AUSTRALIAN PRODUCT INFORMATION

PRAMIN

(metoclopramide hydrochloride) tablets

1 NAME OF THE MEDICINE

Metoclopramide hydrochloride monohydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PRAMIN tablet contains metoclopramide hydrochloride monohydrate as the active ingredient, equivalent to 10 mg of metoclopramide hydrochloride.

Excipients with known effect: contains sugars as lactose and trace amounts of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

PRAMIN 10 mg tablet: white, normal convex, marked "ME" over "10" on one side, G on reverse;

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 (such as cytotoxic agents); uraemia; radiation sickness; malignant disease; post-operative vomiting; labour; infectious diseases. There is no clear benefit in motion sickness or other labyrinth disturbances.

PRAMIN has been found useful in the management of gastric retention after gastric surgery; of diabetic gastroparesis of mild to moderate severity. Once control of diabetes is established by diet and/or insulin, use of metoclopramide should be discontinued.

Young Adults aged 15 – 19 years:

The use of PRAMIN in young adults 15 – 19 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

Metoclopramide injection is not available in the PRAMIN brand. However, injection formulations are available in other brands. Where information obtained from metoclopramide injection formulations is included in this PI, this is intended for prescriber information.

Where correct dosing requires a metoclopramide injection formulation, the specific product information for these formulations should be referred to for complete dosage and administration instructions.

Tablets should not be used in children less than 15 years.

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 metoclopramide, especially for young adults should not normally exceed 0.5 mg/kg body weight 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 in all age groups.

Medical Indications:

Oral:

Usual adult (over 20 years) dose:

Maximum of 10 mg three times daily.

Elderly patients:

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

Young adults 15-19 years:

5 to 10 mg three times daily, commencing at the lower dosage and used as a second line therapy only.

Diagnostic Indications:

A single dose of metoclopramide may be given 5 to 10 minutes before 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 or hepatic function:

In patients with clinically significant degrees of renal or hepatic impairment, clearance of PRAMIN 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

Cases in which gastrointestinal stimulation might be dangerous, e.g., in the presence of gastrointestinal haemorrhage, mechanical obstruction, or perforation.

- *Phaeochromocytoma*. Hypertensive crises have been reported in three patients with this tumour who have been given metoclopramide, probably due to the release of catecholamines from the tumour. Such hypertensive crises may be controlled by phentolamine.
- Patients with known hypersensitivity or intolerance to the drug or any other component of the tablet.
- *Epilepsy.* Metoclopramide should not be used in patients with epilepsy since it may increase the frequency and severity of seizures
- *Concomitant use with other drugs likely to cause extrapyramidal side effects.* The frequency and severity of extrapyramidal reactions may be increased with neuroleptics such as phenothiazines.
- *Patients with porphyria.*.

- Metoclopramide should not be administered to patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased.

- Metoclopramide tablets should not be used in children below 15 years of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions

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 movements of extremities. There is no known effective treatment for tardive dyskinesia; however, in some patients symptoms may lessen or resolve after metoclopramide 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 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 dyskinesia.

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 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.

Dystonia

Dystonic reactions occur in approximately 1% of patients given metoclopramide. These occur more frequently in children and young adults, and may occur after a single dose (see SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Neuroleptic malignant syndrome

This has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy (see SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Prolactin levels

Since metoclopramide elevates prolactin levels and the elevation persists during chronic administration, it should be used with caution in patients with breast cancer. 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 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. However, neither clinical nor epidemiological studies conducted to date have shown an association between chronic administration of these drugs and mammary tumourigenesis; the available evidence is too limited to be conclusive at this time.

Surgery

After operations such as pyloroplasty or gut anastomosis, metoclopramide therapy should be withheld for three or four days as vigorous muscular contractions may impede healing.

Masking of serious illness

The symptomatic relief provided by metoclopramide 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.

Depression

Metoclopramide-induced depression has been reported in patients without a prior history of depression. Symptoms have ranged from mild to severe and have included episodes of spontaneous, uncontrollable crying, somnolence, suicide ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Hypertension

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines. Caution should be exercised when metoclopramide is used in patients with hypertension.

Parkinson's disease

Metoclopramide can exacerbate Parkinsonian symptoms, thus it should be used with caution, if at all, in patients with Parkinsonian syndrome (see SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Vomiting

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

Use in Hepatic Impairment

In patients with clinically significant degrees of hepatic impairment, clearance of PRAMIN is likely to be reduced.

Use in Renal Impairment

In patients with clinically significant degrees of renal impairment, clearance of PRAMIN is likely to be reduced.

Special care should be taken in cases of severe renal insufficiency (See section 4.2 DOSAGE AND ADMINISTRATION).

