1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CLOPAMON INJECTION 10 mg/2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule of CLOPAMON INJECTION 10 mg/2 ml contains 10 mg metoclopramide.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

CLOPAMON INJECTION 10 mg/2 ml is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CLOPAMON INJECTION 10 mg/2 ml is indicated for:

- Digestive disorders:CLOPAMON INJECTION 10 mg/2 ml is of value in any condition associated with gastric status or hypomotility. It is, therefore, useful in the management of post-vagotomy syndrome.
- Nausea and vomiting: CLOPAMON INJECTION 10 mg/2 ml is an effective anti-emetic medicine in the control of nausea and vomiting associated with the following conditions: intolerance to essential medicines possessing emetic properties, uraemic conditions, malignant disease, gastrointestinal disorders and post-anaesthetic vomiting.
- Diagnostic radiology: CLOPAMON INJECTION 10 mg/2 ml is effective in patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine.

- Duodenal intubation: The action of CLOPAMON INJECTION 10 mg/2 ml in promoting stomach emptying, combined with its anti-emetic effect, has proved a very useful aid to gastrointestinal intubation procedures.
- Young adults and children: The use of CLOPAMON INJECTION 10 mg/2 ml in patients under 20 years should be restricted to the following:

  Severe intractable vomiting of known cause.

  As an aid to gastrointestinal intubation and diagnostic radiology.

4.2. Posology and method of administration

Posology

CLOPAMON INJECTION 10 mg/2 ml ampoules should not be diluted for injection since this will upset the isotonicity and stability of the medicine.

Adults:

10 mg (1 ampoule) 1 to 3 times daily IV or IM depending on the severity of the condition.

Dosage for diagnostic radiology

Intravenous:

10 to 20 mg (1 to 2 ampoules) 5 to 15 minutes before the barium meal.

Intramuscular:

10 to 20 mg (1 to 2 ampoules) 10 to 15 minutes before the barium meal.

Special populations

Renal Impairment and hepatic impairment

Care should also be taken when CLOPAMON INJECTION 10 mg/2 ml is administered to patients with renal impairment or to those at risk of fluid retention as in hepatic impairment.

Therapy should be at a reduced dosage.

Paediatric population

Children over 14 years:

10 mg (1 ampoule) 1 to 3 times daily IV or IM depending on the severity of the condition.

Children 5 to 14 years:

2,5 mg (0,5 ml of a 10 mg/2 ml ampoule) I.V. or I.M. twice daily in a tuberculin syringe.

Children 3 to 5 years:

1 mg (0,2 ml of a 10 mg/2 ml ampoule) I.V. or I.M. twice daily in a tuberculin syringe.

Children 1 to 3 years:

0,5 mg (0,1 ml of a 10 mg/2 ml ampoule) I.V. or I.M. in a tuberculin syringe twice daily.

Method of administration

For intravenous or intramuscular administration.

4.3. Contraindications

CLOPAMON INJECTION 10 mg/2 ml is contraindicated in :

- Patients with hypersensitivity to metoclopramide or to any excipients in CLOPAMON INJECTION 10 mg/2 ml (see section 6.1).
- Patients being treated with phenothiazines.
- Patients where stimulation of muscular contractions might adversely affect gastrointestinal conditions, such as in gastrointestinal haemorrhage, obstruction or perforation or immediately after surgery.
- Patients with phaechromocytoma as hypertensive crises have been reported. CLOPAMON INJECTION 10 mg/2 ml should not be given to patients with suspected or confirmed phaeochromocytoma.
- Patients with convulsive disorders (epileptic patients, due to risk of increased frequency and severity of seizures.
- Porphyria.
- CLOPAMON INJECTION 10 mg/2ml is not recommended in pregnancy.

4.4. Special warnings and precautions for use

- There should be at least a 6 hour time interval between each CLOPAMON INJECTION 10 mg/2 ml administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.
- If vomiting persists the patient should be re-assessed to exclude the possibility of an underlying disorder, e.g. cerebral irritation.

