Package leaflet: Information for the user

Cyclimorph® 10 and 15 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.

The product is known by the above-mentioned name but will be referred to as Cyclimorph 10 and 15 Injection throughout the rest of this leaflet.

What is in this leaflet

This medicine contains morphine which is an opioid, which can cause addiction. You can get withdrawal symptoms if you stop being given it suddenly.

1. What Cyclimorph 10 and 15 Injection is and what it is used for

The name of your medicine is Cyclimorph 10 and 15 Injection. Cyclimorph 10 and 15 Injection contains the active substances morphine tartrate and cyclizine tartrate.
It contains morphine which belongs to a class of medicines called opioids, which are 'pain relievers'. This medicine has been provided to you and should not be given to anyone else. Opioids can cause addiction and you may get withdrawal symptoms if you stop being given it suddenly. Your prescriber should have explained how long you will be given this medicine for and when it is appropriate to stop, how it is done safely. Cyclizine tartrate belongs to a group of medicines called anti-emetics which reduce any nausea and vomiting that may occur.

Cyclimorph is used to relieve moderate to severe pain and nausea in certain medical or surgical situations.

2. What you need to know before you are given Cyclimorph 10 and 15 Injection

You should not be given Cyclimorph 10 and 15 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 have any **lung disease** (such as asthma or bronchitis) or have excessive phlegm
- if you have heart failure
- if you have recently suffered any **head injury** or have been told that you have raised pressure around your brain
- if you are less than one year of age
- if you have any **liver or kidney problems**
- if you have an inflammatory **bowel disease** such as ulcerative colitis
- if you have a disease or have recently had surgery affecting the series of passageways that carry bile into the intestines
- if you have a disease affecting the pathways that carry urine from the kidneys to the bladder

- if you are at risk of paralytic ileus (a condition where there is inactivity or paralysis within the bowel which stops the passage of material within the intestine) or delayed gastric emptying
- if you often drink large amounts of **alcohol**
- if you are taking, or have recently taken (within the last 14 days) a medicine from a group of **anti-depressants** called monoamine oxidase inhibitors **(MAOIs)**
- if you are about to have surgery within the next 24 hours or have had surgery within the past 24 hours.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Cyclimorph 10 and 15 injection if you:
- have any heart problems (particularly heart failure)
- have any problems with your thyroid, pituitary or adrenal glands
- have difficulty passing urine (urinary retention)
- have diabetes
- are a man with an enlarged prostate gland
- have a **tumour** of the adrenal gland (phaeochromocytoma)
- are suffering from shock
- are currently suffering from pancreatitis
- are suffering from abdominal pain or lower back pain
- suffer from an eye disease caused by a rise of pressure within the eye (glaucoma)
- suffer from an inflammatory or obstructive disease affecting the stomach and intestines
- suffer from an immune disorder characterised by muscle weakness (myasthenia gravis)
- have 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.
- suffer from any neuromuscular disorder
- suffer from involuntary muscle movement (convulsive disorders)
- have low blood pressure and low level of blood volume(hypovolaemia)
- are debilitated
- are taking any medicine from the group of medicines known as benzodiazepines.
- taking these medicines with Cyclimorph 10 and 15 injections 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).
- have loss of libido, impotence, cessation of menstruation. This may be because of decreased sex hormone production.
- suffer from sickle cell disease (abnormal hemoglobin causes distorted (sickled) red blood cells).

Talk to your prescriber before you are given this medicine if you:
- are or have ever been addicted to opioids, alcohol, prescription medicines, or illegal drugs.
- have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking or sweating, when you have stopped taking alcohol or drugs.
- feel you need to be given more of Cyclimorph Injection to get the same level of pain relief, this may mean you are becoming tolerant to the effects of this medicine or are becoming addicted to it. Speak to your prescriber who will discuss your treatment and may change your dose or switch you to an alternative pain reliever.

Being given this medicine regularly, particularly for a long time, can lead to addiction. Your prescriber should have explained how long you will be given this medicine for and when it is appropriate to stop, how it is done safely.

