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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
METOCLOPRAMIDE S.A.L.F 10mg/2ml:
Each ampoule contains:
Metoclopramide hydrochloride monohydrate 10.5 mg (equivalent to 10 mg of anhydrous substance).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for I.V. or I.M. injection.

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, facilitation of diagnostic procedures and prevention of PONV (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.

For prevention of PONV a single dose of 10 mg is recommended.

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 for prevention of delayed CINV and 48 hours for treatment of established PONV.

Diabetic gastroparesis (adults)
The 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 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.
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 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:
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 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 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 ≤ 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 frequency and intensity of seizures).
- 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).

4.4 Special warnings and precautions for use
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. When metoclopramide is given intravenously, extrapyramidal disorders are less likely at slower infusion rates. 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 section 4.3).
Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.
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.
Because metoclopramide can stimulate gastro-intestinal mobility, the drug theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure.

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 medicines known to prolong QT interval.
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).

Important information about the ingredients of Metoclopramide S.A.L.F:
The drug product contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.
1 ampoule of Metoclopramide S.A.L.F 10 mg/2 ml contains sodium chloride as isotonicizing agent; the total quantity of sodium is less than 1 mmol (23 mg), i.e. it is 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 medicines may be modified.

Anticholinergics and morphine derivatives
Anticholinergics and morphine derivatives may have both a mutual antagonism with metoclopramide on the digestive tract motility.

CNS 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 medicines
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.

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 its plasma concentrations.

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.

4.7 Effects on 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 route
	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 route; Electrocardiogram QT prolonged; Torsades de Pointes
Endocrine disorders*		
	Uncommon	Amenorrhea, Hyperprolactinemia
	Rare	Galactorrhea
	Not known	Gynecomastia
Gastrointestinal disorders		
	Common	Diarrhea
General disorders and administration site conditions		
	Common	Asthenia
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock) particularly with intravenous route
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 medicine) (see section 4.4), Parkinsonism, Akathisia
	Uncommon	Dystonia, 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 route
	Not known	Shock, syncope after injectable use. Acute hypertension in patients with pheochromocytoma (see section 4.3) Transient increase in blood pressure

* 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:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.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: Intestinal motility stimulant.
ATC code: A03FA01 (A: digestive tracts and metabolism).
Metoclopramide is a neuroleptic dopamine antagonist. It prevents vomiting by blocking dopaminergic sites.

5.2 Pharmacokinetic properties

Absorption
Metoclopramide is rapidly absorbed in the digestive tract. Bioavailability is generally 80%, however it varies between individuals as a result of the liver first pass metabolism effect.

Distribution
Metoclopramide is widely distributed in the tissues. The distribution volume is 2.2 to 3.4 L/kg. It does not bind extensively to plasma proteins. It passes through the placenta and into the milk.

Biotransformation
Metoclopramide is not extensively metabolized.

Elimination
Metoclopramide is principally eliminated in the urine in free or sulfate conjugated form.
The elimination half-life is from 5 to 6 hours. It increases in cases of renal or hepatic impairment.

Renal impairment
Metoclopramide clearance is reduced by up to 70% in patients suffering from severe renal impairment, while the plasma elimination half-life is increased (about 10 hours for creatinine clearance of 10-50 mL/minute and 15 hours for creatinine clearance <10 mL/minute).

Hepatic impairment
Accumulation of metoclopramide was observed in patients suffering from cirrhosis of the liver, accompanied by a 50% decrease in plasma clearance.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Injection: Sodium chloride, sodium metabisulphite, water for injection.

6.2 Incompatibilities

Injection: Compatibility studies with METOCLOPRAMIDE S.A.L.F 10 mg/2 ml Injection have not been performed.

6.3 Special precautions for storage

Injection: Store below 25ºC in the original package to protect from light.

6.4 Nature and contents of outer packaging

Injection: Boxes of 5 ampoules, 10 mg/2 ml.

6.5 Special precautions for disposal and other handling

No specific requirements.

6.6 Shelf life

2 years.

7. MANUFACTURER:

S.A.L.F SpA Laboratorio Farmacologico – Via G. Mazzini 9 , 24069 Cenate Sotto (BG) – Italy

8. MARKETING AUTHORIZATION HOLDER

RAZ PHARMACEUTICS LTD., 6 Hamatechet St., Kadima

9. MARKETING AUTHORIZATION NUMBER(S)

158-39-34558-00

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on May 2017.

RAZR07