PP-METOCLOPRAMIDE TABLET

Composition: Each tablet contains Metoclopramide hydrochloride (anhydrous) 10 mg.

Description: A white to off-white round tablet with score on one side.

Action & Pharmacology:
Metoclopramide stimulates the motility of the upper gastrointestinal tract without affecting gastric, biliary or pancreatic secretion. It relaxes the pyrolic sphincter and the duodenal bulb, and increases peristalsis of the small intestines, resulting in accelerated gastric emptying and intestinal transit. However, it has little effect on the motility of the colon or gallbladder. It increases the resting tone of the lower oesophageal sphincter. Metoclopramide has antiemetic properties which appear to be due to antagonism of central and peripheral dopamine receptors in the medullary chemoreceptor trigger zone. Metoclopramide is rapidly and well-absorbed from the gastrointestinal tract but undergoes variable first-pass hepatic metabolism. Peak plasma concentrations occur at about 1-2 hours after an oral dose. Peak concentrations increase linearly with dose. Metoclopramide is excreted mainly in the urine as free and as conjugated metoclopramide and as metabolites. The elimination half-life is about 5-6 hours and may be prolonged in patients with renal failure or hepatic cirrhosis. Metoclopramide rapidly crosses the placenta and is readily excreted in breast milk.

Indications:
Metoclopramide is indicated in the treatment of the following conditions:
- Gastrointestinal disorders associated with delayed gastric emptying eg nausea, vomiting, dyspepsia, heart-burn, flatulence, reflux oesophagitis.
- Delayed chemotherapy induced nausea and vomiting (CINV) or radiotherapy induced nausea and vomiting (RINV), or that following surgery.
- Gastric stasis, nausea and vomiting associated with acute migraine

Contraindication:
- Hypersensitivity to metoclopramide or to any of the excipients listed.
- Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
- Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes.
- History of neuroleptic or metoclopramide –induced tardive dyskinesia.
- Epilepsy (increased crisis frequency and intensity)
- Parkinson's disease
- Combination with levodopa or dopaminergic agonists.
- Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency.
- Use in children less than 1 year of age.

Precautions/Warnings:
Children, young adults and the elderly are more susceptible to the adverse effects of metoclopramide and should be treated with care. Patients on prolonged therapy should be reviewed regularly. Metoclopramide may cause transient increase of aldosterone concentration and should be used with caution in patients who may be at risk of fluid retention and volume overload, such as those with liver cirrhosis or congestive heart failure.

Neuroligical disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/ or when high doses are used. These reactions generally occur at the beginning of treatment, and can occur after a single dose. If extrapyramidal symptoms occur, metoclopramide should be discontinued immediately. These effects are generally completely reversible after treatment discontinuation; however, symptomatic treatment may be required (benzodiazepines in children, and /or aticholinergic antiparkinsonian medicinal products in adults).

An interval of at least six hours should be respected between each dose even if vomiting or rejection of the dose occurs, in order to avoid overdose.

Patients with pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all since such patient may experience exacerbation of Parkinsonism symptoms when taking metoclopramide. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose, particularly in elderly subjects. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia occur. If vomiting persists the patient should be reassessed to exclude possibility of underlying disorder, e.g. cerebral irritation. Following operations such as pyloroplasty or gut anastomosis, metoclopramide should be withheld for 3 to 4 days as vigorous muscular contractions may not help healing.

Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics and with metoclopramide monotherapy. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

Particular caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs.

The absorption of any concurrently administered oral medication may be modified by the effect of metoclopramide on gastric motility.

Methemoglobinemia

Methemoglobinemia, which could be related to NADH-cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must be immediately and permanently discontinued, and appropriate measures initiated (such as treatment with methylene blue).

Cardiac disorders

Serious cardiovascular undesirable effects, including cases of severe bradycardia, circulatory collapse, and cardiac arrest and QT prolongation have been reported during administration of metoclopramide by injection, particularly via the intravenous route.

Particular caution should be exercised when administering metoclopramide, particularly via the intravenous route, in elderly subjects, patients with cardiac conduction disorders (including QT prolongation), patients with electrolyte imbalance, bradycardia and patients taking other drugs known to prolong QT interval.

The intravenous injection must be given as a slow bolus (of at least 3 minutes' duration) in order to reduce the risk of undesirable effects (e.g hypotension, akathisia)

Kidney or liver failure

In patients with kidney failure or severe liver failure, a dose reduction is recommended.

Use in elderly patients:
Elderly patients, especially elderly women, may be more likely to develop tardive dyskinesia due to metoclopramide.

