***Enquiries*:** variations@sahpra.org.za

CLINICAL APPROVAL LETTER: POST REGISTRATION APPLICATIONS

Clinical approval date	21/05/2026
Applicant's cover letter date	20/11/2025
Applicant	Aspen Pharmacare
Proprietary name(s) (including duplicates)	Cyclimorph 10 Cyclimorph 15
API(s)	Morphine tartrate Cyclizine tartrate
Registration number(s)	B769 (Act 101/1965) B770 (Act 101/1965)
Sequence no	0001

Dear Sir/Madam,

Kindly be informed that the Authority has completed the evaluation of the above-mentioned Professional Information (PI) and Patient Information Leaflet (PIL) variation application.

1. The amendments to the PI and PIL are approved.
2. The PI and PIL be accepted as the currently approved PI and PIL
3. The date of revision reflected on this PI and PIL should be**:21/05/2026**
4. The final, dated version of the above PI and PIL must be submitted via docubridge in a closing sequence using the Submission Type "Closing sequence" and Sequence Description "Approved updated PI and PIL within 10 working days.
5. The approved PI and PIL must be uploaded into the SAHPRA repository within 10 working days.

Note to applicant: Amendments to any quality aspects of the medicine within the PI and PIL are subject to P&A unit approval and may only be implemented in the PI if approved by the P&A unit.

Yours Faithfully,

Lutsha Dhlamini

L.DHLAMINI

ASPEN REGULATORY AFFAIRS (AM)
Date: 27 May 2026

MANAGER: CLINICAL POST-REGISTRATION UNIT

1.3.1.1.2 Clean Professional Information

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

CYCLIMORPH 10 injection (10 mg/50 mg per 1 ml)

CYCLIMORPH 15 injection (15 mg/50 mg per 1 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYCLIMORPH 10:

Each 1 ml ampoule of CYCLIMORPH 10 contains 10 mg of morphine tartrate and 50 mg of cyclizine tartrate.

Sugar free.

CYCLIMORPH 15:

Each 1 ml ampoule of CYCLIMORPH 15 contains 15 mg morphine tartrate and 50 mg of cyclizine tartrate.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

CYCLIMORPH 10 is a clear, very slightly coloured solution.

CYCLIMORPH 15 is a clear, very slightly coloured solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CYCLIMORPH is indicated for:

- Medical and surgical conditions where morphine is needed. CYCLIMORPH contains cyclizine, a non-phenothiazine anti-emetic, which minimises the nausea and vomiting which may be caused by the narcotic. It is of particular value in myocardial infarction where it is essential to control morphine-induced nausea and vomiting. CYCLIMORPH can also be used for the relief of severe pain, e.g., pain of terminal illness and cancer pain, for the relief of dyspnoea of left ventricular failure and pulmonary oedema, and relief of postoperative and chronic pain in debilitated patients.

4.2. Posology and method of administration

Adults and children over 12 years:

Usual adult dose: 10 or 15 mg CYCLIMORPH ampoule (equivalent to morphine tartrate 10 mg and cyclizine tartrate 50 mg or morphine tartrate 15 mg and cyclizine tartrate 50 mg) is administered by injection subcutaneously, intramuscularly or intravenously.

If required, repeat no more often than 4 hourly, with not more than 3 doses (representing 150 mg cyclizine tartrate) in any 24 hour period.

Special populations

Elderly population

Morphine doses should be reduced in elderly patients.

Paediatric population

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

Method of administration

Subcutaneous, intramuscularly, or intravenous injection.

4.3. Contraindications

CYCLIMORPH is contraindicated in:

- Patients with hypersensitivity to morphine, cyclizine or to any excipients in CYCLIMORPH (see section 6.1).
- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions as morphine diminishes the cough response.
- Patients experiencing an attack of bronchial asthma, or heart failure secondary to chronic lung disease.
- The presence of acute alcoholism, head injury and raised intracranial pressure.
- Individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.5).
- Patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.
- Patients with paralytic ileus and delayed gastric emptying.
- Severe and prolonged respiratory depression may occur in patients with renal impairment who have been given morphine. CYCLIMORPH should not be

administered to patients with moderate or severe renal impairment (glomerular filtration rate < 20 mL/min).

