AUSTRALIAN PI – APO-METOCLOPRAMIDE (METOCLOPRAMIDE HYDROCHLORIDE MONOHYDRATE)

1 NAME OF THE MEDICINE

Metoclopramide hydrochloride monohydrate.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each APO-Metoclopramide tablet contains 10 mg metoclopramide hydrochloride monohydrate as the active ingredient. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, colloidal anhydrous silica, maize starch, stearic acid and pregelatinised maize starch. The coating for the tablets consists of hypromellose, macrogol 6000, titanium dioxide and purified talc.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults (20 years and over):

- As an adjunct to X-ray examination of the stomach and duodenum.
- To assist in intestinal intubation.
- To control nausea and vomiting associated with the following conditions: intolerance to essential drugs possessing emetic properties; uraemia; radiation sickness; malignant disease; postoperative vomiting; labour; infectious diseases. There is no clear benefit in motion sickness or other labyrinth disturbances.
- Metoclopramide has been found useful in the management of gastric retention after gastric surgery.
- Metoclopramide may be useful in the treatment of diabetic gastroparesis of mild to moderate severity. Once control of diabetes has been established by diet and/or insulin, metoclopramide should be discontinued.

Young Adults:

The use of metoclopramide in patients under 20 years should be restricted to the following situations and only used as second line therapy:

- Severe intractable vomiting of known cause.
- Vomiting associated with radiotherapy and intolerance to cytotoxic drugs.
- As an aid to gastrointestinal intubation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients with Normal Renal and Hepatic Function

The dosage recommendations given below should be strictly adhered to if side effects of the dystonic type are to be avoided. Total daily dosage of APO-Metoclopramide, especially for young adults, should not normally exceed 0.5 mg/kg bodyweight with a maximum of 30 mg daily. Metoclopramide should only be used after careful examination to avoid masking an underlying disorder, e.g. cerebral irritation. Maximum recommended treatment duration is 5 days.

Medical Indications

Adults

20 years and over: Maximum of 10 mg three times daily

Elderly Patients

As for adults. To avoid adverse reactions adhere strictly to dosage recommendations and where prolonged therapy is considered necessary, patients should be regularly reviewed.

Young Adults

15-20 years: 5 to 10 mg three times daily, commencing at the lower dosage and used as second line therapy only.

Children

Tablets should not be used in children <15 years.

Diagnostic Indications

A single dose of APO-Metoclopramide may be given 5 to 10 minutes before the examination.

Subject to bodyweight considerations, the following dosages are recommended:

Adults

20 years and over: 10 to 20 mg

Young Adults

15-19 years: 10 mg.

Patients with Impaired Renal and Hepatic Function

In patients with clinically significant degrees of renal or hepatic impairment, clearance of APO-Metoclopramide is likely to be reduced. It is suggested that therapy be initiated at half the recommended dose. Subsequent dosage will depend on individual clinical response.

4.3 CONTRAINDICATIONS

Metoclopramide should not be used in the following situations:

- whenever stimulation of gastrointestinal motility might be dangerous, e.g. in the presence of gastrointestinal haemorrhage, mechanical obstruction, or perforation
- phaeochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumour. Such hypertensive crises may be controlled by phentolamine
- known hypersensitivity or intolerance to the drug
- porphyria
- epilepsy, as metoclopramide may increase the frequency and severity of seizures
- patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased
- children below 1 year of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Persistent tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on

high dose therapy, especially females. The symptoms are persistent and can oftentimes appear to be irreversible. The syndrome is characterised by rhythmical involuntary movement of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movement of extremities. There is no known effective treatment for tardive dyskinesia, however, in some patients symptoms may lessen or resolve after metoclopramide hydrochloride monohydrate treatment is stopped. Antiparkinson agents usually do not alleviate the symptoms of this syndrome.

Although the risk of tardive dyskinesia with metoclopramide has not been extensively studied, one published study reported a tardive dyskinesia prevalence of 20% among patients treated for at least 3 months. 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.

Metoclopramide hydrochloride monohydrate therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and, if the medication is stopped at that time, the syndrome may not develop. Tardive dyskinesia may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn. 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 the syndrome is unknown. Therefore, metoclopramide should not be used for the symptomatic control of tardive dyksinesia.

Prolonged treatment (greater than 12 weeks) with 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.

Care should be exercised in patients being treated with other centrally active drugs.

Since extrapyramidal symptoms may occur with both metoclopramide hydrochloride monohydrate and neuroleptics such as phenothiazines, care should be exercised in the event of both drugs being prescribed concurrently (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). The frequency and severity of seizures or extrapyramidal reactions may be increased in epileptic patients given metoclopramide hydrochloride monohydrate.

Dystonic reactions

Dystonic reactions occur in approximately 1% of patients given metoclopramide hydrochloride monohydrate. These occur more frequently in children and young adults and may occur after a single dose.