Rarely, increasing the dose of this medicine can make you more sensitive to pain. If this happens, you need to speak to your prescriber about your treatment.

Addiction can cause withdrawal symptoms when you are stopped being given this medicine. Withdrawal symptoms can include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, loss of appetite, shaking, shivering or sweating. Your prescriber will discuss with you how your dose will be gradually reduced before stopping the medicine. It is important that you should not stop being given the medicine suddenly as you will be more likely to experience withdrawal symptoms.

Opioids should only be used by those they are prescribed for. Do not give your medicine to anyone else. Taking higher doses or more frequent doses of opioid, may increase the risk of addiction. Overuse and misuse can lead to overdose and/or death.

Children
Cyclimorph 10 and 15 Injection is not suitable for use in children under 12 years of age.

Other medicines and Cyclimorph 10 and 15 Injection
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you are taking any of the medicines mentioned below or medicines for:

- muscle tension (any medicine to relax your muscles)
- problems such as depression, anxiety or psychosis, or are taking a sedative (usually to treat insomnia)
- ulcers, indigestion or heartburn (e.g. cimetidine)
- heart problems including propranolol, or esmolol; or for high blood pressure including diuretics (water tablets)
- nausea and vomiting (e.g. metoclopramide, domperidone)
- palpitations (e.g. mexiletine)
- the treatment of decreased muscle tone if you suffer from narcolepsy (e.g. sodium oxybate)
- HIV or AIDS (e.g. ritonavir)
- 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 morphine

Or if you are taking:

- any medicines which belong to a group of medicines called anticholinergic medicines. This may be for Parkinson's disease, asthma etc. Check with your doctor if you are not sure.

Concomitant use of Cyclimorph 10 and 15 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 10 and 15 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.

Cyclimorph 10 and 15 Injection with food, drink and alcohol
Do not drink alcohol while being treated with Cyclimorph, as the injection can increase the effects of alcohol.

Pregnancy and breast-feeding
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 you are given this medicine.

Pregnancy
You should not be given Cyclimorph 10 and 15 Injection if you are pregnant or think you might be pregnant unless you have discussed this with your prescriber and the benefits of treatment are considered to outweigh the potential harm to the baby.

If Cyclimorph 10 and 15 Injection is given during pregnancy, your baby may become dependent and experience withdrawal symptoms after the birth which may need to be treated.
Cyclimorph 10 and 15 Injection can cause breathing problems in new-born babies if used during labour.

Breast-feeding
You should not be given Cyclimoprh while you are breast-feeding as morphine passes into breast milk and will affect your baby.

Driving and using machines
Do not drive or operate machinery while you are receiving Cyclimorph 10 and 15 Injection.
The medicine can affect your ability to drive as it may make you sleepy or dizzy.

- do not drive while you are given this medicine until you know how it affects you
- it is an offence to drive if this medicine affects your ability to drive
- however, you would not be committing an offence if:
    - the medicine has been prescribed to treat a medical or dental problem and
    - you have been given it according to the instructions given by the prescriber or in the information provided with the medicine and
    - it was not affecting your ability to drive safely.

Talk to your doctor, pharmacist or nurse if you are not sure whether it is safe for you to drive while taking this medicine.

Cyclimorph 10 and 15 Injection contains:

- Less than 1 mmol sodium (23 mg) per 1ml, that is to say essentially 'sodium-free.
- Sodium metabisulphate which may rarely cause severe hypersensitivity reactions and breathing difficulties (bronchospasm).

3. How Cyclimorph 10 and 15 Injection will be given to you

Your prescriber should have discussed with you, how long the course will last. They will arrange a plan for stopping treatment. This will outline how gradually the dose is reduced and stop being given.

Cyclimorph 10 and 15 Injection is given by injection into a vein, into a muscle or under the skin.

The recommended dose is:

Adults and children over 12 years:
The usual starting dose is between 10 mg and 20 mg. This can be repeated after at least 4 hours.
You should not be given more than 3 doses in 24 hours.

