Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cyclimorph 15 Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cyclimorph 15 Injection 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:
Sodium metabisulphite (E223) (1 mg /1 ml ampoule).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
A clear very slightly coloured solution. pH 4.3 - 5.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cyclimorph Injection is indicated in adults and children for the relief of moderate to severe pain in all suitable medical and surgical conditions (see section 4.3 and 4.4) 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 and children over 12 years:
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

Children 6-12 years: 5-10 mg morphine tartrate as a maximum single dose.

Children 1-5 years: 2.5-5 mg morphine tartrate as a maximum single dose.

Method of administration
Subcutaneous, intramuscular or intravenous injection.

When used intravenously, Cyclimorph Injection should be injected slowly into the bloodstream, over a period of 4 to 5 minutes with the patient in the recumbent position, with only minimal withdrawal of blood into the syringe.

Treatment goals and discontinuation
Before initiating treatment with Cyclimorph Injection, 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 Injection, 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 Injection 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.

Respiratory depression or obstructive airways disease. Patients with excessive bronchial secretions should not be given Cyclimorph Injection as morphine diminishes the cough response.

An attack of bronchial asthma or in heart failure secondary to chronic lung disease.

Head injury or raised intra-cranial pressure.

Acute alcohol intoxication. The antiemetic properties of cyclizine may increase the toxicity of alcohol.

Concomitant in therapy with monoamine oxidase inhibitors or within 14 days of stopping such treatment.

Ulcerative colitis, since such preparations may precipitate toxic dilation or spasm of the colon.

Paralytic ileus and delayed gastric emptying.

Biliary and renal tract spasm and in patients immediately after operative interventions in the biliary tract.

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

4.4 Special warnings and precautions for use

Opioid Use Disorder (abuse and dependence) & Drug Withdrawal (abstinence) syndrome

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Cyclimorph Injection Repeated use of Cyclimorph Injection 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 Cyclimorph Injection 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).

Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Before initiating treatment with Cyclimorph Injection 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.

Cyclomorph Injection 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.

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

Cyclimorph Injection should be used with caution in the presence of the following: convulsive disorders, delirium tremens, severe cor pulmonale, hypothyroidism, adrenocortical insufficiency, hypopituitarism, myxoedema, prostatic hypertrophy, shock, diabetes mellitus, myasthenia gravis, hypotension and hypovolaemia, pancreatitis. Obstructive bowel disorders and inflammatory bowel disorders.

Morphine may lower the seizure threshold in patients with a history of
epilepsy.

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

Cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure. Cyclimorph Injection 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 Cyclimorph during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Cyclizine should be avoided in patients with porphyria. Therefore, use of Cyclimorph Injection 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 reports had an underlying neuromuscular disorder, thus intravenous cyclizine should be used with caution in all patients in general, and patients with underlying neuromuscular disorders in particular.

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 Cyclimorph Injection may be enhanced by combination with other centrally acting agents (see section 4.5). Patients should therefore be cautioned against activities requiring vigilance including driving vehicles and operating machinery.

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.

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 Cyclimorph 15 Solution for 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 Cyclimorph 15 Solution for 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).

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.

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.

Cyclimorph 15 mg Injection contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 1ml, that is to say essentially 'sodium-free'.

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

4.5 Interaction with other medicinal products and other forms of interaction

Cyclizine enhances the soporific effect of pethidine.

Because of its anticholinergic activity cyclizine may enhance the side effects of other anticholinergic drugs, and may have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and some antidepressants (both tricyclics and MAOI's).

Mixed agonist/ antagonist opioid analgesics: Mixed agonist/antagonist opioid analgesics (e.g. pentazocine, nalbuphine, and buprenorphine) can reduce the analgesic effect of morphine by competitive blocking of the receptor. Therefore, these drugs should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic.

Muscle relaxants: Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants.

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 (MAOIs) may prolong and enhance the respiratory depressant effects of morphine. Opioids and MAOIs used together may cause fatal hypotension and coma (see section 4.3).

Cimetidine inhibits the metabolism of morphine.

The analgesic effect of opioids tends to be enhanced by co-administration of dexamphetamine, 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.Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

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.

Dopaminerigcs: hyperpyrexia and CNS toxicity reported with selegiline.

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, neuroleptics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives,

and gabapentin or pregabalin and alcohol. 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 Cyclimorph Injection in pregnancy is not advised.

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

Administration of morphine during labour may cause respiratory depression in the newborn infant.

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

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
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.

