

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Maxolon High Dose
Metoclopramide 5mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20ml ampoule contains Metoclopramide Hydrochloride BP equivalent to 100mg of the anhydrous substance.

Excipient with known effect

Sodium content: 63mg/20ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear colourless solution for intravenous infusion.

4 CLINICAL PARTICULARS

4.1 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 of radiotherapy induced nausea and vomiting (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 established post-operative nausea and vomiting (PONV) as a second line option

4.2 Posology and method of administration

Posology

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 treatment should be made as soon as possible.

Continuous infusion (recommended method):

This medicine is given by IV infusion as a loading dose followed by a continuous infusion to maintain a metoclopramide serum concentration of 0.85 µg - 1.0µg/ml. The loading dose should be given before starting cytotoxic chemotherapy.

| | Maxolon 'High Dose' (Metoclopramide Infusion) | Volume Of Diluent | IV Infusion Time |
|------------------|---|-------------------|------------------|
| Loading dose | 2-4 mg/kg body weight | 50-100 ml | 15-20 minutes |
| Maintenance dose | 3-5 mg/kg body weight | 500 ml | 8-12 hours |

Total dosage in any 24 hour period should not normally exceed 10 mg/kg body weight.

Where cisplatin is to be used the loading dose of this medicine should be at least 3 mg/kg body weight and the maintenance dose at least 4 mg/kg body weight.

Intermittent Infusion (alternative regimen)

This medicine can be given by intermittent IV infusion suitably diluted. The initial dose should be given before starting cytotoxic chemotherapy.

| | Maxolon 'High Dose' (Metoclopramide Infusion) | Volume Of Diluent | IV Infusion Time |
|------------------------------------|---|-------------------|---------------------|
| Initial dose | Up to 2 mg/kg body weight | at least 50 ml | at least 15 minutes |
| Repeat doses at 2 hourly intervals | Up to 2 mg/kg body weight | at least 50 ml | at least 15 minutes |

Total dosage in any 24 hour period should not normally exceed 10 mg/kg body weight.

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).

Compatibility with cytotoxic agents:

This medicine is compatible with a number of cytotoxic drugs; however it should not be mixed in solution with therapeutic agents other than those stated.

This medicine is compatible with cisplatin, cyclophosphamide and doxorubicin hydrochloride and is stable over the concentration ranges listed below for 24 hours at room temperature when protected from light.

40-200 ml cisplatin (1 mg/ml) per 100 mg/20 ml of this medicine in 1 litre of sodium chloride 0.9%.

Up to 40 mg doxorubicin hydrochloride (powder) per 100 mg/20 ml of this medicine.

Up to 4 g cyclophosphamide (1 g/50 ml) per 100 mg/20 ml of this medicine.

Compatibility with morphine/diamorphine:

This medicine is compatible with morphine hydrochloride and diamorphine hydrochloride and is stable over the concentration ranges listed below for 48 hours at room temperature under normal fluorescent lighting.

Up to 100 mg of morphine hydrochloride per 100 mg/20 ml of this medicine.

Up to 50 mg of diamorphine hydrochloride per 100 mg/20 ml of this medicine.

This medicine 100 mg/20 ml also remains stable for 48 hours at room temperature with 100 mg of morphine hydrochloride, or 50 mg diamorphine hydrochloride, when diluted 1 in 10 with sodium chloride 0.9%.

Stability in intravenous fluids:

Ideally intravenous solutions should be prepared at the time of infusion.

However, this medicine has been shown to be stable for at least 48 hours at room temperature in the following solutions when administered in a PVC infusion bag (e.g. Viaflex^R Travenol).

Sodium chloride intravenous infusion B.P. (0.9% w/v)

Glucose intravenous infusion B.P. (5% w/v)

Sodium chloride and glucose intravenous infusion B.P. (sodium chloride 0.18% w/v; glucose 4% w/v)

Compound sodium lactate intravenous infusion B.P. (Ringer-lactate solution; Hartmann's solution)

Note: preparation must be under appropriate aseptic conditions if the above extended storage periods are required. The high dose ampoule presentation is not suitable for multidose use.

Paediatric population:

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 |
| 9-15 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).

For the treatment of postoperative nausea and vomiting, metoclopramide should be administered after the termination of the surgical procedure.

The recommended dose is 0.15 mg/kg body weight given as a slow injection (at least 3 minutes).

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).

Metoclopramide should not be used in children younger than 1 year as there are insufficient data regarding efficacy and safety of the product in this patient population see section 4.3.

Method of administration

This medicine is administered by IV infusion, suitably diluted. The recommended method of administration is by continuous infusion which allows steady serum levels of metoclopramide to be maintained.

