PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

METOCLOPRAMIDE 10 OETHMAAN (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Metoclopramide 10 Oethmaan tablet contains: 10 mg Metoclopramide hydrochloride.

Contains sugar (lactose 62.0 mg per tablet)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White, round, flat, bevel-edged tablets with a score line on one side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Digestive disorders:

Metoclopramide hydrochloride is indicated in conditions associated with gastric stasis or hypomotility. It is useful in the management of postvagotomy syndrome.

Nausea and vomiting:

Metoclopramide hydrochloride is indicated for the control of nausea and vomiting associated with the following conditions: medicine-induced nausea and vomiting, uraemic conditions, malignant disease, gastrointestinal disorders and post-anaesthetic vomiting.

Diagnostic radiology:

Metoclopramide hydrochloride speeds gastric emptying and dilates the duodenal bulb. It is therefore useful in the following situations:

a) Where barium meal studies are delayed by spasm of the duodenal cap making examination for the presence of an ulcer difficult.
b) To facilitate examination of the hypotonic stomach with delayed emptying (gastric stasis and pyloric canal syndrome).
c) To control or prevent nausea and vomiting of barium which occurs in a small minority of patients undergoing barium meal examination.

Duodenal intubation:

Metoclopramide hydrochloride is a useful aid to gastrointestinal intubation procedures.

Young Adults and Children

The use of METOCLOPRAMIDE 10 OETHMAAN in patients under 20 years should be restricted to the following:

- *Severe intractable vomiting of known cause.*
- *As an aid to gastro-intestinal intubation and diagnostic radiology.*

4.2 Posology and method of administration

Posology

See section 4.4.

Adults and children over 14 years:

10 mg (1 x 10 mg tablet) three times daily.

Paediatric population

Children 5 to 14 years:

5 mg three times daily.

Special populations

Patients with renal impairment and hepatic impairment:

Total clearance of metoclopramide is significantly reduced in patients with renal impairment and hence dosage reduction of at least 50 % have been recommended in patients with moderate to severe renal impairment.

Method of administration

For oral use only

4.3 Contraindications

- Hypersensitivity to metoclopramide or to any excipients listed in section 6.1.
- Cases of hypertensive crises have reportedly been associated with metoclopramide hydrochloride after administration to patients with phaeochromocytoma. Until further evaluation, metoclopramide hydrochloride should not be given to patients with suspected or confirmed phaeochromocytoma.
- Patients being treated with phenothiazines.

- METOCLOPRAMIDE 20 OETHMAAN should not be used when stimulation of muscular contractions might adversely affect gastro-intestinal conditions as in gastro-intestinal haemorrhage, obstruction, perforation, or immediately after surgery.
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- METOCLOPRAMIDE 10 OETHMAAN should not be used in patients with epilepsy due to risk of increased frequency and severity of seizures.
- Parkinson's disease.
- Combination with levodopa or dopaminergic agonists (see section 4.5).
- Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency.
- Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4).
- METOCLOPRAMIDE 10 OETHMAAN should not be used during the first three to four days following operations such as pyloroplasty or gut anastomosis as vigorous muscular contractions may not help healing.
- Safety in pregnant and lactating mothers has not been established.
- Patients with convulsive disorders.
- Porphyria.

4.4 Special warnings and precautions for use

WARNING: TARDIVE DYSKINESIA

Chronic treatment with METOCLOPRAMIDE 10 OETHMAAN can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with the duration of treatment and the total

cumulative dose. The elderly, especially elderly women, are most likely to develop this condition.

METOCLOPRAMIDE 10 OETHMAAN therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia; however, in some patients symptoms may lessen or resolve after METOCLOPRAMIDE 10 OETHMAAN treatment is stopped.
Prolonged treatment (greater than 12 weeks) with METOCLOPRAMIDE 10 OETHMAAN should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.

Care should be exercised in patients with underlying neurological conditions and in patients treated with other centrally active medicines (see section 4.3) e.g. epilepsy.

In patients with clinically significant degrees of renal or hepatic impairment, therapy should be at a reduced dosage.

There should be at least a 6 hour time interval between each METOCLOPRAMIDE 10 OETHMAAN 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

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide 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 in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).
Caution is advised in patients with a history of mental depression.

Prolonged treatment with metoclopramide 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). Treatment must be discontinued if clinical signs of tardive dyskinesia appear.
Patients on prolonged therapy should be reviewed regularly.
It is recommended that METOCLOPRAMIDE 10 OETHMAAN should not be prescribed for the long-term treatment of minor symptoms, especially in elderly patients.

