1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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

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 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 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.
- 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

Drug dependence, tolerance and potential for 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.

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 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, 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.

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.

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.

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 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. It also possesses antidiuretic properties. Morphine, as in CYCLIMORPH, has the potential to produce dependence.

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.

Antihistamines may precipitate epileptiform seizures in patients with focal lesions of the cerebral cortex. 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. Elderly patients may be more susceptible to the central nervous system effects and hypotensive effects of cyclizine, as in CYCLIMORPH (see section 4.8).

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.

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).

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.

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.

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.

Excipients

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

4.5. Interaction with other medicines and other forms of interaction

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.

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 or 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 inhibits the metabolism of morphine.

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.

Morphine, as in CYCLIMORPH, 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, 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 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 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.

The general depressant effects of morphine, as in CYCLIMORPH, may be enhanced by other centrally-acting medicines such as alcohol, barbiturates, neuromuscular blocking medicines, phenothiazines and tranquilisers.

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.

Anticholinergic medicines and tricyclic antidepressants:

The side effects of anticholinergic medicines such as atropine and 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).

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.

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).

New-born's 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.

Nervous system disorders	Drowsiness, vertigo.	Headache, nervousness, restlessness, dizziness, insomnia.	Somnolence, raised intracranial pressure, in-coordination, lassitude, sedation, dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, twitching, muscle spasms, 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, visual hallucinations, oculogyric crisis.
Ear and labyrinth disorders			Tinnitus, auditory hallucinations.
Vascular disorder			Orthostatic hypotension, hypertension.
Cardiac disorders			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.
Gastrointestinal disorders	Constipation, nausea, vomiting.	Loss of appetite, gastrointestinal irritation, diarrhoea, dryness of mouth, nose and throat, upset stomach. abdominal pain, pancreatitis	Epigastric pain, increased appetite.
Hepato-biliary disorders		Biliary spasm.	Hepatotoxicity, cholestatic jaundice, cholestatic hepatitis, hepatic dysfunction.
Skin and subcutaneous tissue disorders		Skin rash, urticaria, pruritus.	Drug rash, fixed drug eruption (rash).
Musculoskeletal and connective tissue disorders			Uncontrolled muscle movements, trembling, muscular weakness.
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,	Injection site reactions including vein tracking, and thrombophlebitis; dysphoric mood, anxiety.

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 asked to report any suspected adverse reactions to: SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

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, 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

Not applicable.

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

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

05 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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