- Patients with severe hepatic impairment as it may precipitate hepatic encephalopathy or coma.
- At the recommended dosages, CYCLIMORPH is contraindicated in biliary and renal tract spasm, and in patients immediately after operative interventions in the biliary tract (see section 4.4).
- Pregnancy and lactation, as safety has not been established (see section 4.6).
- The presence of acute alcohol intoxication. The antiemetic properties of cyclizine may increase the toxicity of alcohol.

4.4. Special warnings and precautions for use

Opioid Use Disorder (Drug dependence, tolerance and potential for abuse)

Morphine, as in CYCLIMORPH, 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.

For all patients, prolonged use of CYCLIMORPH 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 medicines, including over the- counter medicines, 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.

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.

Use in patients with a history of mental health disorders

There is an increased risk of addiction to CYCLIMORPH when used in patients with a personal or family history of substance abuse or mental health disorders.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with morphine, as in CYCLIMORPH.

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 CYCLIMORPH during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.
CYCLIMORPH should be used with caution in the very young, the elderly or very ill or debilitated patients since they may be more sensitive to the respiratory depressant effects.

CYCLIMORPH should be used with caution in the presence of the following: convulsive disorders, delirium tremens, severe cor pulmonale, hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostate hypertrophy, myasthenia gravis, shock, diabetes

mellitus, pancreatitis, obstructive bowel disorders, inflammatory bowel disorder, hypotension and hypovolaemia.

Phaeochromocytoma

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

CNS depressant effects

The CNS depressant effects of CYCLIMORPH may be enhanced by combination with other centrally acting medicines (see section 4.5).

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)

Due to a possible association between acute chest syndrome (ACS) and morphine, as in CYCLIMORPH, use in sickle cell disease (SCD) patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Opioid-Induced Hyperalgesia or Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli

(allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

Euphoria

Euphoria is not usually seen at dosages of morphine, as in CYCLIMORPH, appropriate for analgesia, but has been reported at higher doses in tolerant patients.

Hypotension

Hypotension and collapse have been reported with the use of morphine, as in CYCLIMORPH.

Obstructive bowel disorders

Morphine, as in CYCLIMORPH, should be used with caution in patients with obstructive bowel disorders.

Cardiac effects

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

Porphyria

CYCLIMORPH is considered to be unsafe in patients with porphyria. The use of CYCLIMORPH should be avoided in these patients.

Neuromuscular disorders

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

Glaucoma and obstructive gastrointestinal disease

Because CYCLIMORPH 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 medicines

Concomitant use of CYCLIMORPH and sedative medicines such as benzodiazepines or related medicines 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 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, as in CYCLIMORPH, treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep- related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Severe cutaneous adverse reactions (SCARs)

Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

Hepatobiliary disorders

Morphine may cause dysfunction and spasm (see section 4.3) of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include 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.

Elderly patients

Elderly patients may be more susceptible to the central nervous system effects and hypotensive effects of cyclizine, as in CYCLIMORPH (see section 4.8).

Excipients

CYCLIMORPH contains sodium metabisulphite which may cause severe hypersensitivity reactions and bronchospasm.

4.5. Interaction with other medicines and other forms of interaction

Since cyclizine, as in CYCLIMORPH, has antimuscarinic properties, it should be used with care in conditions liable to be exacerbated or otherwise adversely affected by atropine, such as glaucoma, urinary retention and prostate hypertrophy.

Mexiletine

The action of morphine, as in CYCLIMORPH, may affect the activities of other compounds, for example its gastrointestinal effects may delay absorption as with mexiletine.