Tardive dyskinesia (TD) (see **Boxed Warnings**), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities, can develop in patients treated with METOCLOPRAMIDE 10 OETHMAAN. Although the risk of tardive dyskinesia (TD) with METOCLOPRAMIDE 10 OETHMAAN has not been extensively studied, one published study reported a TD prevalence of 20 % among patients treated for at least 3 months.
The prevalence of the syndrome appears to be the highest among the elderly, especially elderly women. It is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

There is no known effective treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks to months after METOCLOPRAMIDE 10 OETHMAAN is withdrawn. METOCLOPRAMIDE 10 OETHMAAN itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of syndrome is unknown. Therefore, METOCLOPRAMIDE 10 OETHMAAN should not be used for the symptomatic control of tardive dyskinesia.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see section 4.8). Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Renal and Hepatic Impairment

In patients with renal and hepatic impairment, therapy should be at a reduced dosage (see section 4.2).

Care should be taken when METOCLOPRAMIDE 10 OETHMAAN is administered to patients with renal impairment or those at a risk of fluid retention as in hepatic impairment.

Metoclopramide should be used with caution in patients with hypertension, since there is limited evidence that the medicine may increase circulating catecholamines in such patients.

Because metoclopramide can stimulate gastro-intestinal mobility, the medicine theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure.

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide. METOCLOPRAMIDE 10 OETHMAAN is contraindicated in Parkinson's disease.

Methaemoglobinaemia

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency has been reported. In such cases, metoclopramide 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 metoclopramide by injection, particularly via the intravenous route (see section 4.8).

Special care should be taken when administering metoclopramide, 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.

Metoclopramide may cause elevation of serum prolactin levels.

Care should be exercised when using METOCLOPRAMIDE 10 OETHMAAN in patients with a history of atopy (including asthma).

METOCLOPRAMIDE 10 OETHMAAN should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions, as in gastrointestinal haemorrhage, obstruction, perforation or for a few days after surgery.

Patients on prolonged therapy should be reviewed regularly.

Care should be exercised when METOCLOPRAMIDE 10 OETHMAAN is given to patients with renal, hepatic, asthma, or a history of depression or porphyria. METOCLOPRAMIDE 10 OETHMAAN is contraindicated in epilepsy and Parkinsons disease (see section 4.3)

As both METOCLOPRAMIDE 10 OETHMAAN and the phenothiazines may cause transient dystonia, both medicines should not be prescribed concurrently (see section 4.3).

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. METOCLOPRAMIDE 10 OETHMAAN 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

METOCLOPRAMIDE 10 OETHMAAN may affect the absorption of other medicines. It may either diminish absorption from the stomach (as with digoxin) or enhance absorption from small intestine (for example, with alcohol, cyclosporine, levodopa, aspirin or paracetamol).

It inhibits serum cholinesterase and may prolong neuromuscular blockade produced by suxamethonium and mivacurium.

Since METOCLOPRAMIDE 10 OETHMAAN increase prolactin blood concentrations, it may interfere with medicines which have a hypoprolactinaemic effect such as bromocriptine.
It should not be given to patients being treated with phenothiazines as extrapyramidal reactions may be precipitated.
Increased toxicity may occur if METOCLOPRAMIDE 10 OETHMAAN is given to patients receiving lithium.
Caution is advisable with other centrally acting medicines such as antiepileptics, antidepressants and sympathomimetics.
Giving METOCLOPRAMIDE 10 OETHMAAN with Central Nervous System medicines can lead to increased sedative effects.
Opioids and antimuscarinics antagonize the gastrointestinal effects of METOCLOPRAMIDE 10 OETHMAAN.
Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).
Alcohol potentiates the sedative effect of metoclopramide.

Serotonergic medicines

The use of metoclopramide with serotonergic medicines such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

Metoclopramide increases cyclosporine bioavailability (C_{max} by 46 % and exposure by 22 %). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Strong CYP2D6 inhibitors

Metoclopramide 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.

Atovaquone

Metoclopramide injection may reduce plasma concentrations of atovaquone.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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

The use of METOCLOPRAMIDE 10 OETHMAAN during pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies.

Breastfeeding:

METOCLOPRAMIDE 10 OETHMAAN is excreted in breast milk at low levels. Adverse reactions in the breastfed baby cannot be excluded. Discontinuation of METOCLOPRAMIDE 10 OETHMAAN in breastfeeding women should be considered.

Fertility

There are no fertility data.

4.7 Effects on ability to drive and use machines

METOCLOPRAMIDE 10 OETHMAAN may cause drowsiness or impaired reactions, so affected patients should not drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