Neurological disorders

- The elderly should be treated with care as they are at increased risk of extrapyramidal reactions usually at the beginning of the treatment and can occur after a single administration. CLOPAMON INJECTION 10 mg/2 ml should be discontinued immediately in the event of extrapyramidal symptoms.
- These effects are generally completely reversible after treatment discontinuation but may require a symptomatic treatment (anticholinergic anti-Parkinsonian medicines in adults).
- Care should be exercised in patients being treated with other centrally active medicines e.g. in epilepsy (see section 4.3).
- Prolonged treatment with CLOPAMON INJECTION 10 mg/2 ml may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia (see section 4.8). Patients on prolonged therapy and long-term treatment should be reviewed regularly. Treatment must be discontinued if clinical signs of tardive dyskinesia appear.
- Neuroleptic malignant syndrome (NMS) has been reported with CLOPAMON INJECTION 10 mg/2 ml in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). CLOPAMON INJECTION 10 mg/2 ml should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome (NMS) and appropriate treatment should be initiated.

Hypertension

- CLOPAMON INJECTION 10 mg/2 ml should be used with caution in patients with

hypertension, since there is limited evidence that the CLOPAMON INJECTION 10 mg/2 ml may increase circulating catecholamines in such patients.

Parkinson's disease

- Symptoms of Parkinson's disease may also be exacerbated by CLOPAMON INJECTION 10 mg/2 ml.

Methaemoglobinaemia

- Methaemoglobinaemia which could be related to NADH cytochrome b_5 reductase deficiency has been reported. In such cases, CLOPAMON INJECTION 10 mg/2 ml should be immediately and permanently discontinued and appropriate measures initiated (such as treatment with methylene blue).

Cardiac disorders

- There have been reports of serious cardiovascular undesirable effects including cases of circulatory collapse, severe bradycardia, cardiac arrest and QT prolongation following administration of CLOPAMON INJECTION 10 mg/2 ml by injection, particularly via the intravenous route (see section 4.8).

  Special care should be taken when administering CLOPAMON INJECTION 10 mg/2 ml, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other medicines known to prolong QT interval.

  Intravenous doses should be administered as a slow bolus (at least over 3 minutes) in order to reduce the risk of adverse effects (e.g. hypotension, akathisia).
- Special care should be taken when administering CLOPAMON INJECTION 10 mg/2 ml intravenously to patients with “sick sinus syndrome” or other cardiac conduction disturbances.

Renal and hepatic impairment

- In patients with renal impairment or with severe hepatic impairment, a dose reduction is

recommended.

Reproductive system

- CLOPAMON INJECTION 10 mg/2 ml may cause elevation of serum prolactin levels.

Atopy and porphyria

- Care should be exercised when using CLOPAMON INJECTION 10 mg/2 ml in patients with a history of atopy (including asthma) or porphyria (see section 4.3).

Post-surgery

- Following operations such as pyloroplasty or gut anastomosis CLOPAMON INJECTION 10 mg/2 ml should be withheld for three or four days as vigorous muscular contractions may not help healing.

Sodium

CLOPAMON INJECTION 10 mg/2 ml contains less than 1 mmol sodium (23 mg) per 2 ml, essentially 'sodium-free'.

Paediatric population

Children and young patients should be treated with care as they are at increased risk of extrapyramidal reactions usually at the beginning of the treatment and can occur after a single administration. CLOPAMON INJECTION 10 mg/2 ml should be discontinued immediately in the event of extrapyramidal symptoms.

These effects are generally completely reversible after treatment discontinuation but may require a symptomatic treatment (benzodiazepines).

4.5. Interaction with other medicines and other forms of interaction

- Levodopa or dopaminergic agonists and CLOPAMON INJECTION 10 mg/2 ml have a mutual

antagonism.

- Alcohol potentiates the sedative effect of CLOPAMON INJECTION 10 mg/2 ml.
- Due to the prokinetic effect of CLOPAMON INJECTION 10 mg/2 ml, the absorption of other medicine may be modified.

Anticholinergics and morphine derivatives

- Anticholinergics and morphine derivatives may both have a mutual antagonism with CLOPAMON INJECTION 10 mg/2 ml on the digestive tract motility.
- Central nervous system depressants (morphine derivatives, anxiolytics, sedative H_1 antihistamines, sedative antidepressants, barbiturates, clonidine and related).
- Sedative effects of central nervous system (CNS)depressants and CLOPAMON INJECTION 10 mg/2 ml are potentiated.

