AUSTRALIAN PRODUCT INFORMATION

METOMAX®

(paracetamol and metoclopramide hydrochloride monohydrate) capsule

1 NAME OF THE MEDICINE

Paracetamol

Metoclopramide hydrochloride (as monohydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each METOMAX capsule contains 500 mg paracetamol and 5.25 mg metoclopramide hydrochloride monohydrate equivalent to 5 mg metoclopramide hydrochloride.

Excipients with known effect: sulfites.

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

3 PHARMACEUTICAL FORM

METOMAX Capsules: The capsules are size 0, hard gelatin capsules with a green cap and yellow body. Printed in black ink is "α" on the cap and "P500 | M5" on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Symptomatic relief of headache, nausea and vomiting associated with migraine.

4.2 DOSE AND METHOD OF ADMINISTRATION

METOMAX should be taken at the first warning of a migraine headache. If symptoms persist, further doses may be taken at four-hourly intervals. Total dosage in any 24 hour period should not exceed the quantity stated.

The dosage recommendations given below should be strictly adhered to if side effects of the dystonic type are to be avoided. It should be noted that a total daily dosage of metoclopramide should not normally exceed 0.5 mg/kg body weight with a maximum of 30 mg daily. METOMAX should only be used after careful examination to avoid masking an underlying disorder e.g. cerebral irritation.

Maximum treatment duration is 5 days. Keep to the recommended dose. Do not use for longer than a few days at a time unless advised to by a doctor.

Adults 18 years and Over

The recommended dose is 1 or 2 capsules initially, and then 1-2 capsules every 4 hours (maximum dose of 6 capsules in 24 hours).

Children and Adolescents under 18 years

METOMAX is not recommended for use in children under 18 years.

Renal and Hepatic Impairment

Therapy should be initiated at half the normal dose since adverse effects are likely to be exacerbated. The dose should then be adjusted depending on the clinical response.

4.3 CONTRAINDICATIONS

- Wherever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.

Stimulation of gastrointestinal motility may aggravate these conditions.

- *Phaeochromocytoma*

  Hypertensive crisis have been reported with the use of metoclopramide in these patients. This is probably due to the release of catecholamines from the tumour. Such hypertensive crises may be controlled by phentolamine.

- *Epilepsy*

  The frequency and severity of seizures may be increased in epileptic patients given metoclopramide. Metoclopramide should not be used in patients with epilepsy since it may increase the frequency and severity of seizures.

- *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.

- Known hypersensitivity or intolerance to paracetamol, metoclopramide or any of the excipients in METOMAX capsules.

- Children and adolescence under 18 years.

Insufficient safety data exist to support the use of METOMAX (metoclopramide/paracetamol combination) in pregnancy or during lactation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

High Anion Gap Metabolic Acidosis

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

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.

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.

Epilepsy

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.

Neuroleptic Malignant Syndrome

Has been reported with metoclopramide in combination with antipsychotics, as well as with metoclopramide monotherapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Breast Cancer and Prolactin levels

Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. 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 antipsychotic drugs.

Neither clinical studies nor epidemiological studies conducted to date, however, 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.

Parkinson’s Disease

Metoclopramide can exacerbate Parkinsonian symptoms, hence should be used with caution, if at all, in patients with Parkinsonian syndrome.

Surgery

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

Masking of Serious Illness

The symptomatic relief provided by metoclopramide may delay recognition of serious disease. This product should not be prescribed or recommended until diagnosis has been established, and should not be substituted for appropriate investigation of the patient's symptoms.

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

Other Paracetamol Containing Products

Patients should be warned not to take this product with other paracetamol-containing products.

Use in Hepatic or Renal Impairment

METOMAX should be administered with caution to patients with renal or hepatic dysfunction.

Plasma concentrations of paracetamol and its conjugates are increased in patients with moderate renal failure. In patients with clinically significant degrees of renal or hepatic impairment, the clearance of metoclopramide is likely to be reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the Elderly

See Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Paediatric Use

METOMAX is not recommended for use in children and adolescents under 18 years of age.

There is a higher incidence of adverse events from metoclopramide in children (see Section 4.3 CONTRAINDICATIONS).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Paracetamol

Anticoagulants. Anticoagulant dosage may require reduction if treatment with METOMAX is prolonged.

Paracetamol absorption is increased by drugs which increase gastric emptying, e.g. metoclopramide, and decreased by drugs which decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations.

Enzyme Inducing Agents. The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant drugs.

Concomitant Use With Flucloxacillin. Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metoclopramide

Anticholinergic Drugs and Narcotic (Opioid-Containing) Analgesics. The effects of metoclopramide on gastrointestinal motility can be antagonised by these.

CNS Depressants. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics or tranquillisers.

Drugs Affected by Increased Gastrointestinal Motility. Since metoclopramide 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).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available

Use in Pregnancy

Pregnancy Category: Metoclopramide hydrochloride (Category A), Paracetamol (Category A)

Metoclopramide/paracetamol combination

Insufficient safety data exist to support the use of METOMAX (metoclopramide/paracetamol combination) in pregnancy (see Section 4.3 CONTRAINDICATIONS).

Use in Lactation

This product should only be used in breastfeeding mothers when the expected benefits to the mother outweigh any potential risk to the baby. Paracetamol and metoclopramide are both excreted in breast milk. The amount available for ingestion by the infant has been reported variously as less than 0.1% of a single dose of paracetamol 500 mg, and as 0.04 to 0.23% of a single 650 mg dose.

Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infant. It is not known whether it has a harmful effect on the newborn. The administration of metoclopramide to breastfeeding mothers may increase the risk of adverse reactions in young children and should be taken into account when making a risk-benefit assessment.

