

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Metoclopramide Injection

2. Qualitative and quantitative composition

Each 2ml contains equivalent to 10mg Anhydrous Metoclopramide Hydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

Clear, colourless, sterile solution.

4. Clinical particulars

4.1 Therapeutic indications

Adult population

Metoclopramide Injection 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 of radiotherapy induced nausea and vomiting (RINV).

Paediatric population

Metoclopramide Injection 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 established post operative nausea and vomiting (PONV) as a second line option

4.2 Posology and method of administration

Posology

The solution can be administered intravenously or intramuscularly.

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

All indications (adult population)

For prevention of PONV a single dose of 10mg 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 population 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 |

The maximum treatment duration is 48 hours for treatment of established post operative nausea and vomiting (PONV).

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

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 \leq 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).

Paediatric population

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

Method of administration:

A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

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 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 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)

It should not be administered to patients where gastro intestinal conditions might be adversely affected, as in gastrointestinal obstruction, perforation, haemorrhage or immediately after surgery.

Metoclopramide should not be used during breast-feeding (see 4.6).

4.4 Special warnings and 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, 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 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.

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 (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).

This medicinal product contains less than 1 mmol sodium (23mg) per 2ml, i.e. essentially 'sodium-free'.

Metoclopramide Injection contains sodium metabisulphite which 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 have both a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative HI 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.

Cyclosporine

Metoclopramide increases cyclosporine bioavailability (C_{max} 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.

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.

Breast-feeding

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 breast-feeding. Discontinuation of metoclopramide in breast-feeding women should be considered.

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 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare

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

| System Organ Class | 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) Sulphaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-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 | Amenorrhoea, Hyperprolactinaemia, |
| Rare | Galactorrhoea |
| Not known | Gynaecomastia |
| Gastrointestinal disorders | |
| Common | Diarrhoea |
| General disorders and administration site conditions | |
| Common | Asthenia |
| 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, 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 disorder | |
| Common: | Hypotension, particularly with intravenous formulation |
| Not known | Shock, syncope after injectable use Acute hypertension in patients with phaeochromocytoma (see section 4.3), Transient increase in blood pressure |

* 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:

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

Extrapyramidal disorders, drowsiness, decreased level of consciousness, confusion, hallucination, 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

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.

Elimination:

It is excreted mainly in the urine as free and as conjugated metoclopramide and as metabolites. It crosses the placenta and is excreted in breast milk.

The elimination half-life is about 6 hours.

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

No further relevant information other than that which is included with other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

HCl

NaHSO₃

10% CH₃COONa

Water for Injections.

6.2 Incompatibilities

If this product is used for the treatment of nausea and vomiting associated with cytotoxic drugs, the cytotoxics should be administered as a separate infusion.

6.3 Shelf life

3 years (36 months).

6.4 Special precautions for storage

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

2ml, glass ampoules, glass type 1 borosilicate glass packed in cardboard cartons to contain 50 x 2ml ampoules.

6.6 Special precautions for disposal and other handling

If only part of an ampoule is used, discard the remaining solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Shandong Shenglu Pharmaceutical Co.,Ltd

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Sishui County, Shandong Province

P.R.China

8. Marketing authorisation number(s)

08432/06783/REN/2018

9. Date of first authorisation/renewal of the authorisation

Feb 24, 2023

10. Date of revision of the text

09/12/2016