Neuroleptic malignant syndrome has been reported with metoclopramide hydrochloride monohydrate in combination with neuroleptics as well as with metoclopramide hydrochloride monohydrate monotherapy (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Prolactin levels

Metoclopramide hydrochloride monohydrate elevates prolactin levels and the elevation persists during chronic administration (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide hydrochloride monohydrate is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia, and impotence have been reported with prolactin elevating drugs, the clinical significance of elevated serum prolactin levels is

unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin stimulating neuroleptic drugs. Neither clinical studies nor epidemiological studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

Other

Following operations such as pyloroplasty or gut anastomosis, metoclopramide hydrochloride monohydrate therapy should be withheld for three or four days as vigorous muscular contractions may not help healing.

Special care should be taken in cases of severe renal insufficiency (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

The symptomatic relief provided by metoclopramide hydrochloride monohydrate may delay recognition of serious disease. It should not be prescribed until diagnosis has been established, and should not be substituted for appropriate investigation of the patient's symptoms. Metoclopramide hydrochloride monohydrate should not be given to children unless a clear indication has been established for its use, because of the higher incidence of adverse reactions in this age group.

If vomiting persists in a patient receiving metoclopramide hydrochloride monohydrate, the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

Patients should be cautioned about engaging in activities requiring mental alertness for a few hours after the drug has been administered.

Metoclopramide induced depression has been reported in patients without a prior history of depression. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Metoclopramide should be used with caution in patients with hypertension as intravenously administered metoclopramide has been shown to release catecholamines.

Metoclopramide can exacerbate parkinsonian symptoms, therefore it should be used with caution, if at all, in patients with parkinsonian syndrome (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Use in the Elderly

See **Section 4.2 Dose and Method of Administration**.

Paediatric use

Metoclopramide should not be given to children under 1 year of age unless a clear indication has been established for its use, because of the higher incidence of adverse reactions in this age group. APO-Metoclopramide tablets is not indicated for patients < 15 years of age.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The effects of metoclopramide hydrochloride monohydrate on gastrointestinal motility are antagonised by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide hydrochloride monohydrate is given with alcohol, sedatives, hypnotics, narcotics or tranquillisers.

Since metoclopramide hydrochloride monohydrate accelerates abnormally slow gastric and small bowel peristaltic activity, it may change absorption of orally administered drugs. The absorption of drugs from the small bowel may be accelerated (e.g. paracetamol, tetracycline, levodopa), whereas absorption of drugs from the stomach may be diminished (e.g. digoxin).

Compatibility: If the standard formulation of metoclopramide hydrochloride monohydrate is used for the treatment of nausea and vomiting associated with cytotoxic drugs, the cytotoxic agent should be administered as a separate infusion.

Metoclopramide may cause extrapyramidal symptoms in some patients. Therefore, caution should be exercised when metoclopramide is used concomitantly with other drugs that are likely to cause extrapyramidal reactions (e.g. neuroleptics such as phenothiazines).

The decrease in gastric emptying time caused by metoclopramide may increase the bioavailability of cyclosporin. Monitoring of cyclosporin concentrations may be necessary.

When metoclopramide is given concurrently with suxamethonium the recovery time is prolonged.

Since metoclopramide influences the delivery of food to the intestine and thus the rate of its absorption, the administration of metoclopramide may result in poor diabetic control in some patients. Therefore adjustment in, or timing of, insulin dosage may be necessary in insulin controlled diabetics.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy (Category A)

Adequate human data on use during pregnancy are not available.

Use in lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent adverse reactions to metoclopramide hydrochloride monohydrate are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients.

Less frequently, insomnia, headache, dizziness, nausea, or bowel disturbances may occur. Rare (less than 1 in 1,000) cases of acute depression have been reported. Anxiety or agitation may occur (especially after rapid injection).

A single instance of supraventricular tachycardia following intramuscular administration has been reported. There have been very rare (less than 1 in 10,000) cases of abnormalities of cardiac conduction (such as bradycardia and heart block) in association with intravenous metoclopramide. Atrial fibrillation (AF), oedema, tachycardia and palpitations have been

associated with the use of metoclopramide. This event is in association with intravenous administration of other brands.

Although uncommon at normal dosage, various extrapyramidal reactions to metoclopramide hydrochloride monohydrate, usually of the dystonic type, have been reported. Reactions include: spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, a bulbar type of speech, spasm of the extraocular muscles including oculogyric crises, unnatural positioning of the head and shoulders and opisthotonos. There may be a generalised increase in muscle tone. The majority of reactions occur within 36 hours of starting treatment and the effects usually disappear within 24 hours of withdrawal of the drug, however, close observation is required and in cases of more severe reactions, an antiparkinson drug such as benztropine or an anticholinergic antihistamine such as diphenhydramine should be given. A fatal dystonic reaction has been reported in a patient who received hexamethylmelamine, cisplatin and high dose metoclopramide. A fatal cardiorespiratory arrest has occurred in at least one patient with an acute dystonic reaction.

Tardive dyskinesia, which may be persistent, has been reported particularly in elderly patients undergoing long-term therapy with metoclopramide hydrochloride monohydrate.