Elderly: A reduced adult dosage should be given.

Use in children
Cyclimorph 10 and 15 Injection is not suitable for use in children under 12 years of age.
This medicine is ONLY available for injection and the dose you are given will be determined by your doctor.

If you are given more Cyclimorph 10 and 15 Injection than you should
Overdosing is unlikely. If it does happen the doctor will treat any symptoms that follow.
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 10 and 15 Injection
You should not suddenly stop being given this medicine. If you want to stop being given this medicine, discuss this with your prescriber first. They will tell you how it is done, usually by reducing the dose gradually so that any unpleasant withdrawal effects are kept to a minimum. Withdrawal symptoms such as restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, shaking, shivering or sweating may occur if you are suddenly stopped being given this medicine.

4. Possible side effects

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

Important side effects or symptoms to look out for and what to do if you are affected:
• itching or skin rashes
• swelling of the face, lips or throat
• serious allergic reaction which causes difficulty in breathing, wheeziness or dizziness.
Tell your doctor immediately. These may be signs of an allergic reaction.

Allergic Reaction: As Cyclimorph Injection contains Morphine and Cyclizine, the type and frequency of side effects associated with either compound may be expected in the combined product.
If you are affected by these important side effects contact a doctor immediately.
The following side effects are reported for either compound with the following frequency:

Uncommon (may affect up to 1 in 100 people)

Drug Withdrawal
When you are stopped being given Cyclimorph Injection, you may experience drug withdrawal symptoms, which include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, shaking, shivering or sweating.

Not known frequency (frequency cannot be estimated from the available data)

- decreased white blood cell count
- decrease in platelets (responsible for blood clotting and protecting from) excessive bleeding
- increased heart rate,
- visual disturbances (blurred vision)
- excessive constriction of the pupil of the eye (miosis)
- constipation, dryness of mouth, nose and throat; nausea, vomiting, **paralysis of gut (Narcotic bowel syndrome)**
- reaction at the site of injection like pain in vein, redness and discoloration
- liver dysfunction, abdominal pain, yellowish discoloration of body (jaundice)
- headache, muscle weakness, difficulty in co-ordination of movements, dizziness, decrease/ loss of consciousness, temporary speech disorder, drowsiness, confusion, nervousness, inability to sleep, restlessness, abnormal false perception of vision and hearing, abnormalities of sensation of touch (paraesthesia), tremor, twitching, muscle spasm, convulsions and disorientation
- **paralysis especially in patients having diseases of nerves and muscles**
- emotional and mental discomfort
- urinary disorders like inability to completely empty the bladder (urinary retention) and difficulty is passing urine
- decrease in testosterone secretion leading to decrease in secondary sexual characteristics (like male hair pattern, hair growth, voice, etc) in men after long-term therapy

- difficulty in respiration, slow breathing and depression of respiration which may cause death
- single cough or an episode of continuous coughing after injection in vein
- rash, itching, skin reaction at same site after repeated exposure
- increase in blood pressure or decrease in blood pressure if you raise suddenly
- involuntary rolling of the eyes (oculogyric crisis).
- an increased sensitivity to pain
- excessive sweating (hyperhidrosis)
- dependence and addiction (see section: "How do I know if I am addicted?")

How do I know if I am addicted?
If you notice any of the following signs whilst being given Cyclimorph, it could be a sign that you have become addicted.

- You are given the medicine for longer than advised by your prescriber
- You feel you need to be given more than the recommended dose
- You are being given the medicine for reasons other than prescribed
- When you are stopped being given the medicine, you feel unwell, and you feel better once given the medicine again

If you notice any of these signs, it is important you talk to your prescriber.

If any of the side effects becomes severe, or if you notice any side effect not listed in this leaflet, please tell your doctor.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Cyclimorph 10 and 15 Injection

Keep this medicine out of the sight and reach of children.
Your Cyclimorph 10 and 15 Injection will be stored at the hospital.
It will be stored in a safe place, protected from light, below 30°C and should not be frozen.
The doctor or nurse will check that the 'expiry date' on the label has not passed before they give you the injection.
This medicine should not be given after the expiry date which is stated on the label, carton 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 10 and 15 Injection contains

- The active substances are morphine tartrate and cyclizine tartrate.
- The other ingredients are sodium metabisulphite, tartaric acid, and water for injections.

