

**Approved Professional Information for Medicines for Human Use:**

**AUSTELL METOCLOPRAMIDE 5 mg/mL INJECTION**

**SCHEDULING STATUS**

S4

**1. NAME OF THE MEDICINE**

AUSTELL METOCLOPRAMIDE 5 mg/mL INJECTION

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each mL contains metoclopramide hydrochloride equivalent to anhydrous metoclopramide hydrochloride 5 mg.

Sugar free.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Injection

AUSTELL METOCLOPRAMIDE is a clear colourless solution free of any particulate matter.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

**Digestive disorders**

AUSTELL METOCLOPRAMIDE is indicated for the treatment of conditions associated with gastric stasis or hypomotility.

**Nausea and Vomiting**

AUSTELL METOCLOPRAMIDE is an effective anti-emetic agent used in the control of nausea and

vomiting associated with the following conditions:

Intolerance to essential drugs possessing emetic properties, uraemic conditions, malignant disease, gastro-intestinal disorders and post-anaesthetic vomiting.

### **Diagnostic radiology**

In patients where delayed gastric emptying interferes with radiological examination of stomach /or small intestine.

### **Duodenal intubation**

The action of AUSTELL METOCLOPRAMIDE in promoting stomach emptying, combined with its anti-emetic effect, has proved a useful aid to gastro-intestinal intubation procedure.

### **Young Adults and Children**

The use of AUSTELL METOCLOPRAMIDE 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**

The dosage recommendations given below should be strictly adhered to if side effects of the dystonic type are to be avoided. (see section 4.4).

AUSTELL METOCLOPRAMIDE should only be used after careful examination to avoid masking an underlying disorder e.g. cerebral irritation.

The total daily dose of AUSTELL METOCLOPRAMIDE should not exceed 0.5 mg per kg body weight.

AUSTELL METOCLOPRAMIDE is used in the following conditions:

Severe intractable vomiting when mechanical obstruction has been excluded, chemotherapy or radiotherapy-induced vomiting, as an aid to gastro-intestinal intubation, and in premedication.

AUSTELL METOCLOPRAMIDE ampoules be diluted for injection since this will upset the isotonicity and the stability of the drug.

**Adults 15 years and over with a mass of 60 kg or more:**

10 mg (1 ampoule) 1 - 3 times daily I.V or I.M. depending on the severity of the condition.

**Special populations**

**Dosage for Diagnostic Radiology:**

Intravenous:

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

Intramuscular:

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

***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.

**Paediatric population**

**Children 15 years and over with a mass of less than 60 kg:**

5 mg (1,0 mL of a 10 mg/2 mL ampoule) I.V. or I.M. 1 - 3 times daily.

**Children 5-14 years:**

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

**Children 3-5 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 1-3 years:**

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

### **Method of administration**

AUSTELL METOCLOPRAMIDE is for intravenous or intramuscular administration.

### **4.3 Contraindications**

- Hypersensitivity to the metoclopramide or to any of the excipients listed in section 6.1.
- Patients being treated with Phenothiazines.
- AUSTELL METOCLOPRAMIDE 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.
- AUSTELL METOCLOPRAMIDE should not be used in patients with pheochromocytoma as hypertensive crises have been reported.
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- AUSTELL METOCLOPRAMIDE 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 5 mg/ml Injection 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

- There should be at least a 6 hour time interval between each AUSTELL METOCLOPRAMIDE 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 AUSTELL METOCLOPRAMIDE should not be prescribed for the long-term treatment of minor symptoms, especially in elderly patients.

#### **TARDIVE DYSKINESIA**

**Chronic treatment with AUSTELL METOCLOPRAMIDE 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.**

**AUSTELL METOCLOPRAMIDE 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 AUSTELL METOCLOPRAMIDE treatment is stopped.**

**Prolonged treatment (greater than 12 weeks) with AUSTELL METOCLOPRAMIDE should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.**

Tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities, can develop in patients treated with AUSTELL METOCLOPRAMIDE. Although the risk of tardive dyskinesia (TD) with AUSTELL METOCLOPRAMIDE 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 AUSTELL METOCLOPRAMIDE is withdrawn. AUSTELL METOCLOPRAMIDE 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, AUSTELL METOCLOPRAMIDE 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.

