

Package leaflet: Information for the user

Cyclimorph®10 Solution for Injection and Cyclimorph®15 Solution for Injection morphine tartrate and cyclizine tartrate

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cyclimorph Injection is and what it is used for
2. What you need to know before you are given Cyclimorph Injection
3. How Cyclimorph Injection will be given to you
4. Possible side effects
5. How to store Cyclimorph Injection
6. Contents of the pack and other information

1. What Cyclimorph Injection is and what it is used for

The name of your medicine is Cyclimorph 10 mg Solution for Injection or Cyclimorph 15 mg Solution for Injection (called Cyclimorph Injection in this leaflet). It contains morphine tartrate which belongs to a group of drugs called opioids. Cyclimorph Injection also contains cyclizine tartrate which is an anti-histamine with activity against feeling sick (nausea) and being sick (vomiting). Cyclimorph Injection is used in adults and children for the relief of moderate to severe pain in which reduction of nausea and vomiting associated with morphine is required.

2. What you need to know before you are given Cyclimorph Injection

You should not be given this medicine :

- if you are allergic to morphine tartrate, cyclizine tartrate or any of the other ingredients of this medicine (listed in section 6)
- if you are suffering from breathing problems or excessive phlegm (such as asthma or bronchitis)
- if you have been told your heart is not working properly (heart failure)
- if you are suffering from a head injury
- if you have raised pressure around the brain
- if you are suffering from stomach problems such as delayed gastric emptying
- if you are suffering from a disease of the intestine such as ulcerative colitis, or obstructive disease of the intestine
- if you are suffering from a disease of the liver or the kidney, including biliary or renal (kidney) tract spasms, or if you have recently undergone surgery on your biliary tract
- if you are intoxicated with alcohol
- if you are taking or have you recently been taking a drug from a group of antidepressants called monoamine oxidase inhibitors (MAOIs).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given Cyclimorph Injection if you

- are debilitated or suffering from shock
- suffer from epilepsy or convulsions
- have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking or sweating, upon stopping taking alcohol or drugs
- are suffering from severe or pulmonale (heart failure caused by long term lung disease)
- are suffering from a disease of the thyroid, pituitary or the adrenal glands
- are suffering from diabetes
- are suffering from myasthenia gravis (a disease causing muscle weakness)

- are suffering from neuromuscular disease (muscle weakness)
- are suffering from pancreatitis (swelling of the pancreas)
- have bowel problems e.g. inflammatory or obstructive bowel disorder
- are suffering from a rare disease called phaeochromocytoma (rare form of tumor affecting part of the body known as the adrenal glands)
- suffer from low blood pressure (hypotension, low blood volume)
- have been told your heart is not working properly (heart failure)
- have been told you have an enlarged prostate gland
- are suffering from a disease called porphyria
- are suffering from an eye disease called glaucoma (caused by a rise of pressure within the eye)
- have been taking this medicine for a long period of time. Tolerance and dependence may occur in susceptible individuals. Stopping this medicine too quickly after using it for a long period of time may result in withdrawal symptoms
- are suffering abstinence symptoms or dependence. The most common abstinence symptoms are mentioned in section 3. If this occurs, your doctor may change the type of medicine or the times between doses.
- have once been dependent on drugs or alcohol. Also tell if you feel that you are becoming dependent on Cyclimorph Injection while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for the pain.
- are taking any medicine from the group of medicines known as benzodiazepines. Taking these medicines with Cyclimorph Injection may result in sedation, difficulties in breathing (respiratory depression), coma and may be fatal. Even if benzodiazepines are prescribed, your doctor may need to change the dose, the duration of treatment or monitor you regularly.
- have increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in strong analgesic (“painkiller”), (see section 2).
- are suffering from weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement.
- have loss of libido, impotence, cessation of menstruation. This may be because of decreased sex hormone production.

If any of the above applies to you, or if you are not sure please tell your doctor before you are given Cyclimorph Injection.

Other medicines and Cyclimorph Injection

Tell your doctor or nurse if you are taking or have recently taken or might take any other medicines

- if you are taking any of the following: phenothiazines (to manage psychosis), sleeping tablets, tranquilisers, muscle relaxants, anticholinergic drugs (such as benzhexol, orphenadrine, procyclidine, atropine, ipratropium or oxybutynin), dopaminergic drugs (such as selegiline), opioid analgesics (such as pethidine, pentazocine, nalbuphine, buprenorphine), diuretics (water tablets), dexamphetamine, hydroxyzine, mexilitine, metoclopramide, cimetidine, ritonavir or propranolol
- if you regularly drink alcohol
- if you are taking medicines for depression (tricyclic antidepressants or monoamine oxidase inhibitors)
- if you are taking or you have recently been taking St. John’s Wort (*Hypericum perforatum*)
- if you are about to undergo any surgical procedures requiring anaesthetics.
- rifampicin to treat e.g. tuberculosis
- Some medicines used to treat blood clots (e.g. clopidogrel, prasugrel, ticagrelor) may have delayed and decreased effect when taken together with opium

Concomitant use of Cyclimorph Injection and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However, if your doctor does prescribe Cyclimorph Injection together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all

sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

The following information is intended for healthcare professionals only:

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

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. If Cyclimorph is used for a long time during pregnancy, there is a risk of the new-born child having drug withdrawal (abstinence) symptoms which should be treated by a doctor.

