S7

Primperan® 10 mg / 2 ml Solution for injection in ampoules

Metoclopramide hydrochloride anhydrous

SANOFI

1. NAME OF THE MEDICINAL PRODUCT

Primperan 10 mg/2 ml solution for injection in ampoules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metoclopramide hydrochloride.....10.50 mg
(Equivalent to anhydrous metoclopramide hydrochloride.....10.00 mg)
for one 2 ml ampoule.

Excipients: sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection I.M./ I.V.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

Primperan 10 mg/2 ml solution for injection in ampoules is indicated for use in adults for:
– prevention of post-operative nausea and vomiting,
– symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks,
– prevention of radiotherapy-induced nausea and vomiting.

Pediatric population

Primperan 10 mg/2 ml solution for injection in ampoules is indicated in children aged 1 to 18 years for:
– prevention of delayed chemotherapy-induced nausea and vomiting as a second-line option,
– prevention of post-operative nausea and vomiting as a second-line option.

4.2. Posology and method of administration

The solution can be administered by the intravenous or intramuscular route.
The intravenous doses must be administered as a slow bolus (for at least 3 minutes).

All indications (adults)

A single 10 mg dose is recommended for the prevention of post-operative nausea and vomiting.
The recommended dose for the symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks and for the prevention of radiotherapy-induced nausea and vomiting is 10 mg, 1 to 3 times daily. The maximum recommended daily dose is 30 mg or 0.5 mg/kg.
Treatment duration when administering by injection should be as short as possible and a switch to administration via oral or rectal route should be instituted as quickly as possible.

All indications (children from 1 to 18 years of age)

The recommended dose is 0.1 to 0.15 mg/kg, 1 to 3 times daily, by intravenous route. The maximum daily dose is 0.5 mg/kg

Dosing table

Age	Bodyweight	Dose	Frequency
1-3 years	10-14 kg	1 mg	up to 3 times a day
3-5 years	15-19 kg	2 mg	up to 3 times a day
5-9 years	20-29 kg	2.5 mg	up to 3 times a day
9-18 years	30-60 kg	5 mg	up to 3 times a day
15-18 years	over 60 kg	10 mg	up to 3 times a day

For the prevention of delayed chemotherapy-induced nausea and vomiting, the maximum treatment duration is 5 days.
For the prevention of post-operative nausea and vomiting, the maximum treatment duration is 48 hours.

Frequency of administration

An interval of at least 6 hours should be left between two doses, even if vomiting or rejection of the dose occurs (see section 4.4).

Special populations

Elderly subjects

In elderly subjects, a dose reduction should be considered, taking into account kidney and liver function and overall frailty.

Kidney failure

In patients with end-stage kidney failure (creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%.
In patients with moderate to severe kidney failure (creatinine clearance between 15 and 60 ml/min), the dose should be reduced by 50% (see section 5.2).

Liver failure

In patients with severe liver failure, the dose should be reduced by 50% (see section 5.2).
Other pharmaceutical forms may be more suitable for use in this patient population.

Pediatric population

Metoclopramide is contraindicated in children aged less than one 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 gastrointestinal perforation, in which the stimulation of gastrointestinal motility is a risk.
-Known history of neuroleptic- or metoclopramide-induced tardive dyskinesia.
-Epilepsy (increase in the frequency and intensity of seizures).
-Parkinson's disease.
-Confirmed or suspected pheochromocytoma, due to the risk of episodes of severe hypertension
-In combination with levodopa or dopamine agonists (see section4.5).
-Known history of methemoglobinemia with metoclopramide or NADH-cytochrome b5 reductase deficiency.
-In children under one year of age due to the 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 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 anticholinergic antiparkinsonian medicinal products in adults).
An interval of at least six hours should be left between each dose (see section 4.2), even if vomiting or rejection of the dose occurs, in order to avoid overdose.
Long-term treatment with metoclopramide may cause potentially irreversible tardive dyskinesia, particularly in elderly subjects. 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 occur.
Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics and with metoclopramide monotherapy (see section 4.8). 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 (see section 4.3).
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. 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, cardiac arrest and QT prolongation have been reported during administration of metoclopramide by injection, particularly via the intravenous route (see section 4.8).
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 (see section 4.2).
This medicine contains sodium. The sodium content is less than 1 mmol per dose, i.e. it is "sodium-free".

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

Contraindicated combinations

Dopaminergic agonists or levodopa and metoclopramide have a mutual antagonism (see section 4.3).

Inadvisable combinations

Alcohol potentiates the sedative effects of metoclopramide.

Combinations to be taken into account

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

Anticholinergic agents and morphine derivatives

Anticholinergic agents or morphine derivatives and metoclopramide have a mutual antagonism on gastrointestinal motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related products)

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 agents

The use of metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Close monitoring of plasma digoxin concentrations is required.

Cyclosporin

Metoclopramide increases cyclosporin bioavailability (Cmax by 46%, and systemic exposure by 22%). Careful monitoring of plasma cyclosporin concentrations is necessary. The clinical consequences are uncertain.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block by inhibiting plasma cholinesterase.

Potent CYP2D6 inhibitors

Increase in the parameters for exposure to metoclopramide when combined with potent CYP2D6 inhibitors, such as fluoxetine and paroxetine. Despite the unknown clinical relevance, adverse effects must be monitored.