Use in the Elderly

To avoid adverse reactions, adhere strictly to dosage recommendations. When prolonged therapy is considered necessary, patients should be regularly reviewed.

Paediatric Use

Metoclopramide tablets are contraindicated in children less than 15 years of age because of the higher incidence of adverse reactions in this age group.

Effects on Laboratory Tests

Metoclopramide may blunt the response to the gonadorelin diagnostic test, by increasing serum prolactin levels. Metoclopramide may alter hepatic function test results.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Due to its pharmacologic effects on transit time in the stomach and small intestine, metoclopramide may alter the absorption of certain drugs. The extent of absorption of drugs that disintegrate, dissolve, and/or are absorbed mainly in the stomach (eg. digoxin) may be diminished by metoclopramide, whereas the rate and extent of absorption of drugs that are mainly absorbed in the small intestine (eg. paracetamol, aspirin, diazepam, ethanol, levodopa, lithium, tetracycline) may be enhanced. The clinical importance of these effects has not been established.

Anticholinergic drugs and opioid analgesics. The effects of metoclopramide on gastrointestinal motility can be antagonised by anticholinergic drugs and opioid analgesics.

CNS Depressants. Metoclopramide may potentiate the action of other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, hypnotics, tranquillisers, anaesthetics or alcohol.

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

Neuroleptics. Metoclopramide may cause extrapyramidal symptoms in some patients. Therefore, when metoclopramide is used concomitantly with other drugs that are likely to cause extrapyramidal reactions (eg. neuroleptics such as phenothiazines), caution should be exercised (see section 4.3 CONTRAINDICATIONS).

Monoamine Oxidase Inhibitors (MAOI). The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving MAOIs.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy: Category A

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Although animal tests in several mammalian species have shown no teratogenic effects, the safety of metoclopramide in pregnancy has not been established. Adequate human data is not available. Therefore, the drug should only be used in pregnant women when the expected benefit outweighs any potential risk.

Use in Lactation

Metoclopramide is excreted in human milk. It is not known whether it has a harmful effect on the newborn. Administration of metoclopramide to breastfeeding mothers is not recommended unless the expected benefits to the mother outweigh any potential risk to the baby. The increased risk of adverse reactions in young children should be taken into account in making a risk-benefit assessment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about engaging in activities requiring mental alertness for a few hours after metoclopramide has been administered.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Neurological

Adverse effects to metoclopramide that are most frequently seen are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients. Insomnia, headache, dizziness, have been reported less frequently. Acute depression has been reported rarely (less than 1 in 1000 cases). Anxiety or agitation may occur. Delirium, severe dysphoria, obsessive rumination and mania have been reported occasionally.

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.

Various extrapyramidal reactions to metoclopramide, usually of the dystonic type, have been reported. Acute dystonic reactions occur in approximately 0.2% of patients treated with 30 to 40 mg of metoclopramide per day. In cancer chemotherapy patients receiving 1 to 2mg/kg per dose, the incidence is 2% in patients over the ages of 30 to 35 and 25% or higher in children and young adults who have not had prophylactic administration of diphenhydramine. 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 crisis, 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 acute dystonic reaction has been reported in a patient who received hexamethylmelamine, cisplatin and metoclopramide high dose.

Dystonic reactions may present rarely as upper airway obstruction with stridor and dyspnoea, possibly secondary to laryngospasm or supraglottic dystonia. A fatal cardiorespiratory arrest occurred in at least one patient with an acute dystonic reaction.

Tardive dyskinesia, which may be persistent, has been reported particularly in elderly patients (particularly women) following long term therapy with metoclopramide. Tardive dyskinesia is most frequently characterised by involuntary movements of the tongue, face, mouth or jaw and sometimes by involuntary movements of the trunk and/or extremities. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with increasing duration of therapy and total cumulative dose. Although tardive dyskinesia can occur after relatively brief therapy with the drug at low doses, it appears to be more readily reversible under such circumstances (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS).

Neuroleptic Malignant Syndrome (NMS)

NMS has been reported very rarely (less than 1 in 10,000). NMS 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 and bromocriptine). Metoclopramide should be stopped immediately if NMS occurs.

Gastrointestinal

Nausea or bowel disturbances have been reported.

Hepatic

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

Renal

Urinary frequency and incontinence.

Cardiovascular

Atrial fibrillation, oedema, ventricular fibrillation, ventricular tachycardia, palpitations and tachycardia have been associated with the use of metoclopramide.

Endocrine

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.

Hypersensitivity

There have been isolated reports of hypersensitivity reactions in patients receiving metoclopramide.

Respiratory

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

Other Effects

There have been isolated reports of blood disorders. Methaemoglobinaemia, particularly following overdose in neonates, has also occurred in patients receiving the drug. A few cases of neutropenia, leucopenia or agranulocytosis, generally without clear-cut relationship to metoclopramide.