Neuroleptics

- CLOPAMON INJECTION 10 mg/2 ml may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.
- Caution should be observed when using CLOPAMON INJECTION 10 mg/2 ml in patients taking other medicine that can also cause extrapyramidal reactions, such as the phenothiazines (see section 4.3).

Serotonergic medicines

- The use of CLOPAMON INJECTION 10 mg/2 ml with serotonergic medicines such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

- CLOPAMON INJECTION 10 mg/2 ml may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

- CLOPAMON INJECTION 10 mg/2 ml increases cyclosporine bioavailability (C_{max} by 46 % and exposure by 22 %). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium

- CLOPAMON INJECTION 10 mg/2 ml may prolong suxamethonium-induced neuromuscular blockade (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors

- CLOPAMON INJECTION 10 mg/2 ml exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.
- The effects of certain medicines with potential central stimulant effects, e.g. monoamine oxidase inhibitors and sympathomimetics, may be modified when prescribed with CLOPAMON INJECTION 10 mg/2 ml and their dosage may need to be adjusted accordingly.

Aspirin, paracetamol

- The effect of CLOPAMON INJECTION 10 mg/2 ml on gastric motility may modify the absorption of other concurrently administered oral medicines from the gastrointestinal tract either by diminishing absorption from the stomach or by enhancing the absorption from the small intestine (e.g. the effects of paracetamol and aspirin are enhanced).

Atovaquone

- CLOPAMON INJECTION 10 mg/2 ml may reduce plasma concentrations of atovaquone.

Lithium

- Increased toxicity may occur in patients receiving lithium.

Hyperprolactinaemic medicines

- CLOPAMON INJECTION 10 mg/2 ml may also increase prolactin blood-concentrations and therefore interfere with medicines which have a hypoprolactinaemic effect e.g. bromocriptine.

4.6. Fertility, pregnancy and lactation

Safety in pregnancy has not been established (see section 4.3)

Pregnancy

Animal tests in several mammalian species have shown no teratogenic effects but CLOPAMON INJECTION 10 mg/2 ml is not recommended during pregnancy.

Breastfeeding

CLOPAMON INJECTION 10 mg/2 ml is excreted in breast milk at low levels. Adverse reactions in the breastfed baby cannot be excluded. Discontinuation of metoclopramide, as in CLOPAMON INJECTION 10 mg/2 ml in breastfeeding women should be considered.

Fertility

There are no fertility data.

4.7. Effects on ability to drive and use machines

CLOPAMON INJECTION 10 mg/2 ml has a minor influence on the ability to drive and use machines. Since adverse reactions such as dizziness, drowsiness have been reported in patients receiving CLOPAMON INJECTION 10 mg/2 ml, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CLOPAMON INJECTION 10 mg/2 ml does not adversely affect their ability to do so (see sections 4.4 and 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

CLOPAMON INJECTION 10 mg/2 ml is a dopamine antagonist and may cause extrapyramidal symptoms which usually occur as acute dystonic reactions, especially in young female patients.

Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients.

b) 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			Methaemoglobinaemia, sulfhaemoglobinaemia
Immune system disorders		Hypersensitivity	Anaphylactic reaction (including anaphylactic shock)
Endocrine disorders		Amenorrhoea, hyperprolactinaemia, galactorrhoea	Transient increases in plasma aldosterone concentrations, gynaecomastia
Psychiatric disorders	Depression,	Hallucination, confusional state	
Nervous system disorders	Drowsiness, dizziness, headache, restlessness, somnolence,	Dystonia (including visual disturbances and oculogyric crisis), dyskinesia,	Tardive dyskinesia, neuroleptic malignant syndrome

	extrapyramidal disorders, parkinsonism, akathisia	depressed level of consciousness, convulsion	
Cardiac disorders		Bradycardia	Cardiac arrest, atrioventricular block, sinus arrest, electrocardiogram qt prolonged, Torsade de Pointes
Vascular disorders	Hypotension,		Acute hypertension, shock, transient increase in blood pressure
Gastrointestinal disorders	Diarrhoea, constipation		
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders			Stimulate serum prolactin levels, breast engorgement, galactorrhoea, lactorrhea
Skin and subcutaneous tissue disorders			Rash, pruritus, angioedema, urticaria

General disorders and administrative site conditions	Asthenia		Inflammation at injection site, local phlebitis

c) Description of selected adverse reactions

The following reactions, sometimes associated, occur more frequently when high doses are used:

- Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the medicine, particularly in children and young adults (see section 4.4).
- Drowsiness, decreased level of consciousness, confusion, hallucination.

