Approved Clean Professional Information for Medicines for Human Use:

METOCLOPRAMIDE 10 mg AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

METOCLOPRAMIDE 10 mg AUSTELL FILM-COATED TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METOCLOPRAMIDE 10 mg AUSTELL film-coated tablet

Each film-coated tablet contains 10 mg Metoclopramide Hydrochloride

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

METOCLOPRAMIDE 10 mg AUSTELL

White to off-white, circular, biconvex tablets with breakline on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METOCLOPRAMIDE 10 mg AUSTELL is used as an adjunct to the X-ray examination of the stomach and duodenum and post-operative hypotonia (postvagotomy syndrome).

It is also used as an anti-emetic for the prevention and treatment of irradiation sickness, post-operative vomiting, and medicine-induced nausea

and vomiting.

4.2 Posology and method of administration

Posology

Adults

The average adult dose is 10 mg eight hourly.

In diagnostic radiology and duodenal intubation: 20 mg before the barium meal.

Special populations

Elderly

In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.

Renal impairment

In patients with end stage renal disease (Creatinine clearance ≤ 15 mL/min), the daily dose should be reduced by 75 %.

In patients with moderate to severe renal impairment (Creatinine clearance 15-60 mL/min), the dose should be reduced by 50 % (see section 5.2).

Hepatic impairment

In patients with severe hepatic impairment, the dose should be reduced by 50 % (see section 5.2).

Other pharmaceutical forms/strengths may be more appropriate for administration to these populations.

4.3 Contraindications

- Hypersensitivity to Metoclopramide Hydrochloride or to any of the excipients listed in section 6.1.
- METOCLOPRAMIDE 10 mg AUSTELL should not be used where gastrointestinal conditions might be adversely affected as in intestinal obstruction or immediately after surgery.
- Patients with phaeochromocytoma or convulsive disorders.
- Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- Epilepsy (increased crises frequency and intensity).
- 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 mg AUSTELL 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.

4.4 Special warnings and precautions for use

WARNING: Tardive Dyskinesia

Chronic treatment with METOCLOPRAMIDE 10 mg AUSTELL 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 mg AUSTELL 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 mg AUSTELL treatment is stopped. Prolonged treatment (greater than 12 weeks) with METOCLOPRAMIDE 10 mg AUSTELL should be avoided.

If vomiting persists the patient should be reassessed 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 medicines in adults).

The time interval of at least 6 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

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.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally acting medicines (see section 4.3).

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methaemoglobinemia

Methemoglobinemia 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. 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).

Renal and Hepatic Impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).
Metoclopramide may cause elevation of serum prolactin levels.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency of glucose-galactose malabsorption should not take this medicine.

Care should be exercised when using METOCLOPRAMIDE 10 mg AUSTELL in patients with a history of atopy (including asthma) or porphyria.
Metoclopramide should not be used in the immediate post-operative period (up to 3 – 4 days) following pyloroplasty or gut anastomosis, as vigorous gastrointestinal contractions may adversely affect healing.

Special care should be taken when administering METOCLOPRAMIDE 10 mg AUSTELL intravenously to patients with “sick sinus syndrome” or other cardiac conduction disturbances.

There have been very rare reports of abnormalities of cardiac conduction with intravenous metoclopramide. METOCLOPRAMIDE 10 mg AUSTELL should be used with care with other medicines affecting cardiac conduction.

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic effect of metoclopramide, the absorption of certain medicines may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may have both a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants

(morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related) Sedative effects of Central Nervous System depressants and metoclopramide are potentiated.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

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.

Ciclosporin

Metoclopramide increases ciclosporin bioavailability (Cmax by 46 % and exposure by 22 %). Careful monitoring of ciclosporin plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

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.

METOCLOPRAMIDE 10 mg AUSTELL may reduce plasma concentrations of atovaquone.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Metoclopramide is excreted in breast milk at low level. Adverse reactions in the breastfed baby cannot be excluded.

Therefore, metoclopramide is not recommended during breastfeeding.

Discontinuation of metoclopramide in breastfeeding women should be considered.

Fertility

Data on metoclopramide use and fertility is not available.

