PRAMIN PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Pramin Tablets

Pramin Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pramin Tablets: Each tablet contains: Metoclopramide hydrochloride 10 mg.
Pramin Injection: Each ampoule contains: Metcolopramide hydrochloride 10 mg/2 ml.

Pramin tablets contain about 75 mg lactose per tablet. Pramin Injection contains about 6 mg sodium per 2 ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pramin Tablets: Tablets for oral administration.

Pramin Injection: Solution for IV or IM injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoclopramide is an antiemetic and stimulates GI motility.

Adult population
Pramin is indicated in adults for:

- Prevention of postoperative nausea and vomiting (PONV)
- Prevention of delayed nausea and vomiting caused by chemotherapy (delayed CINV)
- Prevention of nausea and vomiting caused by radiation therapy
- Symptomatic treatment of nausea and vomiting, including nausea and vomiting caused by migraine attack. In migraine attacks, metoclopramide can be used concomitantly with oral analgesics to improve their absorption.
- Diabetic gastroparesis
- To faciliate diagnostic procedures (i.e., to faciliate small bowel intubation and as an aid in radiological examinations) (injection only)

Pediatric population
Pramin is indicated in children aged 1 to 18 years for:

- Second line-therapy: Treatment of established postoperative nausea and vomiting (PONV)

- Second-line therapy: Prevention of delayed nausea and vomiting caused by chemotherapy (delayed CINV)
- To facilitate diagnostic procedures (i.e., to faciliate small bowel intubation and as an aid in radiological examinations) (injection only)

4.2 Posology and method of administration

Posology

Adult patients

For all adult indications except diabetic gastroparesis and facilitation of diagnostic procedures (see below):

- The recommended dose is 10 mg, 1 to 3 times a day.
- The maximum recommended daily dose is 30 mg or 0.5 mg/kg bodyweight whichever is lower.
- The maximum recommended treatment period is usually 5 days.

Pediatric patients

For all pediatric indications except facilitation of diagnostic procedures (see below):

- The recommended dose is 0.1 mg to 0.15 mg/kg bodyweight, 1 to 3 times a day.

- The maximum recommended daily dose is 0.5 mg/kg bodyweight. The tablets are not suitable for use in children weighing less than 30 kg. Other pharmaceutical forms are more appropriate for use in this population group. (Note: The tablets may be cut in half using the scored line).
- The maximum recommended treatment period is usually 5 days.

Diabetic gastroparesis (adults): Use of Pramin for diabetic gastroparesis may involve a treatment duration longer than 5 days. Therefore, use in this clinical setting should be limited to those patients for whom the potential benefit outweighs the risk acording to the judgement of the treating physician. The recommended dose for diabetic gastroparesis is 10 mg half an hour before each meal (which is 10 mg X 3 daily) for 2-8 weeks, depending on the response and the likelihood of continued well-being on cessation of treatment. The initial route of administration depends on the severity of the observable symptoms. If only the earliest manifestations of gastric stasis are present, the oral route is indicated. However, if the symptoms are more severe, 10 mg i.v. therapy by slow injection should be instituted (for up to 10 days) until symptoms subside. After 10 days, oral administration should be used for maintenance. Since diabetic gastric stasis is frequently recurrent, Pramin therapy should be reinstituted at the earliest manifestation. In patients with diabetic gastroparesis, the maximum recommended treatment period is usually 3 months. Treatment for longer than 3 months should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia (see section 4.4).

Facilitation of diagnostic procedures (adults and pediatric patients)

a) To Facilitate Small Bowel Intubation: If the tube has not passed the pylorus with conventional maneuvers in 10 minutes, a single dose of Pramin Injection 10 mg may be administered slowly by the intravenous route over a 3-minute period, in adults. For single doses in pediatric patients, please refer to the pediatric dosage recmmendations above.
b) To Aid in Radiological Examinations: In patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, a single dose of Pramin Injection 10 mg may be administered slowly by the intravenous route over a 3-minute period, in adults. For single doses in pediatric patients, please refer to the pediatric dosage recommendations above.

Method of administration:

For all presentations, a minimum interval of 6 hours must be observed between 2 doses, even in case of vomiting or rejection of the dose (see section 4.4).

Pramin Injection can be administered intravenously or intramuscularly. The intravenous dose must be administered as a slow bolus (over a duration of at least 3 minutes) in order to reduce the risk of adverse effects (e.g., low blood pressure, akathisia). The duration of treatment by injection must be as short as possible and treatment must be continued orally as soon as possible.

Special populations

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 ≤ 15 ml/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% (see section 5.2).

Hepatic impairment

In patients with severe hepatic impairment, the dose should be reduced by 50% (see section 5.2).

Pediatric population

Metoclopramide is contraindicated in children aged less than 1 year (see section 4.3).

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 crises frequency and intensity).
- Parkinson's disease.
- Combination with levodopa or dopaminergic agonists (see section 4.5)
- Known history of methemoglobinemia with metoclopramide or of NADH cytochrome-b5 reductase deficiency.
- Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4).
- Metoclopramide should not be used during the first three to four days following operations such as pyloroplasty or gut anastomosis as vigorous muscular contractions may adversely affect healing.
- Breast-feeding (see Section 4.6).

4.4 Special warnings and precautions for use

If vomiting persists the patient should be reassessed 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).

The time interval of at least 6 hours specified in the section 4.2 should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.

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.

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.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see sections 4.3 and 4.5).

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methemoglobinemia

Methemoglobinemia 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 and abnormalities of cardiac conduction 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.

Special care should be taken when administering metoclopramide intravenously to patients with ‘sick sinus syndrome'.

Metoclopramide should be used with care with other drugs affecting cardiac conduction.

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.

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 impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).

Other precautions

Metoclopramide may cause elevation of serum prolactin levels.