Metoclopramide

The action of morphine, as in CYCLIMORPH, may affect the activities of other compounds, for example its gastrointestinal effects may be counteractive as with metoclopramide.

Monoamine oxidase inhibitors (MAOIs)

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

Cimetidine

Cimetidine inhibits the metabolism of morphine.

Antihistamines

Antihistamines may precipitate epileptiform seizures in patients with focal lesions of the cerebral cortex.

Anticholinergic medicines

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

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.

Diuretics

Morphine, as in CYCLIMORPH, may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Oral P2Y12 inhibitor antiplatelet medicines

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy, such as clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor, has been observed in patients with acute coronary syndrome treated with morphine, as in CYCLIMORPH. 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

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 medicines are administered concurrently.

St John's Wort

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

Rifampicin

Rifampicin has been reported to reduce circulating levels of morphine, as in CYCLIMORPH and increase its urinary excretion in these patients. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin. The resulting lowered plasma concentration of morphine may induce withdrawal symptoms in the patients.

Ritonavir

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

Centrally nervous system depressants

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including hypnotics, general anaesthetics, alcohol, barbiturates, neuromuscular blocking medicines, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, and gabapentin or pregabalin. The central nervous system depressant effects of this medicine may be enhanced by other centrally acting medicines such as phenothiazines, hypnotics, neuroleptics, alcohol and muscle relaxants. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

Psychotropic medicines

Psychotropic medicines may potentiate the analgesic effects of morphine, as in CYCLIMORPH.

Phenytoin

Phenytoin has been reported to enhance the metabolism of morphine, as in CYCLIMORPH with resulting withdrawal symptoms in the patients.

Tricyclic antidepressants

The side effects of tricyclic antidepressants may be enhanced by the concomitant administration of antihistamines.

Alcohol

The concomitant misuse of cyclizine, as in CYCLIMORPH, with large amounts of alcohol is particularly dangerous since the anti-emetic effect of cyclizine may increase the toxicity of

alcohol (see section 4.4). Drowsiness, dryness of mouth, nose and throat and blurred vision may occur and can be aggravated by simultaneous intake of alcohol and cyclizine, as in CYCLIMORPH.

Sedative medicines such as benzodiazepines or related medicines

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines 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).

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.

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 in pregnancy is not advised (see section 4.3).

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 and an antidote for the child should be readily available.

Breastfeeding

Mothers should not breastfeed their infants while receiving CYCLIMORPH (see section 4.3).

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

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

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

Fertility

Animal studies have shown that morphine, as in CYCLIMORPH, may reduce fertility.

4.7. Effects on ability to drive and use machines

CYCLIMORPH has major influence on the ability to drive and use machines.

Since adverse reactions such as dizziness, sedation, drowsiness and visual disturbances have been reported in patients receiving CYCLIMORPH, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CYCLIMORPH does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Thrombocytopenia, agranulocytosis as well as other blood disorders including haemolytic anaemia.
Immune system disorders			Hypersensitivity reactions, including anaphylaxis, angioedema, allergic skin reactions, hypersensitivity hepatitis, anaphylactoid reactions, anaphylactic shock.
Psychiatric disorders		Mental depression, hallucinations, confusion.	Nightmares, euphoria, dysphoria, anorexia, dependence, anxiety, visual hallucinations, auditory hallucinations.

Nervous system disorders	Drowsiness, vertigo.	Headache, nervousness, restlessness, dizziness, insomnia. myoclonus, mental clouding.	Somnolence, raised intracranial pressure, in-coordination, lassitude, sedation, dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, twitching, muscle spasms, restless leg syndrome, convulsions, disorientation, decreased consciousness, transient speech disorders, paraesthesia, generalised chorea, allodynia, hyperalgesia, hyperhidrosis.
Eye disorders		Blurred or double vision or other changes in vision.	Miosis, oculogyric crisis.
Ear and labyrinth disorders			Tinnitus.
Vascular disorder			Orthostatic hypotension, hypertension.
Cardiac disorders		Bradycardia, palpitations .	Tachycardia.
Respiratory, thoracic and mediastinal disorders		Respiratory depression.	Tightness of the chest, bronchospasm, apnoea, incidence of single cough or paroxysm of coughing immediately after its administration, central sleep apnoea syndrome.
Gastrointestinal disorders	Constipation, nausea, vomiting.	Loss of appetite, gastrointestinal irritation, diarrhoea, dryness of mouth, nose	Epigastric pain, increased appetite.

