YSP PULIN INJECTION 5mg/ml

Ingredient(s):
Each ml contains:
Metoclopramide HCl 5mg
Benzyl Alcohol 0.01ml

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetic):
Metoclopramide is a dopaminergic antagonist neuroleptic. It prevents vomiting by blocking dopamine sites.
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 5-6 hours. This value increases in patients with kidney or liver failure.

Indication(s):
Adult population
This product 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
This product 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 second-line option

Dosage and Administration(s):
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 10mg 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 10mg per dose, 1 to 3 times daily. The maximum recommended daily dose is 30mg or 0.5mg/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 dosage is 0.1 to 0.15mg/kg, 1 to 3 times daily, by intravenous route. The maximum daily dose is 0.5mg/kg.

Dosing table:

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	1mg	Up to 3 times daily
3-5 years	15-19kg	2mg	Up to 3 times daily
5-9 years	20-29kg	2.5mg	Up to 3 times daily
9-18 years	30-60kg	5mg	Up to 3 times daily
15-18 years	Over 60kg	10mg	Up to 3 times daily

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:
A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

Special Populations
Elderly subjects
In elderly subjects, a dose reduction should be considered, based on kidney and liver function, and overall frailty.

Kidney failure
In patients with end-stage kidney failure (creatinine clearance ≤ 15ml/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%.

Liver failure
In patients with severe liver failure, the dose should be reduced by 50%. Other pharmaceutical forms may be more suitable for these patient populations

Pediatric population
Metoclopramide is contraindicated in children aged less than one year.

Mode of Administration
Intramuscular or intravenous use.

Contraindication(s):
- Hypersensitivity to the active substance or to the excipients.
- 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 (increase crises frequency and intensity)
- Parkinson's disease
- Combination with levodopa or dopaminergic agonists.
- Known history of methaemoglobinaemia with metolopramide or of NADH cytochrome-b5 deficiency
- Use in children less than 1 year of age.

Precaution(s) / Warning(s):
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 respected between each dose 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. 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. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

Particularly caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs.

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

<u>Methemoglobinemia</u>
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).

<u>Cardiac disorders</u>
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.

Particularly 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).

<u>Kidney or liver failure</u>
In patients with kidney failure or severe liver failure, a dose reduction is recommended.

> <u>Warning</u>
> As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

Interaction with Other Medicaments:
<u>Contraindicated combinations:</u>
- **Dopaminergic agents including non-antiparkinsonian agents and levodopa:** Mutual antagonism between the dopaminergic agent or levodopa and the neuroleptic.
  An antiemetic with no extrapyramidal effects should be used.
- **MAO-B inhibitors (selegiline):** Mutual antagonism of selegiline (dopaminergic agent) with metoclopramide (antiemetic neuroleptic).

An antiemetic with no extrapyramidal effects should be used.

<u>Inadvisable combination:</u>
- **Alcohol**: Enhances the sedative effect of neuroleptics. Impaired alertness may make driving or using machines dangerous. Consumption of alcoholic beverages or medicinal products containing alcohol should be avoided.

<u>Combination to be taken into consideration:</u>
- **Antihypertensive agents, nitrate derivatives and related substances:** Increased risk of hypotension, particularly postural (additive effect).
- **Other sedatives:** Many medicinal products and substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These medicinal products include morphine derivatives (analgesics, antitussive agents and replacement treatments), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepines anxiolytics (eg.meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1 antihistamines, centrally acting antihypertensive agents, baclofen, pizotifen and thalidomide: increased central depression. Impaired alertness may make driving or using machines dangerous.
- **Beta-blockers:** Vasodilator effect and risk of hypotension, particularly postural hypotension (additive effect).
- **Prilocaine:** Risk of additive methemoglobinemic effects, particularly in newborns.
- **Mivacurium + suxamethonium:** The metoclopramide injection can prolong neuromuscular blockade by inhibiting plasma cholinesterase.