METOCLOPRAMIDE 10 OETHMAAN is a dopamine antagonist and may cause extrapyramidal symptoms which usually occur as acute dystonia 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	Adverse reaction	Frequency
Blood and lymphatic system disorders	Agranulocytosis, Methaemoglobinaemia[1], sulfhaemoglobinaemia[1]	Frequency unknown
Immune system disorders	Hypersensitivity reactions	Less frequent
	Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation. Severe allergic reactions such as oedema of the tongue, peri-orbital oedema may occur.	Frequency unknown
Endocrine disorders[2]	Amenorrhoea, hyperprolactinaemia,	Less frequent

	galactorrhoea	
	Gynaecomastia	Frequency unknown
Psychiatric disorders	Depression	Frequent
	Hallucination, confusional state	Less frequent
Nervous system disorders	Somnolence, restlessness, drowsiness, dizziness, headache, extrapyramidal disorders[3], parkinsonism, akathisia.	Frequent
	Anxiety and agitation, Parkinsonism and Tardive dyskinesia have occasionally occurred, usually during prolonged treatment in the elderly. Dystonia (including visual disturbances and oculogyric crisis), dyskinesia, depressed level of consciousness. Convulsion especially in epileptic patients.	Less frequent
	Tardive dyskinesia[4], neuroleptic malignant syndrome[5]	Frequency unknown
Cardiac disorders	Bradycardia	Less frequent
	Cardiac arrest[6], atrioventricular block, sinus arrest,	Frequency unknown

	electrocardiogram QT prolonged, Torsade de Pointes	
Vascular disorders	Hypotension	Frequent
	Shock, syncope after injectable use. Acute hypertension in patients with phaeochromocytoma (see section 4.3). Transient increase in blood pressure	Frequency unknown
Gastrointestinal disorders	Constipation, diarrhoea	Frequent
Skin and subcutaneous tissue disorders	Skin reactions such as rash, pruritus, angioedema and urticaria	Frequency unknown
Renal and urinary disorders	Urinary incontinence	Frequency unknown
General disorders and administration site conditions	Asthenia	Frequent

[1] Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates (see section 4.4).
Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicines.

[2] Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

[3] METOCLOPRAMIDE 10 OETHMAAN may cause extrapyramidal symptoms, which usually occur as acute dystonic reactions, including spasm of the facial and/or extra ocular muscles, trismus, a bulbar type of speech and unnatural positioning of the head and shoulders. There

may be a general increase in muscle tone. These are common in young patients especially if female. Tardive dyskinesia has been reported (see section 4.4).

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

[5] Neuroleptic malignant syndrome, Neuroleptic malignant syndromes 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). METOCLOPRAMIDE 10 OETHMAAN should be stopped immediately if this syndrome occurs.

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

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 METOCLOPRAMIDE 10 OETHMAAN, particularly in children and young adults (see section 4.4).
- Drowsiness, decreased level of consciousness, confusion, hallucination.

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

4.9 Overdose:

Overdosage with metoclopramide hydrochloride 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. Anti-parkinson medicines, e.g. procyclidine will usually control these reactions.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 5.7.2 Anti-emetics and antivertigo preparations

ATC Code: A03FA01

Pharmacological action:

Metoclopramide hydrochloride belongs to the orthopramide series of synthetic compounds.

Gastrointestinal action:

Metoclopramide hydrochloride increases the number, mean strength and total activity of gastric antral contraction and also 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 hydrochloride has no effect on gastric secretion or on the cardiovascular system.

Metoclopramide hydrochloride has an effect on the gastro-oesophageal junction of the stomach, producing an increase in cardiac sphincter pressure. The increase in pressure seen after

metoclopramide hydrochloride is directly proportional to the initial resting pressure and minimal or absent in those with very low resting pressures.

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

Anti-emetic action:

Metoclopramide hydrochloride has a central anti-emetic effect. The anti-emetic action of metoclopramide hydrochloride is not affected by atropine and other anticholinergic medicines.

Other action:

Metoclopramide hydrochloride stimulates prolactin secretion.

5.2 Pharmacokinetic properties

Absorption

It is well absorbed after oral administration, but hepatic first pass metabolism reduces its bioavailability to about 75 %.

Distribution

The medicine is well distributed rapidly into most tissues and readily crosses the placenta and the bloodbrain barrier.

Biotransformation and Elimination

Up to 30 % of metoclopramide is excreted unchanged in the urine, and the remainder is eliminated in the urine and the bile after conjunction with sulphate or glucoronic acid. The half-life of the drug in circulation is 4 to 6 hours.

Renal impairment

The clearance of metoclopramide is reduced by up to 70 % in patients with severe renal impairment, while the plasma elimination half-life is increased (approximately 10 hours for a creatinine clearance of 10-50 ml/minute and 15 hours for a creatinine clearance <10 ml/minute).

Hepatic impairment

In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50 % reduction in plasma clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Maize starch

Povidone K30

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Tristar blisters 3 years

PVC blisters 3 years

Patient ready packs (PRPs) 3 years

Amber glass bottles 4 years

Securitainers 4 years

6.4 Special precautions for storage

Keep well-closed and store below 25 °C in a dry place and protect from light. Do not remove the blister from the carton until required for use.

6.5 Nature and contents of container

Amber plastic containers, amber glass containers, securitainers, sealed aluminium bags or blister packs of 20 or 100 tablets.

Amber plastic containers, amber glass containers, securitainers or blister packs of 500 or 1 000.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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