		and throat, upset stomach. abdominal pain, pancreatitis	
Hepato-biliary disorders		Biliary spasm.	Hepatotoxicity, cholestatic jaundice, cholestatic hepatitis, hepatic dysfunction, spasm of sphincter of Oddi.
Skin and subcutaneous tissue disorders		Skin rash, urticaria, pruritus.	Drug rash, fixed drug eruption (rash), acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and connective tissue disorders			Uncontrolled muscle movements, trembling, muscular weakness. twitching, muscle spasms.
Renal and urinary disorders		Difficult or painful micturition.	Renal spasm, urinary retention.
Reproductive system and breast disorders			Depressant effect on gonadal hormone secretion which can result in a reduction of testosterone leading to regression of secondary sexual characteristics in men on long-term therapy.
General disorders and administrative site conditions		Redness, swelling, pain, or burning at site of injection, drug withdrawal (abstinence) syndrome, facial flushing.	Injection site reactions including vein tracking, and thrombophlebitis, asthenia.

b) Description of selected adverse reactions

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

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

Rapid IV administration of cyclizine, as in CYCLIMORPH, can lead to symptoms similar to overdose.

Case reports of narcotic bowel syndrome and hyperaesthesia/ allodynia due to morphine, as in CYCLIMORPH, have also been reported.

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.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Morphine:

Symptoms

The symptoms and signs of overdosage with morphine parallel those for other opioids, namely profound respiratory depression, bradycardia, pin-point pupils, hypotension, circulatory failure and pulmonary oedema and coma. Mydriasis may replace miosis as asphyxia intervenes. Opioid overdose can result in death from respiratory failure.

Drowsiness, floppiness, miosis (pin-point pupils), convulsions and apnoea have been reported in children.

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

Treatment

General supportive measures should be employed as required for morphine overdosage. 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 the restoration of spontaneous respiration, the literature should be consulted for appropriate dosage.

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

Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of morphine.

Cyclizine:

Symptoms

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.

Treatment

In the management of acute overdosage with cyclizine, supportive measures for respiration and circulation should be performed if necessary. Convulsions should be controlled in the usual way with parenteral anticonvulsant therapy.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A.2.9. Other analgesics.

Pharmacotherapeutic group**:** Central nervous system depressants.

ATC code: N02AA51

Mechanism of action

Morphine is an opioid agonist analgesic and cyclizine has anti-emetic action.

Morphine:

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

Cyclizine:

Cyclizine is a histamine H_1 receptor antagonist of the piperazine class. It possesses anticholinergic and anti-emetic properties. The exact mechanism by which cyclizine can prevent or suppress both nausea and vomiting from various causes is unknown. Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus.

5.2. Pharmacokinetic properties

Morphine:

Absorption

After subcutaneous or intramuscular injection morphine is readily absorbed into the blood.

Distribution

Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35 % is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2,4 to 6,7 hours for morphine-3-glucuronide have been reported.

Biotransformation

The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses.

Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs.

Elimination

Up to 10 % of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90 % of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

Cyclizine:

Biotransformation

The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine.

Elimination

Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1 % of the total oral dose is eliminated in the urine in 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium metabisulphite, tartaric acid, water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

CYCLIMORPH 10:

1 x 1 ml clear, neutral, Type 1 glass ampoule with double white rings. 10 ampoules are placed in a plastic tray and then packed in an outer cardboard carton together with a leaflet.