4.7 Effects on ability to drive and use machines

METOCLOPRAMIDE 10 mg AUSTELL has moderate influence on the ability to drive and use machines. Metoclopramide may cause drowsiness, dizziness, dyskinesia and dystonias which could affect the vision and also interfere with the ability to drive and operate machinery.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with Metoclopramide Hydrochloride BP

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders			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
Immune system disorders		Hypersensitivity	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation)
Endocrine disorders*		Amenorrhoea, Hyperprolactinaemia Galactorrhoea	Gynaecomastia
Psychiatric disorders	Depression	Hallucination Confused state	
Nervous system disorders	Somnolence Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following	Dystonia including oculogyric crisis, Dyskinesia, Depressed level of consciousness Convulsion especially in epileptic patients	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients

	administration of a single dose of the medicine) (see section 4.4), Parkinsonism, Akathisia		(see section 4.4), Neuroleptic malignant syndrome (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) Atrioventricular block, Sinus arrest particularly with intravenous formulation Electrocardiogram QT prolonged Torsade de Pointes;
Vascular disorders	Hypotension, particularly with intravenous formulation		Shock, syncope after injectable use, Acute hypertension in patients

			with phaeochromocytoma (see section 4.3) Transient increase in blood pressure
Gastrointestinal disorders	Diarrhoea		
General disorders and administration site conditions	Asthenia		

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

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 and 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

Extrapyramidal disorders, drowsiness, decreased level of consciousness, confusion, hallucination, and cardiorespiratory arrest may occur.

Treatment

In case of extrapyramidal symptoms related or not to overdose, the treatment is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian medicine in adults).
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: 11.2 Medicines acting on gastrointestinal tract: Gastrointestinal antispasmodics and cholinolytics (anticholinergics)
Pharmacotherapeutic group: Medicines for Functional Gastrointestinal Disorders - Propulsives
ATC Code: A03FA01

Mechanism of action

Metoclopramide acts on the chemoreceptor trigger zone to produce an anti-emetic effect. It also has a peripheral action which alters upper gut motility, increasing stomach peristalsis and emptying, as well as relaxing the pyloric antrum and duodenal cap. Gastric secretion is unaffected. The direct effects on the gut are antagonized by atropine and

other anticholinergics. Metoclopramide causes a marked increase in the amplitude, frequency and duration of gastric contractions. The action of metoclopramide is not affected by vagotomy.

5.2 Pharmacokinetic properties

Absorption

Metoclopramide is well absorbed following oral and rectal administration. Metoclopramide is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption. However, it undergoes hepatic first-pass metabolism, which varies considerably between subjects, and hence absolute bioavailability and plasma concentrations are subject to wide interindividual variation. On average, the bioavailability of oral metoclopramide is about 80 %, but it varies between about 30 and 100 %. Peak plasma concentrations of metoclopramide occur about 1 to 2 hours after an oral dose. Bioavailability is equally variable after rectal or intranasal doses, although it may be somewhat better if the medicine is given intramuscularly. Metoclopramide is weakly bound to plasma proteins (13 to 30 %).

Distribution

Metoclopramide is widely distributed in the body, and readily crosses the blood-brain barrier into the CNS. It also freely crosses the placenta and has been reported to attain concentrations in foetal plasma about 60 to 70 % of those in maternal plasma. Concentrations in breast milk may be higher than those in maternal plasma, particularly in the early puerperium, although concentrations decrease somewhat in the late puerperium.

Biotransformation

Metoclopramide is metabolised in the liver.

Elimination

The predominant route of elimination of metoclopramide and its metabolites is via the kidney.

Elimination of metoclopramide is biphasic, with a terminal elimination half-life of about 4 to 6 hours, although this may be prolonged in renal impairment, with consequent elevation of plasma concentrations. It is excreted in the urine, about 85 % of a dose being eliminated in 72 hours, 20 % as unchanged metoclopramide and the remainder as sulphate or glucuronide conjugates, or as metabolites. About 5 % of a dose is excreted in faeces via the bile.

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

Intra-granular

Cellulose-microcrystalline

Starch-maize (Dried)

Starch-pregelatinised

Extra-granular

Maize-starch (Dried)

Silica-colloidal anhydrous

Stearic acid (micronized)

Film-coating

Hypromellose 5 cps

Macrogol – 6000

Talc-purified

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ^{o}C in the original packaging.

6.5 Nature and contents of container

METOCLOPRAMIDE 10 mg AUSTELL film-coated tablets are packed in clear PVDC coated PVC/aluminium blister pack of 10 and 25 tablets, which are further placed in an outer carton to give pack sizes of 10, 20, 25, 30, 50, 60 100, 125 and 150 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

METOCLOPRAMIDE 10 mg AUSTELL: 48/11.2/0904

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 September 2022

10. DATE OF REVISION OF THE TEXT