Care should be exercised when using metoclopramide in patients with a history of atopy (including asthma) or porphyria.

Because metoclopramide can stimulate gastro-intestinal mobility, the drug theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure (see section 4.3)

Exipients with known effect:

Pramin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pramin tablets contain Ponceau 4R Lake which may cause allergic reactions.

Pramin Injection contains about 6 mg sodium per 2 ml.

4.5 Interactions with other medicinal products and other forms of interaction

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

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.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

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.

Ciclosporin

Metoclopramide increases ciclosporin bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of ciclosporin 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.

Central stimulants

The effects of certain other drugs with potential central stimulant effects, e.g. monoamine oxidase inhibitors and sympathomimetics, may be modified when prescribed with metoclopramide and their dosage may need to be adjusted accordingly.

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 may reduce plasma concentrations of atovaquone.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity nor foetotoxicity. Metoclopramide can be used during pregnancy if clinically needed. Due to pharmacological properties (as other neuroleptics), in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in the newborn cannot be excluded.

Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Lactation

Metoclopramide is excreted in breast milk at low level. Adverse reactions in the breast-fed baby cannot be excluded. Therefore, metoclopramide is not recommended during breastfeeding. Discontinuation of metoclopramide in breastfeeding women should be considered.

4.7 Effects on ability to drive and use machines

Metoclopramide has moderate influence on the ability to drive and use machines.

Metoclopramide may cause drowsiness, dizziness, dyskinesia and dystonias which could affect the vision and also interfere with the ability to drive and operate machinery.

4.8 Undesirable effects

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 , <1 /10); uncommon (≥1/1000 , <1/100); rare(≥ 1/10,000 , <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders		
	Not known	Methemoglobinemia, which could be related to NADH cytochrome-b5 reductase deficiency, particularly in neonates in whom the use is contraindicated (see section 4.4). Sulfhemoglobinemia, mainly with concomitant administration of high doses of sulfur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, particularly with the Injection
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.4); Atrioventricular block, Sinus arrest particularly with the Injection; Electrocardiogram QT prolonged; Torsade de pointes

Endocrine disorders*		
	Uncommon	Amenorrhea, Hyperprolactinemia
	Rare	Galactorrhea
	Not known	Gynecomastia
Gastrointestinal disorders		
	Common	Diarrhea
General disorders and administration site conditions		
	Common	Asthenia
	Not Known	Injection site inflammation and local phlebitis (injection only)
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock) particularly with the Injection.
Nervous system disorders		
	Very common	Somnolence
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug) (see section 4.4), Parkinsonism, Akathisia
	Uncommon	Dystonia (including visual disturbances and oculogyric crisis), Dyskinesia, Depressed level of consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4), Neuroleptic malignant syndrome (see section 4.4)
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
Vascular disorders		

	Common	Hypotension, particularly with the Injection
	Not known	Shock, syncope after injectable use. Acute hypertension in patients with pheochromocytoma (see section 4.3) Transient increase in blood pressure
Skin disorders		
	Not known	Skin reactions such as rash, pruritus, angioedema and urticaria

* Endocrine disorders during prolonged treatment in relation with hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).

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 the medicinal product, particularly in children and young adults (see section 4.4).
- Drowsiness, decreased level of consciousness, confusion, hallucinations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9. Overdose

Symptoms

Extrapyramidal disorders, drowsiness, decreased level of consciousness, confusion, hallucinations, and cardio-respiratory arrest may occur.

Management

In case of extrapyramidal symptoms related or not to overdose, the treatment is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian medicinal products in adults).

A symptomatic treatment and a continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents stimulating gastro-intestinal motility

ATC code: A03FA01 (Propulsives)

Mechanism of action

The action of metoclopramide is closely associated with parasympathetic nervous control of the upper gastro-intestinal tract, where it has the effect of encouraging normal peristaltic action. This provides for a fundamental approach to the control of those conditions where disturbed gastro-intestinal motility is a common underlying factor.

Metoclopramide stimulates activity of the upper gastro-intestinal tract and restores normal co-ordination and tone. Gastric emptying is accelerated and the resting tone of the gastrooesophageal sphincter is increased. Metoclopramide is a dopamine-receptor antagonist with a direct anti-emetic effect on the medullary chemoreceptor trigger zone.

5.2 Pharmacokinetic properties

Absorption

Metoclopramide is rapidly absorbed from the gastrointestinal tract and undergoes variable first-pass metabolism in the liver.

Biotransformation and Elimination

Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney. It crosses the placenta and is excreted in breast milk. The elimination half-life is about 6 hours.

Renal impairment

The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination half- life is increased (approximately 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for a creatinine clearance <10 mL/minute).

Hepatic impairment

In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: Lactose (about 75 mg), microcrystalline cellulose, corn starch, Ponceau 4R Lake, colloidal silicone dioxide, magnesium stearate.

Injection: Sodium chloride, hydrochloric acid (to adjust PH), water for injection.

6.2 Incompatibilities

Injection: Compatability studies with Pramin Injection have not been performed. According to the literature, metoclopramide injection is compatible for dilution with 5% Dextrose, normal saline, Ringer's injection, and Lactated Ringer's injection.

Tablets: Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The ampoule is for single use.

6.4 Special precautions for storage

Tablets: Store below 25^{o}C.

Injection: Store below 25^{o}C, protect from light.

6.5 Nature and contents of outer packaging

Tablets: Boxes of 30 tablets in blisters.

Injection: Boxes of 5, 25, 50, 100 of 2 ml ampoules.

Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

No specific requirements.

7. MARKETING AUTHORIZATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301

8. MARKETING AUTHORIZATION NUMBER(S)

Pramin Tablets: 051 49 24302

Pramin Injection: 051 52 24303

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