CYCLIMORPH 15:

1 x 1 ml clear, neutral, Type 1 glass ampoule with double red rings. 10 ampoules are placed in a plastic tray and then packed in an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

0800 122 912

8. REGISTRATION NUMBERS

CYCLIMORPH 10: B769 (Act 101/1965).

CYCLIMORPH 15: B770 (Act 101/1965).

9. DATE OF FIRST AUTHORISATION

21 December 2001

10. DATE OF REVISION OF TEXT

TBA

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

1.3.2.2 Clean Patient Information Leaflet

SCHEDULING STATUS

S6

CYCLIMORPH 10 injection (10 mg/50 mg per 1 ml)

CYCLIMORPH 15 injection (15 mg/50 mg per 1 ml)

Morphine tartrate and cyclizine tartrate

Sugar free

Read all of this leaflet carefully before CYCLIMORPH is administered to you

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

What is in this leaflet

1. What CYCLIMORPH is and what it is used for

CYCLIMORPH contains the active ingredients morphine tartrate and cyclizine tartrate.

Morphine tartrate belongs to a group of medicines called opioid analgesics and is used for pain relief.

Cyclizine 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 CYCLIMORPH is administered to you

CYCLIMORPH should not be administered to you:

- if you are hypersensitive (allergic) to morphine tartrate or cyclizine tartrate or any of the other ingredients of CYCLIMORPH (listed in section 6).
- if you have respiratory depression, especially in the presence of cyanosis (low oxygen levels) and excessive bronchial secretions.
- if you have bronchial asthma, or in heart failure secondary to chronic heart disease.
- if you have acute alcoholism, head injury and raised intracranial pressure.
- if you have acute alcohol intoxication.
- if you are receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- if you have ulcerative colitis since it may precipitate toxic dilation or spasm of the colon.
- if you have severe kidney impairment.
- if you have severe liver impairment.
- 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 (a condition that effects the stomach muscles and prevents proper stomach emptying).

- if you have a spasm in the bile duct or kidney duct or if you have recently had an operation in the bile duct.
- if you are pregnant or breastfeeding (see Pregnancy, breastfeeding and fertility).

Warnings and precautions

Take special care with CYCLIMORPH:

- if you are very young, elderly, very ill or debilitated.
- if you have an underactive thyroid, deficiency in pituitary hormone, or a neuromuscular disorder.
- if you have glaucoma.
- if you have an inflammatory or obstructive disease of the gastrointestinal tract.
- if you have severe heart failure.
- if you are alcohol dependant.
- if you have previously suffered from alcohol or drug withdrawal symptoms (such as shaking, confusion, high blood pressure, hallucinations).
- if you have low blood pressure as it may lower your blood pressure even further.
- if you have porphyria.
- if you have diabetes.
- if you are a man with an enlarged prostate gland.
- if you are suffering from shock.
- if you are currently suffering from pancreatitis.

- if you are suffering from abdominal pain or lower back pain, which could be symptoms of a biliary tract problem.
- if you suffer from an immune disorder characterised by muscle weakness (myasthenia gravis).
- if you have a history of drug or alcohol dependence i.e. you have been reliant on particular medicines.
- if you have a personal or family history of substance abuse or mental health disorders you should not receive CYCLIMORPH as there is an increased risk of addiction.
- if you suffer from fits (convulsions).
- if you experience wheezing, trouble breathing, tiredness, swelling of the lower limbs (these are symptoms of cor pulmonale caused by chronic lung disease).
- if you have severe breathing problems as it may cause a disorder in which breathing repeatedly stops and starts during sleep (central sleep apnoea).
- if you have a condition in which the liquid portion of the blood (plasma) is too low (known as hypovolaemia).
- if you have a disorder that occurs when your body does not produce enough of certain hormones (known as adrenal insufficiency). Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.
- if you suffer from a tumour of the adrenal gland with symptoms such as high blood pressure, sweating, rapid heartbeat and headache (known as phaeochromocytoma).
- if you suffer from acute chest syndrome (chest pain, cough, fever, low oxygen level) caused by sickle cell disease (a blood disorder).

