Antiemetic

PII SGP-003
R.O.C. Reg. No.:07630

PULIN Injection

Contents:
Each 2mL ampoule of Pulin Injection contains 10 mg Metoclopramide Hydrochloride.

Therapeutic indications:
Adults:
- Prevention of nausea and vomiting associated with chemotherapy and radiotherapy with low and minimal emetogenicity
- Prevention of post-operative nausea and vomiting
- Symptomatic treatment of acute migraine induced nausea and vomiting
- Adjunct treatment of gastroparesis
- Adjuvant to surgical and radiological procedures

Children (aged 1-18 years):
- Treatment of established post-operative nausea and vomiting (PONV) as a second line option (intravenous use only)

Posology and method of administration:
The solution can be administered intravenously (IV) or intramuscularly (IM).
Adults
The recommended single dose is 10 mg, repeated up to three times daily.
Prevention of PONV: a single dose of 10 mg is recommended.
The maximum recommended daily dose is 30 mg or 0.5 mg/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. Treatment durations beyond 12 weeks should be avoided unless the therapeutic benefit is judged to outweigh the risk to the patient.
Elderly
In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.
Renal impairment
In patients with severe renal impairment (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%.
Children (aged 1-18 years)
The recommended dose is 0.10 to 0.15 mg/kg body weight, repeated up to three times daily by the intravenous route. The recommended 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 injectable treatment duration should be as short as possible.
The recommended maximum treatment duration is 48 hours for treatment of established post operative nausea and vomiting (PONV).
Metoclopramide is contraindicated in children aged less than 1 year. (*See "Contraindications"*)
Due to the potential risk of severe cardiovascular reactions including cardiac arrest, the solutions for injection are restricted to be used only when appropriate resuscitation equipment is available. (*See "Undesirable effects, Cardiovascular disorders"*)
Method of administration
IV doses should be administered as a slow bolus (at least over 3 minutes).
A minimum interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of dose (*See "Special warnings"*).

Pregnancy and lactation:
Pregnancy
As there are no adequate or well controlled studies in pregnant women, metoclopramide should be used only if clearly needed.
Animal studies and clinical experience have not indicated a teratogenic effect.
Nevertheless, metoclopramide is not recommended during the first three months of pregnancy unless there are compelling reasons to do so.
Due to pharmacological properties, as other benzamides, in case of metoclopramide administration before delivery, extrapyramidal disorders in newborn cannot be excluded.
Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.
Lactation
During lactation metoclopramide is found in breast milk and adverse reactions in the breast-fed baby cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from metoclopramide treatment.

Contraindications:
This medicinal product is CONTRAINDICATED in the following situations:
- children less than 1 year of age,
- hypersensitivity to metoclopramide or to one of the other ingredients in the product,
- if stimulation of gastrointestinal motility is hazardous to the patient: in the event of gastrointestinal bleeding, mechanical obstruction or gastrointestinal perforation,
- in patients having previously presented with tardive dyskinesia induced by neuroleptics or metoclopramide,
- in patients with known or suspected pheochromocytoma (apart from as a provocative test); serious hypertensive events have been reported with dopamine antagonists including certain benzamides in this patient category,
- in combination with dopamine agonists and selegiline (see *"Interactions with other medicinal products and other forms of interaction"*),
- known history of methaemoglobinaemia with metoclopramide or NADH-cytochrome b5 reductase deficiency
- Parkinson's disease

Drug interaction:
Contraindicated combinations
+ Dopamine agonists (levodopa, amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lysuride, pergolide, piribedil, pramiprexole, quinagolide, ropinirole)
Mutual antagonism of levodopa, dopamine agonists and neuroleptics.
Use an antiemetic that does not give rise to any extrapyramidal effects.
+ MAO-B inhibitors (selegiline)
Mutual antagonism of selegiline (dopamine agonist) with metoclopramide (antiemetic neuroleptic).
Use an antiemetic that does not give rise to any extrapyramidal effects.
Inadvisable combinations
+ Alcohol:
Alcohol increases the sedative effect of neuroleptics. Driving and using machines may be hazardous due to impaired vigilance.
Avoid consumption of alcoholic beverages and intake of medicinal products containing alcohol.
Combinations to be taken into consideration
+ Antihypertensive agents (all types):
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
+ Other central nervous system depressants: morphine derivatives (analgesics, antitussive agents and replacement treatments), barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, neuroleptics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine) sedative H1 antihistamines, centrally acting antihypertensive agents, baclofen, thalidomide, pizotifen.
Increased CNS depression. Driving and using machines may be dangerous due to impaired vigilance.
+ Beta-blockers in the event of cardiac insufficiency (bisoprolol, carvedilol, metoprolol):
Vasodilator effect and risk of hypotension, particularly orthostatic hypotension (additive effect).
Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.
+ Digoxin:
Metoclopramide decreases digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.
+ Mivacurium and suxamethonium:
Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).
+ Strong CYP2D6 inhibitors such as fluoxetine:
Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine.