In patients with renal and hepatic impairment, therapy should be at a reduced dosage (see dosage and directions for use).

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

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

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

Because metoclopramide can stimulate gastro-intestinal mobility, the drug 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.

AUSTELL METOCLOPRAMIDE 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 drugs 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 and hepatic impairment, therapy should be at a reduced dosage (see section 4.2).

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

Metoclopramide may cause elevation of serum prolactin levels.

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

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

AUSTELL METOCLOPRAMIDE 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. AUSTELL 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).

### **4.5 Interaction with other medicines and other forms of interaction**

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3). Alcohol potentiates the sedative effect of metoclopramide.

### **AUSTELL METOCLOPRAMIDE may affect the absorption of medicines**

#### ***Anticholinergics and morphine derivatives***

Anticholinergics and morphine derivatives may both have 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.

Caution is advisable with other centrally active drugs including antidepressants, anti-epileptics, and sympathomimetics.

Anti-muscarinics and opioid analgesics, antagonise the gastro-intestinal effects of AUSTELL METOCLOPRAMIDE.

### ***Neuroleptics***

Caution should be observed when using AUSTELL METOCLOPRAMIDE in patients taking other medicines that can also cause extrapyramidal reactions, such as phenothiazine.

Increased toxicity may occur if AUSTELL METOCLOPRAMIDE is used in patients receiving lithium.

### ***Serotonergic drugs***

The use of metoclopramide with serotonergic drugs 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<sub>max</sub> by 46% and exposure by 22%). Careful monitoring of cyclosporine 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.

### ***Aspirin, Paracetamol***

The effect of metoclopramide on gastric motility may modify the absorption of other concurrently administered oral drugs from the gastro-intestinal 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**

Metoclopramide injection may reduce plasma concentrations of atovaquone.

AUSTELL METOCLOPRAMIDE may also increase prolactin blood concentrations and therefore interfere with medicines, which have a hydroprolactinaemic effect such as bromocriptine. It has been suggested that it should not be given to patients receiving monoamine oxidase inhibitors.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

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

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

### **Breastfeeding**

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

### **Fertility**

There are no fertility data.

## **4.7 Effects on ability to drive and use machines**

AUSTELL METOCLOPRAMIDE may cause drowsiness or impaired reactions; Patients so affected, should not drive or operate machines.

Patient should not drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how AUSTELL METOCLOPRAMIDE affects them.

## 4.8 Undesirable effects

### a) Summary of the safety profile

AUSTELL METOCLOPRAMIDE 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

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

| System Organ Class                   | Frequency |                            |  |
|--------------------------------------|-----------|----------------------------|--|
|                                      | Frequent  | Less Frequent              | Not known  |
| Blood and lymphatic system disorders |           |                            | Methaemoglobinaemia <sup>1</sup> ,<br>Sulphaemoglobinaemia <sup>1</sup>                        |
| Immune system disorders              |           | Hypersensitivity reactions | Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation |

|                                  |   |  |   |
|----------------------------------|---|--|---|
| Endocrine disorders <sup>2</sup> |   | Amenorrhoea,<br>Hyperprolactinaemia,<br>Galactorrhoea  | Gynaecomastia   |
| Psychiatric disorders            | Depression  | Hallucination, confusional state   |   |
| Nervous system disorders         | Somnolence, restlessness, drowsiness, dizziness, headache, extrapyramidal disorders <sup>3</sup> , parkinsonism, akathisia. | Anxiety and agitation may occur, especially after rapid injection.<br><br>Parkinsonism and Tardive dyskinesia have occasionally occurred, usually during prolonged treatment in the elderly.<br><br>Dystonia (including visual disturbances and oculogyric | Tardive dyskinesia <sup>4</sup> , neuroleptic malignant syndrome <sup>5</sup> |