- if you suffer from an increased sensitivity to feeling pain (allodynia) and an extreme response to pain (known as hyperalgesia).
- if higher doses of CYCLIMORPH are administered and you experience an unrealistic feeling of well-being (known as euphoria).
- if CYCLIMORPH is administered long-term and you experience a decrease in sexual desire, a loss of sexual ability (if you are male) and if you are female, you experience the absence of menstrual periods.
- if you feel that you need to be given more of CYCLIMORPH 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.
- if you experience withdrawal symptoms such as 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 doctor will discuss with you how your dose will be gradually reduced before stopping the medicine. It is important that you should not stop being administered CYCLIMORPH suddenly as you will be more likely to experience withdrawal symptoms.
- if you develop a severe rash with inflamed skin and pus-filled spots and fever which can be symptoms of severe cutaneous adverse reactions (SCARs) or acute generalized exanthematous pustulosis (AGEP). These conditions can be life-threatening and you must see your doctor urgently.
- overuse of misuse may result in overdose or death.

Children and adolescents

CYCLIMORPH injection should not be used in children under 12 years of age.

Other medicines and CYCLIMORPH

Always tell your healthcare provider if you are taking any other medicine (this includes complementary or traditional medicines).

Tell your doctor if you are taking any of the following:

- Monoamine oxidase inhibitors (MAOI), a medicine used to treat depression.
- Rifampicin, an antibiotic, used in the treatment of tuberculosis.
- Phenytoin, an anticonvulsant, used to treat epilepsy.
- St John's Wort, used for depression.
- Alcohol.
- Barbiturates or neuromuscular blocking medicines used in surgery e.g. phenobarbitone.
- Tranquilisers or benzodiazepines e.g. diazepam.
- Psychotropic medicines such as phenothiazines used to treat mental disorders.
- Medicines for irregular heartbeats (e.g. mexiletine).
- Medicines for heart problems including propranolol, or esmolol; or for high blood pressure including diuretics (water tablets).
- Metoclopramide, used to treat nausea and vomiting.
- Cimetidine, used to treat ulcers.
- Dexamphetamine, used to treat attention deficit hyperactivity disorder (ADHD).

- Central nervous system (CNS) depressants, used to treat anxiety, tension, and sleep disorders, as well as alcohol.
- Atropine an anticholinergic medicine, used during surgical procedures.
- Medicines referred to as water tablets (anti-diuretics), used to treat conditions including high blood pressure and cardiac problems.
- Tricyclic antidepressants, used to treat depression.
- Antihistamines such as hydroxyzine.
- Oral P2Y12 inhibitor antiplatelets such as aspirin.
- Ritonavir used along with other medicines to treat HIV.
- Protein concentration or hormone laboratory testing, since the ingredients used in some methods may be affected by morphine.

CYCLIMORPH with food, drink and alcohol

Do not drink alcohol while being treated with CYCLIMORPH, as the injection can increase the effects of alcohol.

Alcohol can also enhance the CNS depressant effect of CYCLIMORPH.

Pregnancy, breastfeeding and fertility

You should not receive CYCLIMORPH if you are pregnant or breastfeeding your baby (see section 2).

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before receiving this medicine.

CYCLIMORPH may reduce fertility.

Driving and using machines

CYCLIMORPH has major influence on the ability to drive and use machines.

Patients experiencing hypotension, drowsiness or sedation while receiving CYCLIMORPH, should refrain from driving or using machines.

It is not always possible to predict to what extent CYCLIMORPH may interfere with your daily activities. You should ensure that you do not engage in the above activities until you are aware of the measure to which CYCLIMORPH affects you (see section 4).

CYCLIMORPH contains sodium metabisulphite

Sodium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm.