Pregnancy

(Cyclimorph Injection can cause breathing problems in new-born babies if used during labour).

Breast-feeding

Cyclimorph Injection is excreted in breast milk.

Fertility

Cyclimorph Injection may disrupt ovulation and menstruation in women.

Driving and using machines

Cyclimorph Injection may cause low blood pressure and make you feel dizzy or drowsy. Do not drive or operate machinery if this medicine affects you in this way.

Cyclimorph Injection contains:

- **Sodium:** This medicine contains less than 1mmol sodium (23 mg) per 1ml, that is to say essentially 'sodium free'.
- **sodium metabisulphite:** May rarely cause severe hypersensitivity reactions (skin-rash, itching or shortness of breath, swelling of the face and throat and collapse).and bronchospasm (breathing difficulties)

3. How Cyclimorph Injection will be given to you

Cyclimorph Injection is usually given by injection into a vein (i/v), into a muscle (i/m) or under the skin (s/c). Your doctor will decide on a dose and duration of Cyclimorph Injection therapy which is right for you.

The recommended dose is:

Adults and children over 12 years: recommended starting dose is between 10 and 20 mg.

Use in children and adolescents

Children aged 6-12 years: The maximum single dose is between 5 and 10 mg.

Children aged 1-5 years: The maximum single dose is between 2.5 and 5 mg.

Use in the elderly:

A reduced adult dosage may be given to elderly patients.

Additional doses may not be given more frequently than 4 hourly. Not more than 3 doses (representing 150 mg of cyclizine tartrate i.e. 3 ml of Cyclimorph 10 or 15 Injection) should be given in any 24 hour period.

If you are given more Cyclimorph Injection than you should

If you think that you have been given too much Cyclimorph Injection or if someone else takes it by mistake tell your doctor immediately. Symptoms of overdose include difficulty in breathing, fast or slow heart beat, pin point pupils, low blood pressure, dry mouth, nose and throat, blurred vision, drowsiness, dizziness,

difficulty controlling movements, increased movements, muscle weakness, difficulty passing water, kidney failure, disorientation, impaired judgment, hallucinations, fits, fever and loss of consciousness.

People who have taken an overdose may get pneumonia from inhaling vomit or foreign matter, symptoms may include breathlessness, cough and fever.

People who have taken an overdose may also have breathing difficulties leading to unconsciousness or even death.

If you stop being given Cyclimorph Injection

Do not stop treatment with Cyclimorph unless agreed with your doctor. If you want to stop the treatment with Cyclimorph, ask your doctor how to slowly decrease the doses so you avoid abstinence symptoms. Abstinence symptoms may include body aches, tremors, diarrhoea, stomach pain, nausea, flu-like symptoms, fast heartbeat and large pupils. Psychological symptoms include an intense feeling of dissatisfaction, anxiety and irritability. Ask your doctor before stopping treatment with Cyclimorph Injection. Stopping treatment abruptly after prolonged use may cause withdrawal symptoms.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects are reported for either compound with a not known frequency (frequency cannot be estimated from the available data)

- Anaphylaxis -a serious allergic reaction which may include rash, breathing difficulty, dizziness, swelling of the face and throat and collapse
- high blood pressure, or conversely, low blood pressure/fainting
- circulatory failure (low blood pressure, loss of consciousness)
- coma (unconsciousness lasting more than six hours)
- vein inflammation (thrombophlebitis)
- fluid in the lung with difficulty in breathing (pulmonary oedema)
- heart failure
- irregular heart beat (arrhythmias)
- increase or decrease in heart rate
- feeling your heart beat (palpitation)
- headaches
- fits (seizures)
- dizziness
- pins and needles/tingling feeling in the limbs
- increase sensitivity to touch and pain (hyperaesthesia/ allodynia)
- difficulty in speaking
- paralysis (loss of muscle function)
- loss of coordination
- tremor (shaking)
- muscle twitches, spasms or tremors or unusual body movements, particularly of your hands, arms or legs
- drowsiness
- breathlessness or breathing difficulties
- nervousness, agitation, unease or restlessness
- confusion
- difficulty in sleeping
- intense feelings of well-being (euphoria)
- seeing or hearing “unreal” sights and sounds (hallucinations)
- a skin rash or itching or pain/irritation at or near the site of injection
- increased sweating (hyperhidrosis)
- feeling cold (hypothermia)
- difficulty in passing water
- flushing (redness of the face)
- feeling of weakness (asthenia)