|  |   |  |  |
|--|---|--|--|
|  |   | crisis), dyskinesia, depressed level of consciousness.<br><br>Convulsion especially in epileptic patients. |  |
| Cardiac disorders                      |   | Bradycardia, particularly with intravenous formulation   | Cardiac arrest <sup>6</sup> , atrioventricular block, sinus arrest, electrocardiogram QT prolonged, Torsade de Pointes                                   |
| Vascular disorders                     | Hypotension                                     |  | Shock, syncope after injectable use. Acute hypertension inpatients with phaeochromocytoma (see section 4.3).<br><br>Transient increase in blood pressure |
| Gastrointestinal disorders             | Bowel upset such as diarrhoea and constipation. |  |  |
| Skin and subcutaneous tissue disorders |   |  | Skin reactions such as rash, pruritus, angioedema and urticaria  |

|  |          |  |   |
|--|----------|--|---|
| Renal and urinary disorders                          |          |  | Urinary incontinence                            |
| General disorders and administration site conditions | Asthenia |  | Injection site inflammation and local phlebitis |

<sup>1</sup> 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.

<sup>2</sup> Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

<sup>3</sup> AUSTELL METOCLOPRAMIDE may cause increased risk of 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).

<sup>4</sup> Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4).

<sup>5</sup> 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).

AUSTELL METOCLOPRAMIDE should be stopped immediately if this syndrome occurs.

<sup>6</sup> 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 AUSTELL METOCLOPRAMIDE, 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. 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**

Over dosage of AUSTELL METOCLOPRAMIDE could give rise to the dyskinetic reactions manifested as major restlessness, agitation, irritability, spasm of facial and neck muscles and muscles of the tongue. In severe cases opisthotonos can result. Very seldomly AV block has been observed.

### **Treatment**

Should active therapy be required for a dystonic reaction, an anti-Parkinson drug may be used. Further treatment is symptomatic and supportive.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

Pharmacotherapeutic group: Propulsive agents stimulating gastrointestinal motility.

ATC Code: A03FA01

Metoclopramide is a dopaminergic antagonist and can block the gastro-intestinal effects caused by the local or systemic administration of dopaminergic agonists.

It promotes the release of acetylcholine from the myenteric neurons.

Metoclopramide enhances the motility of the smooth muscles from the oesophagus through the proximal small muscle bowel and accelerates gastric emptying and the transit of intestinal contents from the duodenum to the ileocecal valve.

Metoclopramide decreases receptive relaxation in the upper stomach and increases antral contractions.

Metoclopramide acts on the chemoreceptor trigger zone to produce a central anti-emetic effect.

### **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 blood–brain 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 glucuronic acid. The half–life of the drug in circulation is 4 to 6 hours.

### **5.3 Preclinical safety data**

Not available.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Disodium EDTA (Disodium Edetate)

Glacial Acetic Acid

Sodium Chloride

Sodium Acetate

Water for Injection

10 % Glacial Acetic Acid or 20 % w/v Sodium Acetate Solution

### **6.2 Incompatibilities**

AUSTELL METOCLOPRAMIDE should not be diluted for injection since this will upset the isotonicity and the stability of the drug.

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

Store at or below 25 °C.

Protect from light.

### **6.5 Nature and contents of container**

Amber coloured glass ampoules of 10 x 2 mL or 10 x 10 x 2 mL or 5 x 10 x 2 mL.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

## **7. HOLDER OF CERTIFICATE OF REGISTRATION**

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG, 2193

## **8. REGISTRATION NUMBER**

37/5.7.2/0312

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

3 June 2005

## **10. DATE OF REVISION OF THE TEXT**

09 January 2024