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

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 Cyclimorph Injection may be enhanced by combination with other centrally acting agents (see section 4.5). Patients should therefore be cautioned against activities requiring vigilance including driving vehicles and operating machinery.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: 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:
Adverse reactions attributable to morphine include:

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Not known	Anaphylactic shock, anaphylactoid reactions
Psychiatric disorders	Not known	Confusional state, dysphoria, restlessness, agitation, insomnia, euphoria, hallucinations, mood altered, dependence
Nervous system disorders	Not known	Intracranial pressure increased,headache, convulsions, paraesthesia, hyperaesthesia/ allodynia, dizziness, syncope,

		coma, somnolence. A case of psychomotor hyperactivity following intravenous administration of morphine during induction of anaesthesia has been reported, allodynia, hyperalgesia (see section 4.4), hyperhidrosis
Eye disorders	Not known	Miosis, visual disturbance
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Bradycardia, palpitations, tachycardia, heart failure
Vascular disorders	Not known	Orthostatic hypotension, facial flushing, hypertension, circulatory failure
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression, bronchospasm, pulmonary oedema, respiratory failure, Central sleep apnoea syndrome
Gastrointestinal disorders	Not known	Constipation, nausea, vomiting, abdominal pain, anorexia, dry mouth, dyspepsia, narcotic bowel syndrome, ileus, taste perversion, pancreatitis
Hepatobiliary disorders	Not known	Biliary colic, exacerbation of pancreatitis, increased hepatic enzymes, spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders	Not known	Urticaria, hyperhidrosis, rash, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Not known	Muscle spasm, hypertonia, myoclonus
Renal and urinary disorders	Not known	Dysuria, renal colic, urinary retention, ureteric spasm
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, amenorrhea, erectile dysfunction
General Disorders	Not known	Drug withdrawal (abstinence) syndrome: dysphoric mood, anxiety

Adverse reactions attributable to cyclizine include:

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Not known	Agranulocytosis
Immune system disorders	Not known	Hypersensitivity, anaphylactic reaction, hypersensitivity hepatitis has occurred
Psychiatric disorders	Not known	Restlessnessor agitation, nervousness, euphoria, insomnia auditory and visual hallucinations (particularly when dosage recommendations have been exceeded), disorientation
Nervous system disorders	Not known	Case reports of paralysis have been received in patients using intravenous cyclizine. Some of the patients mentioned in these reports had an underlying neuromuscular disorder. Thus, intravenous cyclizine should be used with caution in all patients in general, and patients with underlying neuromuscular disorders in particular. Headache, somnolence, incoordination, sedation, dyskinesia, dystonia, extrapyramidal disorder, tremor, convulsions, dizziness, depressed level of consciousness, speech disorder, paraesthesia, generalised chorea
Eye disorders	Not known	Blurred vision, oculogyric crisis
Ear and labyrinth disorders	Not known	Tinnitus
Cardiac disorders	Not known	Tachycardia, palpitations, arrhythmias
Vascular disorders	Not known	Hypertension and hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Nasal dryness, dry throat, bronchospasm and apnoea
Gastrointestinal disorders	Not known	Dryness of mouth, constipation
Hepatobiliary disorders	Not known	Hepatic function abnormal, jaundice, cholestatic, hepatitis cholestatic, hepatitis

Skin and subcutaneous tissue disorders	Not known	Urticaria, pruritus, rash, angioedema, dermatitis allergic, fixed drug eruption
Musculoskeletal and connective tissue disorders	Not known	Twitching, muscle spasms
Renal and urinary disorders	Not known	Urinary retention

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

Adverse effects related to Injection formulation

System Organ Class	**Adverse reactions**
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Bradycardia, palpitations
Vascular disorders	Thrombophlebitis
Gastrointestinal disorders	Constipation
Skin and subcutaneous tissue disorders	Urticaria, erythema, pruritus
General disorder and administration site condition	Injection site reaction, asthenia, malaise, hypothermia, pain

Cyclimorph IV Injection has demonstrated significant incidence of single cough or paroxysm of coughing immediately after its administration.

Drug dependence and withdrawal (abstinence) syndrome
Repeated use of Cyclimorph Injection 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). 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.

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 HPRA Pharmacovigilance.
Website: www.hpra.ie.

4.9 Overdose

Symptoms
The signs of overdosage with Cyclimorph Injection 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. Death may occur from respiratory failure. Pneumonia aspiration.

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

Rhabdomyolysis progressing to renal failure 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.

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: piperazine derivatives.
ATC code: R06AE53

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.

It may inhibit the part of the midbrain known collectively as the emetic centre.

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 μ^1-receptor subtype may mediate the analgesic and euphoric actions of morphine whilst activity at the μ^2-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.

Clinical efficacy and safety
Cyclizine produces its anti-emetic effect within two hours and lasts approximately four hours.

5.2 Pharmacokinetic properties

Absorption 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 70 ng/ml, occurring at about 2 hours after administration. Urine collected over 24 hours contained less than 1% of the total dose administered. 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 cyclizine
Cyclizine is metabolised to its N-dimethylated derivative norcyclizine, which has little antihistaminic (H_1) activity compared to cyclizine.

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 2.95h (range 0.8-5h) respectively.

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.

5.3 Preclinical safety data

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.

Carcinogenicity:
No long-term studies have been conducted in animals to determine whether cyclizine or morphine are potentially carcinogenic.

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.

Fertility

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid
Sodium metabisulphite (E223)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

6.3 Shelf life

Unopened: 3 years.

Once Opened: From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

Ampoules comply with the requirements of the European Pharmacopoeia for Type I neutral glass. Cyclimorph Injection is supplied in boxes of 5 x 1ml ampoules.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

For single use only. Discard any remaining solution.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/003/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

December 2023