Read all of this leaflet carefully before you start using 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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. 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 use Cyclimorph Injection
3. How to use Cyclimorph Injection
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 use Cyclimorph Injection
Do not use Cyclimorph Injection:
- 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 or pharmacist before using Cyclimorph Injection if any of the following apply to you:
- if you are debilitated or suffering from shock.
- if you suffer from epilepsy or convulsions.
- If you have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking or sweating, upon stopping taking alcohol or drugs.
- if you are suffering from severe cor pulmonale (heart failure caused by long term lung disease).
- if you are suffering from a disease of the thyroid, pituitary or the adrenal glands.
- if you are suffering from diabetes.
• if you are suffering from myasthenia gravis (a disease causing muscle weakness).
• if you are suffering from neuromuscular disease (muscle weakness).
• if you are suffering from pancreatitis (swelling of the pancreas).
• if you have bowel problems e.g. inflammatory or obstructive bowel disorder.
• if you are suffering from a rare disease called phaeochromocytoma (rare form of tumor affecting part of the body known as the adrenal glands).
• if you suffer from low blood pressure (hypotension, low blood volume).
• if you have been told your heart is not working properly (heart failure).
• if you have been told you have an enlarged prostate gland.
• if you are suffering from a disease called porphyria.
• if you are suffering from an eye disease called glaucoma (caused by a rise of pressure within the eye).
• if you 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.

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 pharmacist if you are taking, 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, mexiletine, 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.

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.
(Cyclimorph Injection can cause breathing problems in new-born babies if used during labour).
Cyclimorph Injection is excreted in breast milk.
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 medicinal product contains less than 23 mg per dose, i.e. essentially ‘sodium free’.

3. How Cyclimorph Injection is given
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.

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 receive 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.

If you stop using Cyclimorph Injection
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.
• anaphylaxis (a severe allergic reaction which may include rash, breathing difficulty, 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 (hyperesthesia/ 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
• contraction of the pupil (pin-point pupils)
• tolerance and dependence may occur
• 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 (amenorhea)
• sexual dysfunction
• single cough or bouts of coughing may occur.

This product contains sodium metabisulphite (E223) which may rarely cause an allergic-type reaction (skin-rash, itching or shortness of breath, swelling of the face and throat and collapse).

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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cyclimorph Injection
Your Cyclimorph Injection should be stored in a safe place not above 25°C, in the outer carton in order to protect from light and should not be frozen.

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

The doctor or nurse will check that the ‘expiry date’ on the label has not been passed.

6. Contents of the pack and other information

What Cyclimorph Injection contains
The active ingredients 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 injection solution also contains tartaric acid, sodium metabisulphite (E223) and water for injections.

What Cyclimorph Injection looks like and the 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.
Cyclimorph is the registered trademark of Amdipharm AG

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 a 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.

**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.

**Use in the 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.

**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**

Cyclimorph Injection is contraindicated in individuals with:

- Hypersensitivity to morphine, cyclizine or 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

In common with other opioid containing preparations, Cyclimorph Injection has the potential to produce tolerance and physical and psychological dependence in susceptible individuals. Abrupt cessation of therapy after prolonged use may result in withdrawal symptoms.

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.

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.

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.

Cyclimorph 10 mg and 15 mg Injection contain sodium
This medicinal product contains less than 23 mg per dose, i.e. essentially ‘sodium-free’.

This medicinal product 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.

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.

Dopaminergics: hyperpyrexia and CNS toxicity reported with selegiline.

4.6 Fertility, pregnancy and lactation

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 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.

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

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.

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.

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

As Cyclimorph Injection contains morphine and cyclizine, the type and frequency of adverse effects associated with such compounds may be expected.

Following are the adverse reactions attributable to morphine and cyclizine with an unknown frequency:

**Adverse reactions attributable to morphine include:**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic shock</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusional state, dysphoria, restlessness, agitation, insomnia, euphoria, hallucinations, mood altered</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>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.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Miosis, visual disturbance</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia, palpitations, tachycardia, heart failure</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Orthostatic hypotension, facial flushing, hypertension, circulatory failure</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory depression, bronchospasm, pulmonary oedema, respiratory failure</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, nausea, vomiting, abdominal pain, anorexia, dry mouth, dyspepsia, Narcotic bowel syndrome, ileus, taste perversion</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Biliary colic, exacerbation of pancreatitis, increased hepatic enzymes</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, hyperhidrosis, rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasm, hypertonia, myoclonus</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Dysuria, renal colic, urinary retention, ureteric spasm</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>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</td>
</tr>
</tbody>
</table>

**Adverse reactions attributable to cyclazine include:**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity, anaphylactic reaction, hypersensitivity hepatitis has occurred</td>
</tr>
</tbody>
</table>
Psychiatric disorders | Restlessness or agitation, nervousness, euphoria, insomnia, auditory and visual hallucinations (particularly when dosage recommendations have been exceeded), disorientation

Nervous system disorders | 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 | Blurred vision, oculoductory crisis

Ear and labyrinth disorders | Tinnitus

Cardiac disorders | Tachycardia, palpitations, arrhythmias

Vascular disorders | Hypertension and hypotension

Respiratory, thoracic and mediastinal disorders | Nasal dryness, dry throat, bronchospasm and apnoea

Gastrointestinal disorders | Dryness of mouth, constipation

Hepatobiliary disorders | Hepatic function abnormal, jaundice cholestatic, hepatitis cholestatic, hepatitis

Skin and subcutaneous tissue disorders | Urticaria, pruritus, rash, angioedema, dermatitis allergic, fixed drug eruption

Musculoskeletal and connective tissue disorders | Twitching, muscle spasms

Renal and urinary disorders | Urinary retention

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

**Adverse effects related to Injection formulation**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
</tr>
</tbody>
</table>
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.

**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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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. 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:
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
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.

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. 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
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
Cyclizine is metabolised to its N-dimethylated derivative norcyclizine, which has little antihistaminic (H₁) activity compared to cyclizine.

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.

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.

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.

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.

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.

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 ampoules in outer carton.
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 single use only. Discard any remaining solution.

7. MARKETING AUTHORISATION HOLDER
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 2003.

10. DATE OF REVISION OF THE TEXT

January 2015