Blood and lymphatic system disorders:

Methaemoglobinaemia, which could be related to NADH cytochrome b_5 reductase deficiency, particularly in neonates (see section 4.4).

Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicines.

Nervous system disorders:

Parkinsonism has been reported during prolonged and long-term treatment should be regularly reviewed.

Less frequent occurrences of the neuroleptic malignant syndrome (NMS) have been reported. This syndrome is potentially fatal and comprises hyperpyrexia, altered consciousness, muscle rigidity, autonomic instability and elevated levels of Creatinine phosphokinase and must be treated urgently (recognised treatments include dantrolene and bromocriptine). CLOPAMON INJECTION 10 mg/2 ml should be stopped immediately if this syndrome occurs.

Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the medicine) (see section 4.4).

Convulsions especially in epileptic patients.

Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4).

Cardiac disorders

Bradycardia, particularly with intravenous formulation.

Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.4).

Sinus arrest particularly with intravenous formulation.

Vascular disorders

Hypotension, particularly with intravenous formulation.

Shock, syncope after injectable use.

Acute hypertension in patients with phaeochromocytoma (see section 4.3).

Reproductive system and breast disorders

CLOPAMON INJECTION 10 mg/2 ml stimulates serum prolactin levels, and may cause breast engorgement, galactorrhoea, lactorrhea or related disorders. The conditions return to normal after withdrawal of the medicines.

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: https://www.sahpra.org.za/health-products-vigilance/

4.9. Overdose

Symptoms

Overdosage of CLOPAMON INJECTION 10 mg/2 ml could give rise to dyskinetic reactions

manifested as motor restlessness, agitation, irritability, spasm of facial and neck muscles and the muscles of the tongue. In severe cases opisthotonos can result.

Extrapyramidal disorders, drowsiness, a decreased level of consciousness, confusion, hallucination and cardio-respiratory arrest may occur.

Treatment

Anticholinergic anti-Parkinson medications, e.g. procyclidine, will usually control these symptomatic reactions in adults and benzodiazepines in children.

A symptomatic treatment and a continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 5.7.2 Anti-emetics and antivertigo preparations

Pharmacotherapeutic group: Propulsives, agents stimulating gastrointestinal motility.

ATC code: A03FA01

Mechanism of action

Gastrointestinal action: metoclopramide increases the number, mean strength and total activity of gastric antral contractions and produces a significant increase in the strength of duodenal contractions. These changes would all tend to increase the speed of gastric emptying, which has been observed radiologically and by other methods. Metoclopramide has no effect on gastric secretion or on the cardiovascular system.

Metoclopramide has an effect on the gastro-oesophageal junction of the stomach, producing an increase in cardiac sphincter pressure. The increase in pressure seen after administration of metoclopramide is directly proportional to the initial resting pressure and is minimal or absent in those with very low resting pressures.

The action of metoclopramide on the gastrointestinal tract is antagonised by atropine and other anticholinergic medicine if they are administered in the previous 3 hours.

Anti-emetic action: metoclopramide acts on the chemo-emetic trigger zone to produce a central anti-emetic effect. The anti-emetic action of metoclopramide is not affected by atropine and other anticholinergic medicine.

Other action: metoclopramide stimulates prolactin secretion.

5.2. Pharmacokinetic properties

Elimination

Approximately 30 % of metoclopramide is excreted unchanged in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride and water for injection.

6.2. Incompatibilities

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

6.3. Shelf life

48 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Protect from light.

Should inadvertent exposure occur, reject ampoules showing a yellow discolouration.

Keep in original packaging until required for use.

6.5. Nature and contents of container

1 x 2 ml clear glass ampoules. 10 ampoules are packed in a polystyrene container together with a leaflet.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

CLOPAMON INJECTION 10 mg/2 ml ampoules should not be diluted for injection since this will upset the isotonicity and stability of the medicine (see section 4.2).

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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