1. Name of the Medicinal Product:

a) Name of the Product : METOMIDE (Metoclopramide Injection USP 10mg/2mL)

b) Strength : 10 mg/2 mL

c) Pharmaceutical Dosage Form : Solution for Injection

2. Quantitative and Qualitative Composition:

Composition:

Each 2mL ampoule contains

Metoclopramide Hydrochloride	USP	
Equivalent to Metoclopramide		10 mg
Water for Injection	BP	q.s.

S.No	Ingredients	Specification[1]	Label Claim (mg/ml)	Qty/ 2mL (mg)	Function of the Ingredients
	Active				
1.	Metoclopramide Hydrochloride*#	USP	10mg / 2mL	11.4403	Active
	Excipients				
2.	Sodium Chloride	BP	----	17.0000	Istonic agent
3.	Hydrochloric acid	BP	----	q.s.	pH adjuster
4.	Sodium hydroxide	BP	----	q.s.	pH adjuster
5.	Water for Injection	BP	----	q.s. to 2.0 mL	Vehicle

11.216 mg of Metoclopramide hydrochloride USP equivalent to Metoclopramide 10mg

*Denotes that the Metoclopramide Hydrochloride has been taken as 100% assay and 0% LOD. The quantity of Metoclopramide Hydrochloride shall vary based on the assay, water content and Correction factor.

Container Closure System: (10 x 2ml ampoules)

Metoclopramide Injection USP 10mg/2ml is packed in 2ml Amber coloured USP Type I glass ampoule. 10 such ampoules are packed in a plastic ampoule tray, pre – folded literature will be placed in plastic ampoule tray and one ampoule tray in one printed carton.

3. Pharmaceutical Forms:

Solution for Injection.

A clear and colourless solution free from visible particulate filled in 2mL amber coloured ampoule.

4. Clinical Particulars:

1. Therapeutic Indications

Adult population:

Metoclopramide is indicated in adults for:

- Prevention of post operative nausea and vomiting (PONV)
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting
- Prevention or treatment of nausea and vomiting (feeling or being sick), including nausea and vomiting that may result from anticancer medicines (CINV) or radiation treatment (RINV)

Paediatric population

Metoclopramide is indicated in children (aged 1-18 years) for:

- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option
- Treatment of post operative nausea and vomiting (PONV) as a second line option.

This medication should not be used in children under 1 year old. For other indications, the use in the paediatric population is not recommended.

2. Posology and Method of Administration

The solution can be administered intravenously or intramuscularly.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes).

For both adults and children, metoclopramide should only be used for a maximum of 5 days.

All indications (adult patients)

For prevention of post operative nausea and vomiting PONV a single dose of 10 mg is recommended.

For the symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting and for the prevention of radiotherapy induced nausea and vomiting (RINV): the recommended single dose is 10 mg, repeated up to three times daily

The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.

The injectable treatment duration should be as short as possible and transfer to oral or rectal treatment should be made as soon as possible.

All indications (paediatric patients aged 1-18 years)

The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by intravenous route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

Age	Body Weight	Dose	Frequency
1-3 years	10-14 kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60kg	10 mg	Up to 3 times daily

For the prevention of delayed nausea and vomiting, the maximum treatment duration is 5 days.
For the treatment of nausea and postoperative vomiting (PONV) proven, the maximum treatment duration is 48 hours.

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%.

Hepatic impairment:

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

Paediatric population

Metoclopramide is contraindicated in children aged less than 1 year.

A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose.

Method of administration: For I.M./I.V. use

3. Contraindications

Hypersensitivity to the active substance or to any of the excipients. When the stimulation of gastrointestinal motility constitutes a danger: gastrointestinal bleeding, mechanical obstruction or perforation.

Among carriers, known or suspected pheochromocytoma because of the risk of episodes of severe hypertension.

Antecedent known of tardive dyskinesia with neuroleptics or metoclopramide.

Epilepsy (increased crises frequency and intensity)

Parkinson's disease

Combination with levodopa or dopaminergic agonists.

Known history of methaemoglobinaemia with metoclopramide or NADH cytochrome-b5 Reductase deficiency .

Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders

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 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 (at least 6 hours) specified for children in the dosage section 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. Treatment must be discontinued if clinical signs of tardive dyskinesia appear.

The neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy. 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.

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

Methaemoglobinemia

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.

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.

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.

Metoclopramide may cause elevation of serum prolactin levels. Care should be exercised when using Maxolon in patients with a history of atopy (including asthma) or porphyria.

Special care should be taken when administering Maxolon intravenously to patients with “sick sinus syndrome” or other cardiac conduction disturbances.

5. Interaction with other medicinal products and other forms of interaction

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism. 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 have both 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 may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

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

6. Fertility, Pregnancy and Lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity nor fetotoxicity. 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.

Breastfeeding

Metoclopramide is excreted in breast milk at a 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 human data on the effect of Metoclopramide on fertility are available.