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

Sexual dysfunction, priapism and muscle spasm may also occur.

Hyperthermia has also been observed.

Sulfhaemoglobinaemia in adults.

Reporting Suspected Adverse Effects

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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Clinical Features

Overdose of metoclopramide may be expected to produce effects that are extensions of common adverse reactions: drowsiness, disorientation and extrapyramidal reactions have been the principal effects reported. Other reported effects associated with metoclopramide overdose have included feelings of anxiety or restlessness, headache, vertigo, nausea, vomiting, constipation, weakness, hypotension and xerostomia. AV block has been observed very rarely.

Management

Treatment of metoclopramide overdosage generally involves symptomatic and supportive care. Extrapyramidal reactions may be controlled by anti-Parkinsonian agents such as benztropine, or antihistamines with anticholinergic action such as diphenhydramine. Appropriate therapy should be instituted if hypotension or excessive sedation occurs. Methaemoglobinaemia should be treated with methylene blue. Haemodialysis and continuous ambulatory peritoneal dialysis appears ineffective in removing metoclopramide.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Metoclopramide increases the motility of the stomach, pylorus and small intestine without stimulating gastric, biliary or pancreatic secretions. Its mode of action is unclear, however it appears to sensitise tissues to the action of acetylcholine. The gastrointestinal stimulant action is exerted peripherally, not by central stimulation of the vagus nerve, and it is blocked by anticholinergic drugs such as atropine.

The anti-emetic properties of metoclopramide result from its antagonism of central dopamine receptors and from its effect on the stomach. It 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 and has little, if any, effect on the motility of the colon or gall bladder.

Metoclopramide causes increased prolactin secretion due to blocking of dopamine receptors in the hypothalamus and hypophysis which normally suppress prolactin secretion. Metoclopramide also increases the rate of secretion of aldosterone. *In vitro* studies suggest that metoclopramide acts directly on adrenal tissue to stimulate aldosterone secretion.

Metoclopramide has dopamine antagonist activity. Like the phenothiazines and related drugs, which are also dopamine antagonists, it produces sedation and may produce extrapyramidal reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS). Metoclopramide 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 of metoclopramide is 30 to 60 minutes following an oral dose and effects persist for one to two hours.

After oral administration of metoclopramide there is marked variability in peak plasma concentrations observed. The variation in peak plasma levels between individuals is thought to be due to first-pass metabolism

Distribution

Plasma protein binding of metoclopramide appears to be minor (13 to 22%).

Metabolism

About 80% of the drug is excreted in urine in the first 24 hours. Approximately half the amount excreted is a glucuronide or sulphate conjugate with the remainder unchanged.

Excretion

Elimination half-life varies in different studies from 2.5 to 5 hours. In one study 78% of the drug was excreted in the urine during the first 24 hours after a 10mg oral dose.

Impaired renal function results in reduced clearance of metoclopramide and an increased elimination half-life (15 hours). In a study of 6 patients with chronic renal failure total body clearance of metoclopramide was 16.7 litres/hour compared to 52.5 litres/hour in normal individuals. This difference in clearance was not explained by the change in renal clearance and suggested impaired metabolism or an alteration in enterohepatic circulation.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following excipients: lactose anhydrous, pregelatinised maize starch, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle with PP child-resistant closure or PVC/PVdC-Al blister pack.

* Pack sizes: available in bottles of 6, 25, 30, 50, 90, 100 and 1000 tablets or a blister pack of 25 tablets

* Not all pack sizes are marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

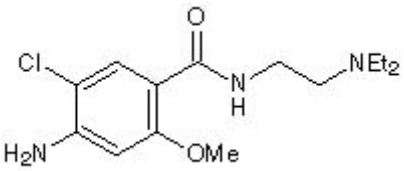
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride monohydrate.

Structural formula:



.HCl. H_2O

Molecular formula: $C_{14}H_{22}ClN_3O_2,HCl,H_2O$ Molecular weight: 354.3

Metoclopramide hydrochloride is a white or almost white, crystalline powder; odourless or almost odourless. It is soluble in 0.7 parts of water, in 3 parts of ethanol (96%) and in 55 parts of chloroform. It is practically insoluble in ether.

CAS Number

54143-57-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/09/1991

10 DATE OF REVISION

17/01/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.1	Correction to indications for young adults and children.
4.2	Information statement regarding injection formulations added. Information for use of tablets in children under 15 years added. Correction to 'Medical' and 'Diagnostic' indications sections.
4.3	Correction to contraindicated age group.
4.4	Correction to 'Paediatric Use' sub-section.
4.5	Deletion of compatibility information.

PRAMIN_pi\Jan25/00