4.6. Pregnancy and lactation

Pregnancy

The extensive data on pregnant women (more than 1000 pregnancies) have not indicated any teratogenic or fetotoxic effects. Metoclopramide can be used during pregnancy if necessary. For pharmacological reasons (by analogy with other neuroleptic agents), if metoclopramide is administered at the end of pregnancy, extrapyramidal syndrome in the newborn cannot be ruled out. Metoclopramide must be avoided at the end of pregnancy. If it is used, the neonate must be monitored.

Lactation

Metoclopramide is excreted in breast milk at low levels. Undesirable effects in the breast-fed baby cannot be ruled out. Metoclopramide is not therefore recommended during breast-feeding. Discontinuation of metoclopramide must be considered in breast-feeding women.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

The undesirable effects are listed by System-Organ Class. Undesirable effects have been ranked by frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), frequency not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effect
Blood and lymphatic system disorders		
	Frequency not known	Methemoglobinemia, possibly due to NADH cytochrome b5reductase deficiency,particularly in neonates(see section4.4) Sulfhemoglobinemia mainly with concomitant administration of high doses of sulfate-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, particularly with the intravenous forms
	Frequency not known	Cardiac arrest, occurring shortly after administration by injection, and possibly following on from bradycardia (see section 4.4 atrioventricular block, sinus arrest particularly with the intravenous route; QT interval prolongation on ECG; torsades de pointes
Endocrine disorders*		
	Uncommon	Amenorrhea, hyperprolactinemia
	Rare	Galactorrhea
	Frequency not known	Gynecomastia
Gastrointestinal disorders		
	Common	Diarrhea
General disorders and administration site conditions		
	Common	Asthenia
Immune system disorders		
	Uncommon	Hypersensitivity
	Frequency not known	Anaphylactic reaction (including anaphylactic shock)particularly with the intravenous route
Nervous system disorders		
	Very common	Drowsiness
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose) (see section 4.4), parkinsonism, akathisia
	Uncommon	Dystonia, dyskinesia, consciousness disorders
	Rare	Seizures, especially in epileptic patients
	Frequency not known	Tardive dyskinesia which may be persistent, during or after long-term treatment, particularly in elderly patients (see section 4.4), neuroleptic malignant syndrome (see section 4.4)
Psychiatric disorders		
	Common	Depression with mild to severe symptoms including suicidal ideation
	Uncommon	Hallucination
	Rare	Confusional state
Vascular disorders		
	Common	Hypotension, particularly with the intravenous forms.
	Frequency not known	Transient increase in blood pressure, shock, syncope after use of the injection form. Hypertensive crisis in patients with pheochromocytoma (see section 4.3)

* Endocrine disorders during long-term treatment in relation to hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).
The following effects, sometimes in combination, usually occur when high doses are used:
– Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonism, akathisia, including after administration of a single dose of the medicinal product, particularly in children and young adults (see section 4.4).
– Drowsiness, consciousness disorders, 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. Healthcare professionals are asked to report any suspected adverse reactions .

4.9. Overdose

Symptoms

Extrapyramidal symptoms, drowsiness, consciousness disorders, confusion, hallucinations, hypertensive crisis and even cardiorespiratory arrest may occur.

Management of overdose:

Treatment of extrapyramidal symptoms, whether or not related to overdose, is only symptomatic (benzodiazepines in children, and/or anticholinergic antiparkinsonian medicinal products in adults).
Symptomatic treatment and continuous monitoring of cardiovascular and respiratory function should be implemented, depending on clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: **PROPULSIVES**
ATC Code: A03FA01
(A: Alimentary tract and metabolism)
Metoclopramide is a dopaminergic antagonist neuroleptic. It prevents vomiting by blocking dopamine sites.

5.2. Pharmacokinetic properties

Distribution

Metoclopramide is extensively distributed in tissue. The volume of distribution is 2.2 to 3.4 l/kg. Plasma protein binding is low. The drug crosses the placental barrier and is excreted in breast-milk.

Metabolism

Metoclopramide undergoes slight metabolism.

Excretion

Metoclopramide is mainly excreted in the urine in the unbound or sulfoconjugated form
The elimination half–life is 5 to 6 hours. The half-life increases in patients with kidney or liver failure.

Kidney failure

Metoclopramide clearance is reduced by up to 70% in patients with severe kidney failure, whereas 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 of <10 ml/minute).
Liver failure
Accumulation of metoclopramide has been observed in patients with cirrhosis of the liver, 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, water for injection.

6.2 Incompatibilities

Because of the lack of compatibility studies, this medicinal product must not be mixed with other medicines.

6.3 Shelf life

3 years.
After opening: the product must be used immediately.

6.4. Special precautions for storage

Refere to the outer pack

6.5 Nature and contents of container

Type I colorless glass ampoule containing 2ml. Box of 3,6,12 or 60

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORIZATION HOLDER

SANOFI-AVENTIS FRANCE
82, avenue Raspail
94250 Gentilly
France

8 . MARKETING AUTHORIZATION NUMBER(S)

318257-9: 2 ml in (colorless glass) ampoule, box of 3 (not marketed)
322026-8 : 2 ml in (colorless glass) ampoule, box of 6 (not marketed)
308616-6:2 ml in (colorless glass) ampoule, box of 12
551753-5:2 ml in (colorless glass) ampoule, box of 60 (not marketed)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

April9, 1974

10 . DATE OF REVISION OF THE TEXT

September 2016/V1

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable .

GENERAL CLASSIFICATION FOR PRESCRIPTION AND SUPPLY

List I.

Manufactured by Sanofi Egypt S.A.E under license from Sanofi-Aventis .France

This insert was last approved on February 2018