What Cyclimorph 10 and 15 Injection looks like and contents of the pack
Cyclimorph 10 and 15 is supplied as ampoules, in boxes of 5 x 1 ml ampoules.
Each Cyclimorph 10 Injection ampoule contains 10 mg of morphine tartrate and 50 mg of cyclizine tartrate (equivalent to 39.01 mg cyclizine).
Each Cyclimorph 15 Injection ampoule contains 15 mg of morphine tartrate and 50 mg of cyclizine tartrate (equivalent to 39.01 mg cyclizine).

Marketing Authorisation Holder and Manufacturer
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Cyclimorph is a registered trademark of Amdipharm AG.

Technical Leaflet On
Cyclimorph 10 Injection, Cyclimorph 15 Injection

IMPORTANT: This leaflet provides information to assist with handling and administration of Cyclimorph 10 and Cyclimorph 15 for injection. **Please refer to the Summary of Product Characteristics (SmPC) for full prescribing information.**

Presentation
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.

Also contains sodium metabisulphite (E223), tartaric acid and Water for Injections.
For a full list of excipients, see SmPC section 6.1.

Uses
Cyclimorph Injection is indicated for the relief of moderate to severe pain in all suitable medical and surgical conditions (see SmPC sections 4.3 and 4.4) in which reduction of the nausea and vomiting associated with the administration of morphine is required.

Routes of Administration
By subcutaneous, intramuscular or intravenous injection.

Posology-All routes
Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with morphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section Contraindications, Special Warnings and Precautions).

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.

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.

Children
Cyclimorph Injection should not be used in children under 12 years of age.

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.

Contraindications, Special Warnings and Precautions
Cyclimorph Injection is contraindicated in individuals with known hypersensitivity to morphine, cyclizine or any of the other constituents; in patients with respiratory depression; in patients with excessive bronchial secretions; during an attack of bronchial asthma or in heart failure secondary to chronic lung disease; in patients with head injury or raised intra-cranial pressure; in children less than one year of age with other opioid containing preparation; and for pre-operative use or during the first 24 hours post-operatively.

Cyclimorph Injection should not be administered to patients with moderate or severe renal impairment (glomerular filtration rate <20 ml/min) and should not be administered to patients with severe hepatic impairment as it may precipitate coma.

Cyclimorph Injection is contraindicated in the presence of acute alcohol intoxication; **in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment**; in patients with ulcerative colitis; in patients with paralytic ileus and delayed gastric emptying; in biliary and renal tract spasm; and in patients immediately after operative interventions in the biliary tract.

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.
A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.
The risks of developing tolerance should be explained to the patient.
Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Cyclizine and Morphine.
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.
The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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 (including consideration of dose administered) in the presence of the following: convulsive disorders; delerium tremens; severe cor pulmonale; hypothyroidism; adrenocortical insufficiency; hypopituitarism; prostatic hypertrophy; shock; diabetes mellitus; myasthenia

gravis; hypotension and hypovolaemia; pancreatitis; obstructive bowel disorders; and inflammatory bowel disorders.

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 morphine 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 case reports had an underlying neuromuscular disorder. Thus intravenous cyclizine should be used with caution in all patients in general, and in patients with underlying neuromuscular disorders in particular.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Cyclimorph Injection 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 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.

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).

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased Sex Hormones and increased prolactin
Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

This medicine contains less than 1 mmol sodium (23 mg) per 1ml, that is to say essentially 'sodium-free'.
This medicinal product contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

Drug interactions
The central nervous system depressant effects of Cyclimorph Injection may be enhanced by other centrally-acting agents such as phenothiazines, hypnotics, 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 (MAOI's) may prolong and enhance the respiratory depressant effects of morphine. Opioids and MAOI's used together may cause fatal hypotension and coma (see Contraindications).

