SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRİMSEL 10 mg/2 mL I.M./I.V. Ampoule Containing Solution for Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each ampoule (2 mL) contains 10 mg of metoclopramide hydrochloride.

Excipients:

Sodium chloride……14 mg

Sodium metabisulfite ……3 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colorless, odorless, sterile solution in an amber glass ampoule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In Adult population:

PRİMSEL is indicated in adults for:

- Prevention of post-operative nausea and vomiting
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting
- Prevention of radiotherapy induced nausea and vomiting

In Paediatric population:

PRİMSEL is indicated in children (1 – 18 years) for:

- Prevention of delayed chemotherapy induced nausea and vomiting as a second line option
- Treatment of established post-operative nausea and vomiting as a second line option

4.2. Posology and method of administration

Posology / frequency and duration of administration:

The solution can be administered intravenously or intramuscularly.

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

Adult patients:

For prevention of post-operative nausea and vomiting 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 andvomiting (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 treatment should be made as soon as possible.

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 in all indications.

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 60 kg	10 mg	Up to 3 times daily

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting as second line option.

The maximum treatment duration is 48 hours for treatment of established post-operative nausea and vomiting as second line option.

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

The maximum recommended treatment duration is 5 days.

Prevention of chemotherapy-induced nausea and vomiting (pediatric patients aged 1-18 years)

It should be used under the age of 18 after careful consideration of the benefit/risk balance.

Method of administration:

PRİMSEL can be administered intravenously or intramuscularly.

Intravenous doses should be administered by slow injection (for at least 3 minutes).

There should be least 6 hours intervals between two administration doses, including vomiting and when the dose is withdrawn.

Additional information on special populations:

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%

No dose adjustment is required in mild renal impairment. (see section 5.2).

Hepatic impairment:

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

Paediatric population:

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

Geriatric population:

In elderly patients a dose reduction should be considered, based on renal and hepatic function and general situation.

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 ofgastrointestinal motility constitutes a risk,
- Confirmed or suspected phaeochromocytoma, 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 methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency,
- Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4),

- Should not be used during the first three to four days following operations such gastrointestinal system.

4.4. Special warnings and special precautions for use

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

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, when 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 section 4.3).

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.

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

Because metoclopramide can stimulate gastro-intestinal mobility, the drug theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure.

Methaemoglobinaemia

Methaemoglobinaemia 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.

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).

It should not be used with alcohol.

Metoclopramide may cause elevation of serum prolactin levels.

Additional information about the excipients it contains

PRİMSEL contains less than 1 mmol (23 mg) sodium per 2 mL dose; in other words, it can be considered as “sodium-free”.

Since PRİMSEL contains sodium metabisulfite as an excipient, it may rarely cause severe hypersensitivity reactions and bronchospasm.

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 drugs)

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.

Cyclosporine:

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

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 injection may reduce plasma concentrations of atovaquone.

Apomorphine:

Administration of metoclopramide prior to apomorphine may reduce the emetic response to apomorphine; also, concomitant use may potentiate the CNS depressant effects of apomorphine or metoclopramide.

Bromocriptine:

Metoclopramide may increase serum prolactin concentrations and interfere with the effects of bromocriptine, necessitating dosage adjustment for bromocriptine.

Mexiletine:

Concomitant use with metoclopramide may accelerate the absorption of mexiletine.

Diagnostic methods:

Concomitant use of metoclopramide in the gonadorelin test may blunt the gonadoreline response by increasing serum prolactin levels.

Concomitant use of metoclopramide may result in elevated aldosterone and serum prolactin levels.

4.6. Pregnancy and lactation

General advice

Pregnancy category: B

Women with child-bearing potential / Contraception

There are no data on the use of metoclopramide in women of childbearing potential using contraceptives.

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity or 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 a low level. Adverse reactions in the breast-fed baby cannot be excluded. Therefore, metoclopramide is not recommended during breastfeeding. Discontinuation of metoclopramide inbreastfeeding women should be considered.

Fertility

No effect on fertility has been reported.

4.7. Effects on 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 to <1/10); uncommon (>1/1000 to <1/100); rare

(>1/10,000 to <1/1000); very rare (<1/10,000), unknown (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 inneonates (see section 4.4) Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicinal products
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock, especially with I.V. formulations)
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
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, Dyskinesia, 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)
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
Vascular disorder		
	Common	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use. Acute hypertension inpatients with phaeochromocytoma (see section 4.3).
Gastrointestinal disorders		
	Common	Diarrhoea
General disorders and administration site conditions		

	Common	Asthenia

*Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

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, hallucination.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Symptoms

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

Treatment

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 : Drugs used in functional gastrointestinal diseases, propulsives

ATC code : A03FA01

Metoclopramide is a centrally acting antiemetic that inhibits the central and peripheral effects of apomorphine. It increases the movements of the upper digestive system by sensitizing the tissues to the effect of acetylcholine. It increases the tone and intensity of gastric contractions (especially antral), duodenum and jejunum movements, while relaxing the pyloric sphincter and duodenal bulb. Thus, it accelerates the emptying of the stomach and the passage of food from

the intestines. It does not affect the movements of the colon and gallbladder, stomach, bile and pancreatic secretions.

5.2. Pharmacokinetic properties

Absorption:

The onset of pharmacological action is 1-3 minutes after IV administration; It begins to appear 10-15 minutes after IM administration and these effects last for 1-2 hours.

Distribution:

Metoclopramide is widely distributed in the body. The volume of distribution of metoclopramide is Vd: 3.5 L/kg.

Biotransformation:

It is metabolized in the liver.

Elimination:

Its elimination is biphasic. The terminal elimination half-life is about 4-6 hours, but in case of renal failure, this period is prolonged as a result of an increase in plasma concentrations. Excretion occurs with urine. Approximately 85% of the dose is excreted within 72 hours. 20 to 30% of the metoclopramide is removed from the body unchanged, the rest in the form of sulfate or glucronide conjugates or metabolites. Approximately 5% of the dose is excreted with feces.

Linear/Non linear State

No data available.

Characteristics of patients

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 fora 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 valid.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Soodium metabisulfite
Water for injection

6.2. Incompatibilities

Any dilutions of it should be protected from light during infusion. Degradation is indicated by a yellow discoloration. Such solution must not be used.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C, protect it from light.

6.5. Nature and contents of container

Solution for injection filled in amber type I glass ampoules,
PRİMSEL is packaged in cardboard boxes containing 5 ampoules of 2 mL in each box.

6.6. Instructions for use and handling and disposal

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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