Insufficient safety data exist to support the use of METOMAX (metoclopramide/paracetamol combination) during lactation (see Section 4.3 CONTRAINDICATIONS).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be cautioned about engaging in activities requiring mental alertness for a few hours after taking this product.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Paracetamol

Reports of adverse reactions are rare. Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted: dyspepsia, nausea, allergic and haematological reactions.

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed (frequency cannot be estimated from the available data) in patients with risk factors using paracetamol (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Metoclopramide

The most frequent adverse reactions to metoclopramide 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.

Raised serum prolactin levels have been observed during metoclopramide therapy: this effect is similar to that noted with many other compounds.

Although uncommon at normal dosage, various extrapyramidal reactions to metoclopramide, 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.

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

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 creatine phosphokinase (CPK) and must be treated urgently (recognised treatments include dantrolene and bromocriptine). This medicine should be stopped immediately if this syndrome occurs.

Methaemoglobinaemia has also been reported.

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.

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 and frequency, sexual dysfunction, priapism and muscle spasm may also occur.

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.

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

Symptoms

Toxic symptoms of paracetamol overdose include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

Paracetamol overdose can result in severe liver damage and sometimes acute renal tubular necrosis.

In adults, hepatoxicity may occur after ingestion of a single dose of paracetamol 10 to 15 g (20 to 30 capsules or 10 to 15 times the normal dose); a dose of 25 g (50 capsules) or more is potentially fatal.

Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop. Liver damage and death may occur.

Extrapyramidal side effects are the most frequently reported adverse reactions to metoclopramide overdosage. Very rarely AV block has been observed.

Treatment

Prompt treatment is essential even when there are no obvious symptoms.

Treatment consists primarily of management of paracetamol toxicity. Gastric emptying, close observation and supportive therapy is the management plan of choice for metoclopramide intoxication.

In cases of overdosage, methods of reducing absorption of ingested drug are important. Prompt administration of activated charcoal 50 g in 150 mL of water and 150 mL sorbitol 50% solution by mouth may reduce absorption. It is recommended that intravenous fluids such as Normal Saline be given concurrently. Gastric lavage is indicated if the patient is unwilling or unable to drink an activated charcoal/sorbitol mixture. Methionine and acetylcysteine may be used as antidotes if given within a few hours of paracetamol overdosage.

If the history suggests that paracetamol 15 g or more has been ingested, administer the following antidote.

Intravenous acetylcysteine 20%. Administer acetylcysteine immediately without waiting for positive urine test or plasma level results if 8 hours or less since overdose ingestion. Initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in glucose 5% 500 mL over four hours and 100 mg/kg in glucose 5% 1 L over 16 hours.

If more than 8 hours have elapsed since the overdosage was taken, the antidote may be less effective.

When treatment for paracetamol toxicity has been initiated; antiparkinson and antihistamine/anticholinergic drugs such as diphenhydramine hydrochloride can be administered to effectively control extrapyramidal reactions of metoclopramide. 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 Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Paracetamol is a para-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity.

Metoclopramide 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 on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

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

Paracetamol

Absorption

After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma concentrations occur 20 to 120 minutes after administration, with a mean value of about 51 minutes.

Distribution

Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg.

Paracetamol can cross the placenta and is excreted in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45 to 55%) or sulfate (20 to 30%). A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation.

Excretion

Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85 to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1.9 to 5.7 hours, with a mean value of about 3.2 hours. Food intake delays paracetamol absorption.

Metoclopramide

The onset of pharmacological action is 30 to 60 minutes following an oral dose.

Absorption

After oral administration, the peak plasma concentrations occur in 38 minutes to 2.5 hours, with a mean value of about 1 hour.

Distribution

Metoclopramide is excreted in breast milk. 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

The elimination half-life varies from 3.2 to 14 hours, with a mean value of about 6.7 hours. Impaired renal function results in reduced clearance of metoclopramide 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

- colloidal anhydrous silica
- magnesium stearate
- purified talc
- sodium starch glycollate
- black ink (ID 2328, ID 2343)
- gelatin capsule size 0 (ID 11306)

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 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

METOMAX capsules	:	Container type: PVC/PVDC/Al blisters
		Pack size: 10 capsules

Australian Register of Therapeutic Goods (ARTG)

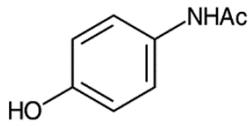
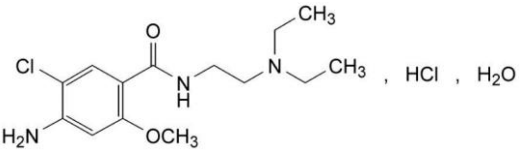
AUST R 121343 – METOMAX capsule blister pack

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

	Paracetamol	**Metoclopramide hydrochloride monohydrate**
		
Chemical name	*N*-(4-hydroxyphenyl)acetamide	4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride monohydrate
Molecular formula	$C_8H_9NO_2$	$C_{14}H_{22}ClN_3O_2$, HCl, H_2O
Molecular weight	151.2	354.3

CAS Number

	103-90-2	54143-57-6
	Paracetamol is a white crystalline powder, sparingly soluble in water, freely soluble in alcohol, very slightly soluble in ether and in methylene chloride.	Metoclopramide hydrochloride is a white or almost white, crystalline powder or crystals, very soluble in water, freely soluble in alcohol, sparingly soluble in methylene chloride, practically insoluble in ether.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

16/08/2005

10 DATE OF REVISION

17/11/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.4	Warning for high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis added.
4.5	Warning for concomitant use of paracetamol and flucloxacillin.
4.6	Remove pregnancy categorisation definition.
4.8	Inclusion of HAGMA as potential adverse effect related to paracetamol.

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