Cimetidine inhibits the metabolism of morphine.
Because of its anticholinergic activity cyclizine may enhance the side effects of other anticholinergic drugs.
The analgesic effect of opioids tends to be enhanced by co-administration of dexamfetamine, hydroxyzine, and some phenothiazines although respiratory depression may also be enhanced by the latter combination.
Morphine may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

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

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

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

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

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

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

Pregnancy
In the absence of definitive human data with the combination, the use of Cyclimorph Injection in pregnancy is not advised.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.
If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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

Lactation
Cyclizine is excreted in human milk, however, the amount has not been quantified.

Administration to nursing women is not recommended as Morphine may be secreted in breast milk and may cause respiratory depression in the infant.
Morphine can significantly suppress lactation. Morphine is excreted in human milk, but the amount is generally considered to be less than 1% of any dose.

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

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 drug interactions). Patients should therefore be cautioned against activities requiring vigilance including driving vehicles and operating machinery.
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- the medicine is likely to affect your ability to drive
- do not drive until you know how the medicine affects you
- it is an offence to drive while under the influence of this medicine
- however, you would not be committing an offence (called 'statutory defence') if:
    - the medicine has been prescribed to treat a medical or dental problem and
    - you have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - it was not affecting your ability to drive safely.

Undesirable Effects
As Cyclimorph Injection contains morphine and cyclizine, the type and frequency of adverse effects associated with either compound may be expected in the combined product. The following adverse reactions are reported events for either compound with a frequency of Not known.

Blood and lymphatic system disorders
Decreased white blood cell count (agranulocytosis)
Decreased platelets count (thrombocytopenia)

Immune system disorders
Hypersensitivity reactions, including anaphylaxis, angioedema, allergic skin reaction; hypersensitivity hepatitis, anaphylactic shock, anaphylactoid reactions.

Psychiatric disorders
Dysphoria, drug dependence (see Contraindications, Special Warnings and Precautions)

Nervous system disorders
Somnolence, restlessness and paraesthesia, raised intracranial pressure; headache; dystonia; dyskinesia; extrapyramidal motor disturbances; tremor; dizziness; decreased consciousness/loss of consciousness; transient speech disorders; generalised chorea; vertigo, sedation, confusion, nervousness, insomnia, auditory and visual hallucinations, extrapyramidal motor disturbances, tremor, twiching, muscle spasm, convulsions and disorientation, allodynia, hyperalgesia (see section 4.4), hyperhidrosis.

Eye disorders
Miosis; blurred vision, oculogyric crisis

Cardiac disorders
Increased heart beat (tachycardia)

Vascular disorders
Hypertension; orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Bronchospasm; respiratory depression ; apnoea;

Gastrointestinal disorders
Constipation; dryness of mouth, nose and throat; nausea; vomiting

Hepatobiliary disorders
Hepatic dysfunction, cholestatic jaundice; cholestatic hepatitis; biliary tract spasm

Skin and subcutaneous tissue disorders
Drug rash; urticaria; fixed drug eruption (rash)

Renal and urinary disorders
Urinary retention; renal spasm and difficulty with micturition

Reproductive system and breast disorders
Morphine has a depressant effect on gonadal hormone secretion of testosterone leading to regression of secondary sexual characteristic in men on long-term therapy.

General disorders and administration site conditions
Injection site reactions including vein tracking, erythema, pain, thrombophlebitis, dysphoric mood, anxiety

Uncommon: drug withdrawal syndrome

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

Larger doses of morphine produce respiratory depression bradycardia, pin point pupils and hypotension with circulatory failure and deepening coma. Death may occur from respiratory failure.

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

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Overdose

Signs

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 from respiratory failure.

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

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

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

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

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

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Treatment

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.

Special Precautions for Storage

Store below 30°C, and protect from light. Do not freeze.

Marketed by

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Cyclimorph 15 Injection: PL 20072/0008

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