3. How CYCLIMORPH will be administered to you

CYCLIMORPH is administered subcutaneously, intramuscularly or intravenously.

The usual adult dose is 1 ampoule of CYCLIMORPH 10 or CYCLIMORPH 15.

If required, CYCLIMORPH can be administered no more often than 4 hourly. You should not be administered more than 3 doses in any 24-hour period.

Your doctor will tell you how long your treatment with CYCLIMORPH will last. Do not stop treatment early. If you have the impression that the effect of CYCLIMORPH is too strong or too weak, tell your doctor or pharmacist.

You will not be expected to give yourself CYCLIMORPH. CYCLIMORPH will be administered to you by a person who is qualified to do so.

Use in the elderly:

If you are an elderly patient your doctor will reduce the dose.

If you are administered more CYCLIMORPH than you should

Since a healthcare professional will administer CYCLIMORPH, he/she will control the dosage.

However, in the event of overdosage your doctor will manage the overdosage.

If you forget to receive CYCLIMORPH

Since a healthcare provider will administer CYCLIMORPH, it is unlikely that the dose will be missed.

If you stop receiving CYCLIMORPH

Some people may become addicted to CYCLIMORPH when treatment continues for a long time.

Some people may experience drug withdrawal symptoms after stopping treatment with CYCLIMORPH. If any of the side effects becomes severe, or if you notice any side effect not listed in this leaflet, please tell your doctor.

If you no longer require CYCLIMORPH, your doctor will taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

4. Possible side effects

CYCLIMORPH can have side effects.

Not all side effects reported for CYCLIMORPH are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving CYCLIMORPH, please consult your doctor, pharmacist or other health care professional for advice.

If any of the following happens, stop receiving CYCLIMORPH and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing,
- rash or itching,
- fainting,
- rapid appearance of small pustules on the skin, which can be accompanied by fever, burning, and itching, as

  these may be due to a serious allergic reaction know as acute generalised exanthematous pustulosis (AGEP) or fixed drug eruption (FDE).

These are all very serious side effects. If you have them, you may have had a serious reaction to CLCLIMORPH. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Reduced platelet count (thrombocytopaenia), responsible for blood clotting and protecting from excessive bleeding),
- lack of iron in the body which often cause shortness of breath, noticeable heartbeats, a pale complexion, tiredness and lack of energy (anaemia),
- fitting (convulsions),

- inability of the liver to function well, abdominal pain, yellowish discoloration of eyes and skin (jaundice, liver damage, sphincter of Oddi spasm),
- a liver condition where bile flow is obstructed, leading to jaundice, pruritus (itching), and dark urine due to inflammation in the liver (cholestatic hepatitis)
- lowered white blood cells (agranulocytosis),
- seeing or hearing things that are not really there (visual and auditory hallucinations),
- involuntary and erratic movement (dyskinesia), or repetitive, involuntary muscle movements (dystonia),
- slow and shallow breathing (respiratory depression), tightness of chest,
- a sleep disorder where breathing repeatedly stops and starts during sleep because the brain doesn't send proper signals to the muscles that control breathing (central sleep apnoea syndrome),
- decreased consciousness,
- serious sleep disorder in which breathing repeatedly stops and starts,
- fast heartbeat (tachycardia) or slow heartbeat (bradycardia),
- increased pressure in the brain,
- movements of the eyeballs into a fixed position, usually upwards (oculogyric crisis).
- severe stomach pain, which may reach to your back. This could be a sign of inflammation of your pancreas (pancreatitis),
- difficulty in complete or partial emptying of the bladder (urinary retention).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- Drowsiness, a spinning sensation,
- nausea, vomiting, constipation.