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)

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 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).

Since extrapyramidal symptoms may occur with both metoclopramide and neuroleptics such as the phenothiazines, particular care should be exercised in the event of these drugs being prescribed concurrently.

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.

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).

Risk-benefit should be carefully considered in patients with significant hepatic or renal impairment (loss of conjugation and increased risk of extrapyramidal effects) or with Parkinson's disease (symptoms may be exacerbated).

Precautions:

If vomiting persists the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

Care should be exercised in patients being treated with other centrally acting drugs.

This medicine should be used with care in combination with other serotonergic drugs including SSRIs.

Patients receiving this drug for the disorders associated with delayed gastric emptying should be reviewed at an early stage for response to treatment.

Metoclopramide may cause elevation of serum prolactin levels.

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

Important information on sodium

This medicinal product contains less than 1 mmol sodium (23mg) per 6 ml, i.e. 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). Metoclopramide should be used with care in association with other drugs acting at central dopamine receptors such as bromocriptine and pergolide.

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, morphine derivatives and other opioid analgesics

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

The absorption of aspirin and paracetamol may be modified by the effect of metoclopramide on gastric motility.

Concomitant use of anticholinergic drugs may inhibit the favourable effects on gastrointestinal motility.

Since extrapyramidal reactions may occur with this medicine, Phenothiazines and Tetrabenazine, care should be exercised in the event of co-administration of these drugs.

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.

Monoamine oxidase inhibitors

The effects of certain other drugs with potential central stimulant effects, e.g. monoamine oxidase inhibitors and sympathomimetics, may be modified when prescribed with metoclopramide and their dosage may need to be adjusted accordingly.

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.

Antiprotozoals

This medicine may reduce plasma concentrations of atovaquone.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor fetotoxicity of Metoclopramide hydrochloride. 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 breastfeeding. Discontinuation of metoclopramide in breastfeeding women should be considered.

Fertility

No data available.

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 ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), 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 | 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 |
| Immune System disorders | | |
| | Uncommon | Hypersensitivity |
| | Not known | Anaphylactic reaction (including anaphylactic shock particularly with |

| | | |
|---------------------------------|-------------|--|
| | | intravenous formulation) |
| Endocrine disorders* | | |
| | Uncommon | Amenorrhoea, Hyperprolactinaemia |
| | Rare | Galactorrhoea |
| | Not known | Gyneacomastia |
| 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 (including visual disturbances and oculogyric crisis), 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) |
| 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; dyspnoea |
| Vascular disorders | | |
| | 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 |
| 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

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

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In cases of overdose, acute dystonic/extrapyramidal reactions have occurred. Very rarely AV block has been observed.

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

This medicine is indicated for the treatment of nausea and vomiting associated with intolerance to cytotoxic drugs. It is specially formulated to ensure compatibility in solution with cisplatin.

Mechanism of action

This medicine exerts a three-fold anti-emetic action: by inhibiting central dopamine receptors this medicine raises the threshold of the chemoreceptor trigger zone, and reduces the reaction of the adjacent vomiting centre to centrally-acting emetics. This medicine decreases the sensitivity of the visceral afferent nerves to the vomiting centre, reducing the effect of locally-acting emetics and irritant substances. In the upper gastro-intestinal tract this medicine promotes normal gastric emptying and it may thus abolish gastric stasis which is part of the vomiting reflex.

This medicine is not intended for use in the wider range of indications for which this medicine at standard dose is indicated.

5.2 Pharmacokinetic properties

Absorption

Based on current literature, a metoclopramide concentration range of about 0.85µg/ml would appear desirable for the control of cytotoxic drug induced emesis. Such plasma concentrations may be achieved by the administration of a loading dose of 2-4 mg/kg infused over 15-30 minutes prior to cytotoxic drug therapy followed by a maintenance continuous infusion of 3-5 mg/kg over 8-12 hours.

Biotransformation

Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney.

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 additional data available.

6 PHARMACEUTICAL PARTICULARS

- 6.1 List of excipients**
Sodium chloride
Water for injections

- 6.2 Incompatibilities**
Not applicable

- 6.3 Shelf life**
3 years

- 6.4 Special precautions for storage**
If ampoules are removed from their carton, they should be stored away from light. If inadvertent exposure occurs, ampoules showing discolouration must be discarded.

- 6.5 Nature and contents of container**
Clear glass 20ml ampoules (Ph. Eur. Type I neutral glass) packed in boxes of 10.

- 6.6 Special precautions for disposal**

Protect from light.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0052

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
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16 June 1995

10 DATE OF REVISION OF THE TEXT

28/02/2024