Undesirable effects:
Central nervous system and psychiatric disorders:
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 drug, particularly in children and young adults (See Warnings)
- Drowsiness, decreased level of consciousness, confusion, hallucination.

Other reactions may occur:
- Tardive dyskinesia: during prolonged treatment, particularly in elderly patients,
- Drowsiness, fatigue, dizziness, more rarely headache, insomnia,
- Depression,
- In exceptional cases, neuroleptic malignant syndrome (*See "Special warnings and special precautions for use"*).
- Seizures.
- Suicidal ideation.

Gastrointestinal disorders
- Diarrhoea and intestinal gas.

Haematological disorders
- Methaemoglobinaemia which could be related to NADH-cytochrome b5 reductase deficiency, particularly in neonates (*See "Special warnings and special precautions for use"*).
- Sulphaemoglobinaemia have been reported, mainly during concomitant administration of sulphatereleasing medicinal products at high doses.

Endocrine disorders
- Occasionally symptomatic hyperprolactinaemia (amenorrhoea, galactorrhoea, gynecomastia) during prolonged treatment.
- Moderate sweating.

General disorders
- Allergic reactions including immediate hypersensitivity reactions: urticaria, angio-oedema, anaphylactic shock (particularly with intravenous formulation).
- Asthenia.

Cardiovascular disorders
- Hypotension, particularly with the injection forms.
- Very rare cases of bradycardia and atrioventricular heart block have been reported, particularly with the injection forms.
- Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia. (*See "Posology and method of administration"*)
- QT prolongation and torsades de pointes (*See "Special warnings and special precautions for use"*).
- Blood pressure increase in patients with or without phaeochromocytoma (*See "Contraindications"*).
- Shock, syncope after injectable use.

Special warnings and special precautions for use:
Special warnings
- Neurological undesirable effects (extrapyramidal syndrome) may develop, particularly in children and in young adults and/or when high doses are used (*See "Undesirable effects"*).
- Since neuroleptic malignant syndrome has been reported in exceptional cases, treatment must be immediately discontinued in the event of unexplained hyperthermia or hyperthermia associated with other symptoms of malignant syndrome (pallor, vegetative disorders, impaired consciousness, muscular rigidity).
- Respect the time interval (of at least 6 hours) between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.In the event of profuse vomiting, it is essential to guard against dehydration. The patient may be rehydrated orally using "sweet-saline" solutions (oral rehydration solutions) given in small quantities at regular intervals.
- Cases of methaemoglobinaemia, possibly due to NADH-cytochrome b5 reductase deficiency, have been reported. In such an event, treatment must be immediately and definitively discontinued, and appropriate measures implemented.
- Metoclopramide may induce Torsade de Pointes, therefore caution should be exercised in patients with known risk factors for prolongation of the QT interval i.e.:
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesaemia)
- congenital long QT syndrome
- bradycardia
- Concomitant use of medicinal products that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Special precautions for use
- Use of this medicinal product is not recommended in epileptic patients (increased frequency and intensity of fits).
- In patients with renal impairment and with severe hepatic impairment, a dose reduction is recommended (*See "Posology and method of administration"*).
- IV injections should be made slowly, at least over 3 minutes.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should be kept as short as possible, in accordance to one's clinical judgement. Treatment durations beyond 12 weeks should be avoided unless the therapeutic benefit is judged to outweigh the risk to the patient.

Incompatibilities:
None known to date.

Effects on ability to drive and use machines:
Drivers and machine operators must be made aware of the risk of drowsiness related to use of the medicinal product.

Overdose
No fatalities have been observed following massive intake of metoclopramide, either accidental or as a suicide attempt.
Extrapyramidal disorders and drowsiness, decreased level of consciousness, confusion, hallucinations *Management of overdose:* Treatment of extrapyramidal syndrome, which may or may not be related to overdose, is purely symptomatic (benzodiazepines in children, benzodiazepines and/or anticholinergic anti-parkinsonians in adults). Administration may be repeated in order to prevent symptoms from recurring.
In the event of methaemoglobinaemia, methylene blue at a dose of 1 mg/kg has been effective when administered as a slow infusion.

Pharmacological Properties
Pharmacodynamic properties
GASTROPROKINETICS, ATC code: A03FA01
(A: Alimentary tract and metabolism)
Metoclopramide is a dopamine antagonist neuroleptic.
It prevents vomiting by blocking dopamine sites.
Pharmacokinetic properties
Distribution:
Metoclopramide is widely distributed into tissue. The volume of distribution is 2.2 to 3.4 l/kg. Plasma protein binding is low. The medicine crosses the placental barrier and passes into breast-milk.
Metabolism:
Metoclopramide undergoes slight metabolism.
Excretion:
Metoclopramide is mainly excreted in the urine in the unbound or sulpho-conjugated form. The elimination half-life is 5 to 6 hours. This value increases in the event of renal or hepatic impairment.

Storage conditions:
Store below 30℃ and protect from light.
Keep medicine away from children.

Packagings:
2mL x 100Ampoules.

Manufacturer:
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