Less frequent side effects:

- Sleepless nights (insomnia),
- confusion, mental clouding
- depression (feeling down/ feeling low),
- headache, nervousness, dizziness,
- loss of appetite,
- irritation of the digestive tract,
- sharp pain under the rib cage in the upper right side or centre of the stomach (gallbladder spasm or epigastric pain),
- restlessness,
- uncontrolled muscle jerking (myoclonus),
- loose stools (diarrhoea), upset stomach,
- dryness of mouth, nose and throat,
- difficult and painful urination,
- allergic skin reaction/nettle-rash triggered by food, medicine or other irritants (urticaria), itching (pruritis) and skin rash,
- reddening of the face due to increased blood flow to surface blood vessels (facial flushing),
- redness, swelling, pain, or burning at site of injection,

- blurred or double vision or other changes in vision,
- 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.

Side effects with an unknown frequency:

- Nightmares,
- ringing in the ears,
- uncontrolled muscle movements, or trembling,
- lack of energy (lassitude), a state of calm or sleep,
- weakness of lack of strength (asthenia),
- lack of coordination, disorientation,
- anxiety, a feeling unease or dissatisfaction (dysphoric mood),
- an irresistable urge to move the legs (restless leg syndrome) which can be worse while trying to sleep,
- hives,
- pain in the upper middle of the stomach (epigastric pain),
- tightness of the chest,
- increased appetite,
- eating disorders and muscular weakness,
- a sudden, involuntary contraction of the smooth muscle in the walls of the ureter, the tube that carries urine from the kidney to the bladder (renal spasm),
- single cough or an episode of continuous coughing after injection in vein,
- narrower pupil of the eye (miosis),

- low blood pressure that happens when standing after sitting or lying down or high blood pressure,
- low hormone levels leading to a decrease in male characteristics like male hair pattern, hair growth, voice etc in men after long term medical treatment,
- feeling or state of intense excitement and happiness (euphoria),
- disorder that causes involuntary, unpredictable body movements (generalised chorea),
- pain from stimulus that does not normally provoke pain (allodynia) or abnormally heightened sensitivity to pain (hyperalgesia),
- excessive sweating (hyperhidrosis),
- short term speech disorder,
- tingling or pricking (‘pins and needles’),
- inflammation of a vein with formation of a clot (thrombophlebitis),
- injection site reactions including vein tracking.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (whoumc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

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

5. How to store CYCLIMORPH

Store all medicines out of reach of children.

Store at or below 25 °C.

Do not freeze.

Protect from light.

Keep in original packaging until required for use.

Do not store in bathrooms.

Do not use after the expiry date stated on the label.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What CYCLIMORPH contains

CYCLIMORPH 10:

The active substance per 1 ml ampoule is 10 mg of morphine tartrate and 50 mg of cyclizine tartrate.

The other ingredients are sodium metabisulphite, tartaric acid, water for injections.

Sugar free.

CYCLIMORPH 15:

The active substance per 1 ml ampoule is 15 mg morphine tartrate and 50 mg cyclizine tartrate.

The other ingredients are sodium metabisulphite, tartaric acid, water for injections.

Sugar free.

What CYCLIMORPH looks like and contents of the pack

CYCLIMORPH 10 is a clear, very slightly coloured solution.

1 x 1 ml clear, neutral, Type 1 glass ampoule with double white rings. 10 ampoules are placed in a plastic tray and then packed in an outer cardboard carton together with a leaflet.

CYCLIMORPH 15 is a clear, very slightly coloured solution.

1 x 1 ml clear, neutral, Type 1 glass ampoule with double red rings. 10 ampoules are placed in a plastic tray and then packed in an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

Holder of Certificate of Registration

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

Hotline: 0800 122 912

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TBA

Registration numbers

CYCLIMORPH 10: B769 (Act 101/1965)

CYCLIMORPH 15: B770 (Act 101/1965)

Access to the corresponding Professional Information

SAHPRA Repository of Professional Information and Patient Information Leaflets:

https://www.sahpra.org.za/pi-pil-repository/

Aspen Pharmacare:

E-mail: Medinfo@aspenpharma.com

Tel: 0800 118 088