7. Effects on Ability to drive and use machines

Metoclopramide may cause side effects including drowsiness, dyskinesia, dystonias and visual disturbances which could interfere with the ability to drive or operate machinery.

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 (≥1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders		
	Not known	Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates (see section 4.4) Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, especially with intravenous preparations
	Not Known	Cardiac arrest, occurring shortly after injectable use, and that may follow bradycardia (see Section 4.4); atrioventricular block, sinus pause especially in intravenous preparations; extended Electrocardiogram QT; 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

	Not Known	Injection site inflammation and local phlebitis
Immune system disorders		
	Uncommon	hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock, especially in intravenous preparations)
Nervous system disorders		
	Very common	Drowsiness
	Common	Extrapyramidal disorder (especially in children and young adults and / or when the recommended dose is exceeded, even after administration of a single dose of drug) (see section 4.4) Parkinson-like symptoms, akathisia
	Uncommon	Dystonia (including visual disturbances and oculogyric crisis), dyskinesia, decreased consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after long- term treatment, especially in elderly patients (see section 4.4), malignant neuroleptic syndrome (see section 4.4)
Mental disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confused state
	Not known	Suicidal ideation
Vascular disorders		
	Common	Hypotension, especially in intravenous preparations
	Not known	Shock, syncope (fainting) following injectable use. Acute hypertension in patients with pheochromocytoma (see section

		4.3) Transient increase in blood pressure
Skin disorder		
	Not known	Skin reactions such as rash, pruritus, angioedema and urticaria

* Endocrine disorders during long-term treatment with regard to hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).

The following reactions, sometimes associated, occur more frequently when high doses areused:

-Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even after administration of a single dose of the drug, especially in children andyoung adults.

- Sleepiness, reduced consciousness, confusion, and hallucination.

9. Overdose

Symptoms

Extrapyramidal disorder, somnolence, decreased consciousness, confusion, hallucination, and cardio-respiratory arrest may occur.

Therapy

In the case of extrapyramidal symptoms, whether or not related to overdosing, it is the only symptomatic treatment (benzodiazepines in children and / or anticholinergic drugs against the Parkinson's disease in adults).

Symptomatic treatment and continuous monitoring of cardiovascular and respiratory functions should be guided by the clinical condition.

5. Pharmacological Properties:

1. Pharmacodynamic properties:

Pharmacotherapeutic group: Preparations for nausea / vomiting.

ATC code: A03F A01

Metoclopramide is a substituted benzamide. It is used, among other things because of the anti-emetic properties. The anti-emetic effect is the result of two mechanisms acting on the central level:

- antagonism of the dopamine D2 receptors in the chemoceptor trigger zone and in the vomiting center in the medulla involved in vomiting induced by apomorphine;

- antagonism of the serotonergic 5HT3 receptors and agonism of the 5HT4 receptors involved in vomiting induced by chemotherapy.

In addition to the central working, has metoclopramide through a peripheral mechanism of action a stimulating effect on the digestive motility. There is an anti-dopaminergic effect and a reinforcement of the action of acetylcholine. As a result, an accelerated gastric emptying takes place and there is a increasing the pressure of the lower esophageal sphincter. Metoclopramide has no influence on the gastric secretion.

2. Pharmacokinetic properties:

After intramuscular administration, the relative bioavailability as compared to the intravenous application of 60 to 100%. Peak plasma levels are reached within 0.5 to 2 hours.

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

Metoclopramide is excreted primarily in the urine, both in the natural form as in sulphate or glucuronide form. The main metabolite is N-4 Sulphur conjugate.

The plasma elimination half-life is 5 to 6 hours, regardless of route of administration.

Renal impairment

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

Hepatic impairment

In patients with cirrhosis of the liver accumulation of metoclopramide was observed, accompanied with a 50% reduction in plasma.

3. Preclinical Safety Data

“There are no non-clinical findings of relevance for the prescriber no already described in other relevant sections of the SmPC.”

6. Pharmaceutical Particulars:

1. List of Excipients

Sodium Chloride, Hydrochloric acid, Sodium Hydroxide and Water for Injection.

2. **Incompatibilities:**

Not applicable

3. **Shelf Life:**

36 months.

From a microbiology point of view, the product should be used immediately.

4. **Special Precaution for Storage:**

Do not store above 30°C. Protect from light. Keep out of reach of children.

5. **Nature and composition of container:**

Metoclopramide Injection USP 10mg/2ml is available in 2ml amber glass ampoule USP Type I..

6. **Instructions for use/handling**

No special requirements

7. **Special precautions for disposal and other handling**

Not applicable

8. **Restriction on sale/distribution**

Nil

7. **Marketing Authorization Holder/Manufacturer**

Steril-Gene Life Sciences (P) Ltd No.45,
Mangalam Main Road, Mangalam Village,
Villianur Comuune, Puducherry-605110.

8. **Marketing Authorization Number:**

TAN 22 HM 0251

9. **Date of first Registration/Renewal of Registration:**

19th July, 2022

10. Date of last Revision Text

11. Legal Category

POM