Use in pregnancy and lactation:
Metoclopramide crosses the placenta and should be used during pregnancy only if clearly indicated.
It is excreted in breast milk. Caution should be exercised when metoclopramide is administered to nursing mothers.

Use in children:
Paediatric patients, especially neonates, are more susceptible to the adverse effects of metoclopramide.

Effect on ability to drive or operate machinery:
Metoclopramide may impair the mental and/or physical abilities required for driving or operating machinery. If affected, the patient should be cautioned to refrain from such activities.

Drug Interactions:
Concurrent administration of anticholinergic drugs and narcotic analgesics may antagonize the effects of metoclopramide on gastrointestinal tract motility. Metoclopramide may potentiate the sedative effects of alcohol, sedatives, hypnotics, narcotics or tranquillizers.
Concurrent administration of metoclopramide with phenothiazines may increase the frequency and severity of extrapyramidal reactions.
As metoclopramide may release catecholamines in patients with essential hypertension, it should be used with caution, if at all, in patients receiving MAO inhibitors.
The absorption of other drugs may be affected by metoclopramide; absorption of drugs from the stomach may be diminished (eg digoxin) while absorption of drugs from the small intestines may be increased (eg acetaminophen, tetracycline, cyclosporine).
Because metoclopramide may influence the delivery of food to the small intestines and its rate of absorption, insulin dosage and timing of dosage in diabetic patients may need to be adjusted.

Recommended dosage & administration:
The usual recommended dosage is:
Adults: 10mg three times daily
Young adults (15-20 years): 5-10mg three times daily, starting with the lower dose.
The maximum daily dose is 30mg or should not exceed 0.5mg/kg body weight.
The maximum recommended treatment duration is 5 days.

Prevention of delayed chemotherapy induced nausea and vomiting (CINV) (paediatric patients aged 1-18 years)
The recommended dose is 0.1 to 0.15mg/kg body weight, repeated up to three times daily by oral route. The maximum dose in 24 hours is 0.5mg/kg body weight.

Dosing table

Age	Body Weight	Dose	Frequency
9-18 years	30-60kg	5mg	Up to 3 times daily
15-18 years	Over 60kg	10mg	Up to 3 times daily

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

Tablets are not suitable for use in children weighing less than 30kg. Other pharmaceutical forms may be more appropriate for administration to this population.

Frequency of administration:
A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

Special population

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

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

In patients with moderate to severe renal impairment (creatinine clearance 15-60 ml/min) the dose should be reduced by 50%.

Hepatic impairment:
In patients with severe hepatic impairment, the dose should be reduced by 50%.

Route of Administration:
Oral administration

Side-effects:
Metoclopramide is a dopamine-antagonist and may cause extrapyramidal symptoms which usually occur as acute dystonic reactions especially in children and young female patients. Symptoms include oculogyric crises, involuntary movements of limbs, facial grimacing, torticollis, opisthotonus and rhythmic protrusion of tongue. The risk may be reduced by keeping the daily dose below 0.5mg/kg body weight. Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients. Other adverse effects include restlessness, drowsiness, fatigue, insomnia, headache and bowel upsets such as diarrhoea. Hypotension, hypertension and depression may occur, with isolated cases of blood disorders, hypersensitivity reactions, urinary incontinence, visual disturbances, and neuroleptic malignant syndrome. May induce an acute hypertensive response in patients with phaeochromocytoma. Metoclopramide stimulates prolactin release and may cause galactorrhoea, amenorrhoea, gynaecomastia, impotence and other related disorders. Fluid retention due to transient increase of plasma aldosterone concentrations has also been reported. When given at high doses in connection with cancer chemotherapy, the most common side effect is mild sedation.

Overdosage & treatment:
Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Symptoms usually disappear within 24 hours. Where necessary, anticholinergic or anti-parkinsonism drugs, or antihistamines with anticholinergic properties may be helpful. Haemodialysis or peritoneal dialysis is not effective for drug removal in overdose situation.
In children, overdose symptoms include seizures, extrapyrimidal reactions and lethargy, while methemoglobinemia may be observed in premature and full-term neonates. Methemoglobinemia may be reversed by the intravenous administration of methylene blue.

Storage conditions:
Store below 30 ^{o}C.
Protect from light.
Keep out of reach of children.

Pack Sizes:
10 tablets in a blister. 3, 6, 10, 50 or 100 blisters in a box.

Manufactured by:
NORIPHARMA SDN. BHD.
Lot 5030, Jalan Teratai,
5 1/2 Mile off Jalan Meru,
41050 Klang, Selangor, Malaysia.

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