Pregnancy and Lactation:
<u>Pregnancy</u>
Metoclopramide can be used during pregnancy based on available data.
If high doses are administered at the end of pregnancy, there is a potential risk of extrapyramidal syndrome in the neonate by analogy with other neuroleptics which cannot be ruled out. In this situation, monitoring of the newborn should take this factor into account.

<u>Lactation</u>
Women may breast-feed provided that treatment is occasional, for example, in cases of post-Cesarean vomiting, if the infant was born at term and in good health. Breast feeding is not recommended in the event of premature birth or prolonged or high-dose treatment.

Side Effect(s):
<u>Effects on ability to drive and use machines</u>
Drivers and machine operators must be made aware of the risk of drowsiness related to use of this medicinal product.

<u>Central nervous system and psychiatric disorders</u>
- Early-onset extrapyramidal symptoms: increased risk of occurrence in young adults and/or when the recommended dose is exceeded, including after administration of a single dose: these symptoms include acute dystonia and dyskinesia possibly manifested by abnormal movements of the head and neck (facial spasms, trismus, oculogyric crises, eye rolling, protrusion of the tongue, swallowing difficulties, dysarthria, torticollis), generalized hypertonia, or even opisthotonos.
- Parkinsonian syndrome, tremor, akathisia.
- Tardive dyskinesia: during prolonged treatment, particularly in elderly patients; this usually involves orofacial dyskinesia. The extremities and the trunk appear to be less affected. Choreoathetotic movements may be observed.
- Drowsiness, lassitude, hallucinations, confusion, dizziness, more rarely headache, insomnia.
- Isolated cases of depression.
- Seizures, particularly in patients with epilepsy [see Precaution(s)/ Warning(s)] or with other predisposing factors and/or during overdose.
- In exceptional cases, neuroleptic malignant syndrome [see Precaution(s)/ Warning(s)].

Gastrointestinal disorders
- Diarrhea and flatulence

Hematological disorders
- Very rare cases of methemoglobinemia, possibly due to NADH-cytochrome b5 reductase deficiency, have been reported, particularly in newborns.
- Very rare cases of sulfhemoglobinemia have been reported, mainly during concomitant administration of sulfate releasing medicinal products at high doses.

Endocrine disorders
- Occasionally symptomatic hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia) during prolonged treatment.
- Moderate sweating.

Systemic disorders
- Allergic reactions including immediate hypersensitivity reactions: Urticaria, angioedema, anaphylactic shock.

Cardiovascular disorders
- Cases of cardiac arrest, particularly with the injectable form
- Hypotension, particularly with the injectable forms.
- Very rare cases of bradycardia and atrial block have been reported, especially with the injection dosage form.

Symptoms and Treatment for Overdosage, and Antidote(s):
Cases of cardiorespiratory arrest and/or death have been observed following overdose, especially in infants and children. Extrapyramidal symptoms, drowsiness, consciousness disorders, confusion, hallucinations and seizures may occur.
Symptomatic treatment and continuous monitoring of cardiovascular and respiratory function should be implemented, depending on clinical condition.
Treatment of extrapyramidal symptoms, whether or not related to overdose, is only symptomatic (benzodiazepines in children, benzodiazepines and/or anticholinergic antiparkinsonian agents in adults). Administration of these drugs may be repeated in order to prevent symptoms from recurring.

In patients who develop methemoglobinemia, methylene blue at a dose of 1mg/kg has been effective when administered as a slow infusion.

Shelf-Life:
3 years

Storage Condition(s):
Store at temperature below 30°C. Protect from light and moisture.

Incompatibilities:
As no compatibility studies have been conducted, this medicinal product should not be mixed with other medicinal products.

Product Description:
A clear and colorless solution.

Dosage Forms and Packaging available:
2ml x 30, 2ml x 50 and 2ml x 100 vials.
2ml x 10, 2ml x 50 and 2ml x 100 amber ampoules.

Y. S. P.®
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