Very rare (less than 1 in 10,000) occurrences of the Neuroleptic Malignant Syndrome have been reported. This syndrome is potentially fatal and comprises hyperpyrexia, altered consciousness, muscle rigidity, autonomic instability and elevated levels of CPK and must be treated urgently recognised treatments include dantrolene). Metoclopramide hydrochloride monohydrate should be stopped immediately if this syndrome occurs.

Parkinsonian symptoms, including tremor, rigidity, bradykinesia and akinesia, occur rarely in patients receiving metoclopramide but may be associated with usual or excessive doses or with decreased renal function.

There have been isolated reports of hypersensitivity reactions (such as urticaria, maculopapular rash) in patients receiving metoclopramide.

There have been a few cases of neutropenia, leucopenia and agranulocytosis generally without clear cut relationship to metoclopramide.

Methaemoglobinaemia has also been reported.

Sulfhaemoglobinaemia in adults.

Hyperthermia has also been observed.

Raised serum prolactin levels have been observed during metoclopramide therapy; this effect is similar to that noted with many other compounds. Galactorrhoea and breast enlargement have also been observed during metoclopramide therapy.

Respiratory failure, secondary to dystonic reaction, acute asthmatic symptoms of wheezing and dyspnoea may occur.

Urinary incontinence, sexual dysfunction, priapism and muscle spasm may also occur.

Rarely, when metoclopramide was administered with other drugs with known hepatotoxic potential, cases of hepatotoxicity characterised by such findings as jaundice and altered liver function tests were reported.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose of metoclopramide may be expected to produce effects that are extensions of common adverse reactions: drowsiness, disorientation and extrapyramidal side effects. Very

rarely AV block has been observed. Management of overdosage consists of close observation and supportive therapy. Antiparkinson and antihistamine/anticholinergic drugs such as diphenhydramine hydrochloride monohydrate have effectively controlled extrapyramidal reactions. Other reported effects associated with metoclopramide overdose have included feelings of anxiety or restlessness, headache, vertigo, nausea, vomiting, constipation, weakness, hypotension and xerostomia. Haemodialysis appears ineffective in removing metoclopramide. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of the drug.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Metoclopramide hydrochloride monohydrate stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions.

Its mode of action is unclear. It seems to sensitise tissues to the action of acetylcholine. The effect of metoclopramide hydrochloride monohydrate on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide hydrochloride monohydrate increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower oesophageal sphincter. It has little, if any effect on the motility of the colon or gall bladder.

Metoclopramide hydrochloride monohydrate has dopamine antagonist activity. Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide hydrochloride monohydrate produces sedation and may produce extra-pyramidal reactions (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Metoclopramide hydrochloride monohydrate inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The onset of pharmacological action is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

There is marked variability in peak plasma concentrations of metoclopramide hydrochloride monohydrate after oral administration, which appears to be due to interindividual differences in first-pass metabolism.

Distribution

Plasma protein binding is 13 to 22%.

Metabolism

About 80% of the drug is excreted in the urine in the first 24 hours, approximately half as the glucuronide and sulfate conjugates and half as unchanged drug.

Excretion

Elimination half-life varies in different studies from 2.5 to 5 hours. Impaired renal function results in reduced clearance of metoclopramide hydrochloride monohydrate and an increased half-life (15 hours).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **Section 2 and 3 Qualitative and quantitative composition and pharmaceutical form**.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See **Section 4.5 Interactions with other medicines and other forms of interactions**.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tablets should be stored below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mg film coated tablets (AUST R 196502)

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

Blister packs (PVC/PVDC/Al) of 10, 20, 25, 30, 50, 60 100, 125 or 150 tablets film coated tablets.

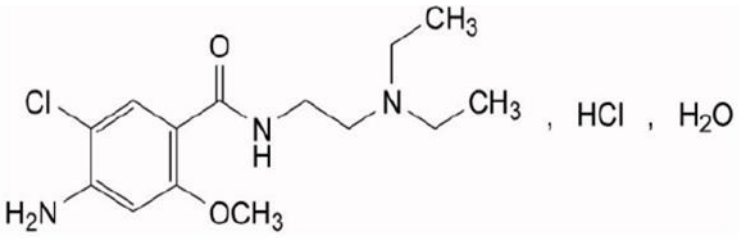
Not all pack sizes available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Name: N-(diethyl-aminoethyl)-2-methoxy-4-amino-5-chlorbenzamide monohydrochloride monohydrate

Chemical Formula: $C_{14}H_{22}ClN_3O_2$, HCl, H_2O

Molecular Weight: 354.3

CAS number

54143 -57-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

3 June 2015.

10 DATE OF REVISION

1 March 2018.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted to new PI form approved by TGA on 8 November 2017.
1, 2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2	Updated the ingredient name from “Metoclopramide hydrochloride” to “Metoclopramide hydrochloride **monohydrate**” to comply with the new Australian Approved Name (AAN) as per current TGA approved terminology for medicines in the TGA eBusiness Services code tables.
2 and 3	Updated the ingredient name from “Cellulose microcrystalline” to “**Microcrystalline cellulose**” to comply with the new Australian Approved Name (AAN) as per current TGA approved terminology for medicines in the TGA eBusiness Services code tables.