanged morphine, it constitutes the major mechanism of elimination of conjugated morphine metabolites including the active morphine-6-glucuronide.

Elimination of morphine

The mean elimination half-life for morphine in blood and plasma is 2.7h (range 1.2-4.9h) and 2.95 (range 0.8-5h) respectively.

5.3 Preclinical safety data

A. Mutagenicity

Cyclizine was not mutagenic in an Ames test (at a dose level of 100 μg/plate), with or without metabolic activation.

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 by the same authors 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 cyclizine or morphine are potentially carcinogenic.

C. Teratogenicity

Some animal studies indicate that cyclizine may be teratogenic at dose levels up to 25 times the clinical dose level. In another study, cyclizine was negative at oral dose levels up to 65 mg/kg in rats and 75 mg/kg in rabbits.

Morphine was not teratogenic in rats when dosed for up to 15 days at 70 mg/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.

D. Fertility

In a study involving prolonged administration of cyclizine to male and female rats, there was no evidence of impaired fertility after continuous treatment for 90-100 days at dose levels of approximately 15 and 25 mg/kg/day.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tartaric Acid
Sodium Metabisulphite
Water for Injections

6.2 Incompatibilities

See Interactions with other medicaments *and* other forms of interaction and Contra-indications.

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

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C.
Protect from light. Do not freeze.

6.5. Nature and contents of container

Ampoules which comply with the requirements of the European Pharmacopoeia for type I neutral glass.

Pack size: l ml ampoules: Box of five.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 20072/0008

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