- generally feeling unwell
- ringing in the ears (tinnitus)
- vertigo (dizziness accompanied by a spinning sensation)
- colicky stomach
- stomach pain
- feeling sick and vomiting
- a dry mouth, nose or throat
- constipation
- loss of appetite (anorexia)
- indigestion (dyspepsia)
- bowel obstruction (ileus/ narcotic bowel syndrome)
- taste alteration
- worsening of pancreatitis (this can cause severe pain in the stomach and back, nausea, vomiting, constipation and dry mouth)
- increased liver enzymes (detected by blood tests)
- loin pain (pain in the back below the ribs)
- cholestatic jaundice (yellowing of the skin and whites of the eyes)
- blurred vision, disturbances in vision
- involuntary rolling of the eyes
- contraction of the pupil (pin-point pupils)
- tolerance and dependence may occur
- abstinence symptoms or dependence (for symptoms see section 3: If you stop taking Cyclimorph).
- upsets to blood counts which could cause unexpected bruising and bleeding, or make infections more likely
- if used long term in men, may depress male hormone leading to loss of body hair and small testicles
- absence of menstrual periods (amenorrhea)
- sexual dysfunction
- single cough or bouts of coughing may occur.

Tell your doctor if you notice any side effects from your medicine, even if they are not mentioned here.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the HPRA Pharmacovigilance.

Website: www.hpra.ie.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Cyclimorph Injection

Keep this medicine out of the sight and reach of children.

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

Do not freeze.

Do not use this medicine after the expiry date which is stated on the carton and label after Exp. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cyclimorph Injection contains

- The active substances are morphine tartrate and cyclizine tartrate.
Cyclimorph 10 Solution for Injection contains morphine tartrate 10 mg and cyclizine tartrate 50 mg per ml (equivalent to 39.01 mg cyclizine), in a 1 ml ampoule.
Cyclimorph 15 Solution for Injection contains morphine tartrate 15 mg and cyclizine tartrate

50 mg per ml (equivalent to 39.01 mg cyclizine), in a 1 ml ampoule.

- The other excipients are tartaric acid, sodium metabisulphite (E223) and water for injections.

What Cyclimorph Injection looks like and contents of the pack

Cyclimorph Injection is a clear, slightly coloured solution in a glass ampoule. Cyclimorph Injection is supplied in boxes of 5 x 1 ml ampoules.

Marketing Authorisation Holder

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

Manufacturer

Cenexi SAS
52 rue Marcel et Jacques Gaucher
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To the Medical and Pharmaceutical Professionals

Cyclimorph 10 Solution for Injection and Cyclimorph 15 Solution for Injection.

1. NAME OF THE MEDICINAL PRODUCT

Cyclimorph 10 Solution for Injection.

Cyclimorph 15 Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cyclimorph 10 Injection contains morphine tartrate 10 mg and cyclizine tartrate 50 mg (equivalent to 39.01 mg cyclizine) in each 1 ml ampoule.

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

Excipients with known effect:

Sodium metabisulphite (E223) (1 mg per 1 ml ampoule).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection (Injection).

A clear very slightly coloured solution. pH 4.3 to 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 10 or 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.

Discontinuation of therapy

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

Method of administration

Subcutaneous, intramuscular or intravenous injection.

When used intravenously, Cyclimorph Injection should be injected slowly into the bloodstream, with only minimal withdrawal of blood into the syringe.

4.3 Contraindications

Hypersensitivity to the active substances 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.

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

Concomitant 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

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

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.

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 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 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 10 mg and 15 mg Injection contain 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

The central nervous system depressant effects of Cyclimorph Injection may be enhanced by other centrally-acting agents such as phenothiazines, hypnotics, tranquillisers, anaesthetics, neuroleptics, alcohol and 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.

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 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.

Dopaminergic: 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).

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: ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ 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, hyperesthesia/ 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 |
| Gastrointestinal disorders | Not known | Constipation, nausea, vomiting, abdominal pain, anorexia, dry mouth, dyspepsia, Narcotic bowel syndrome, ileus, taste perversion |
| Hepatobiliary disorders | Not known | Biliary colic, exacerbation of pancreatitis, increased hepatic enzymes |
| Skin and subcutaneous tissue disorders | Not known | Urticaria, hyperhidrosis, rash |
| 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 | Restlessness or 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

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see 4.4.

Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, “drug craving” is often involved.

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 judgment, 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 H₁ 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 κ -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.

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.

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.

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-Ciocalteu 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 μ g/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 1 ml 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

Cyclimorph 10 Solution for Injection: PA 1142/3/1
Cyclimorph 15 Solution for Injection: PA 1142/3/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 April 1978
Date of latest renewal: 1 April 2008

10. DATE OF REVISION OF THE TEXT

11/2020