## Summary of Product Characteristics

### 1. NAME OF THE MEDICINAL PRODUCT
METOCLOPRAMIDE S.A.L.F 10mg/2ml

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1ml solution contains:
Metoclopramide hydrochloride monohydrate 5.25 mg (equivalent to 5 mg of Metoclopramide hydrochloride anhydrous).
Each ampoule of 2ml contains:
Metoclopramide hydrochloride monohydrate 10.5 mg (equivalent to 10 mg of Metoclopramide hydrochloride anhydrous).

Excipients with known effect:
Each ampoule of 2ml contains 2.96 mg of sodium metabisulphite.
Each ampoule of 2ml contains 1.29 mg of sodium.
For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM
Solution for I.V or I.M injection.
Clear colorless solution.

### 4. CLINICAL PARTICULARS
#### 4.1. Therapeutic indications
Metoclopramide is an antiemetic and stimulates GI motility.

**Adult population**
METOCLOPRAMIDE S.A.L.F 10mg/2ml 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 facilitate diagnostic procedures (i.e., to facilitate small bowel intubation and as an aid in radiological examinations).

**Pediatric population**
METOCLOPRAMIDE S.A.L.F 10mg/2ml 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 facilitate small bowel intubation and as an aid in radiological examinations).

#### 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 maximum recommended treatment period is usually 5 days.

**Diabetic gastroparesis (adults)**
Use of METOCLOPRAMIDE S.A.L.F 10mg/2ml 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 according 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, METOCLOPRAMIDE S.A.L.F 10mg/2ml 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 METOCLOPRAMIDE S.A.L.F 10mg/2ml 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.
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 METOCLOPRAMIDE S.A.L.F 10mg/2ml 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**
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).
METOCLOPRAMIDE S.A.L.F 10mg/2ml 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 hemorrhage, 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 S.A.L.F 10mg/2ml 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.

• Metoclopramide should not be used during 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 usually occur 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 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 (e.g., class IA and III antiarrhythmic drugs, tricyclic antidepressants, macrolides, antipsychotics (see section 4.8)).

Special care should be taken when administering metoclopramide S.A.L.F 10mg/2ml intravenously to patients with ‘sick sinus syndrome' or other cardiac conduction disturbances.

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 S.A.L.F 10mg/2ml 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)

Important information about some of the ingredients:
Metoclopramide S.A.L.F. 10 mg/2 ml contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.
Each ampoule of Metoclopramide S.A.L.F. 10 mg/2 ml contains less than 1 mmol (23mg) sodium per dose, i.e., essentially 'sodium-free'.

**4.5. Interaction 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.

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

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.

Rifampicin
In a published study conducted in 12 healthy volunteers, the administration of 600 mg of rifampicin for 6 days led to reduced plasma metoclopramide exposure (AUC area under the curve) and maximum concentration (Cmax) by 68% and 35%, respectively. Although the clinical significance is uncertain when metoclopramide is combined with rifampicin, or with other strong inducers (e.g. carbamazepine, phenobarbital, phenytoin), patients should be monitored for a possible lack of anti-emetic activity.

**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 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.

Fertility
No data available.

**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 dystonia 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 intravenous formulation. |
| | 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 intravenous formulation; 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 |
| **Immune system disorders** | Uncommon | Hypersensitivity |
| | Not known | Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation. |
| **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 intravenous formulation |
| | 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 authorization 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.
After intramuscular administration, the relative bioavailability compared to intravenous application is 60 to 100%.
Peak plasma levels are reached within 0.5 to 2 hours.

Distribution:
The distribution volume is 2-3 l/kg; 13-22% is bound to plasma proteins.

Biotransformation:
Metoclopramide is metabolised in the liver.

Elimination
The predominant route of elimination of metoclopramide and its metabolites is via the kidney, both in unchanged form and in sulfate or glucuronide conjugate form. The main metabolite is N-4 sulfur conjugate. It crosses the placenta and is excreted in breast milk. The elimination half-life is about 5 to 6 hours, regardless of the route of administration.

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**
Sodium chloride, Sodium metabisulphite, Water for injections.

**6.2. Incompatibilities**
Compatibility studies with METOCLOPRAMIDE S.A.L.F 10mg/2ml 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.

**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**
Store below 25°C in the original package to protect from light.

**6.5. Nature and contents of container**
Yellow type I glass ampoules.
Each pack contains 5 ampoules of 2 ml.

**6.6. Special precautions for disposal and other handling**
No specific requirements.

**7. MARKETING AUTHORIZATION HOLDER AND IMPORTER**
RAZ PHARMACEUTICS LTD.,
31 Gesher Haetz, Industrial Park Emek Hefer, Israel

**8. MARKETING AUTHORIZATION NUMBER**
158-39-34558-00

Revised in August 2024

RAZS3100-03

JFIMETORAZ NO-6828A3 r3 Piz