℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Paracetamol Infusion IP (10 mg/ml)

VARMOL® (1% w/v)

Each 100 ml contains:

Paracetamol IP	1000 mg
Mannitol IP	5.0 gm
Water for Injection IP	q.s.

DESCRIPTION

Paracetamol is an Analgesic and Antipyretic. Its Chemical name is 4-hydroxyacetanilide and its Molecular formula is $C_8H_9NO_2$ and Molecular weight is 151.2 g/mol.

THERAPEUTIC INDICATIONS

- short-term treatment of moderate pain, especially following surgery
- short-term treatment of fever

when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

POSOLOGY AND METHOD OF ADMINISTRATION

The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg

Posology: Dosing based on patient weight (please see the dosing table here below)

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol (10 mg/ml) per administration based on upper weight limits of group (ml)**	Maximum Daily Dose *
> 33 kg to ≤50 kg	15 mg/kg	1.5 ml/kg	75 ml	60 mg/kg not exceeding 3 g
>50 kg with additional risk factors for hepatotoxicity	1 g 1 g	100 ml	100 ml	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 ml	100 ml	4 g

***Maximum daily dose:** The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account.

****Patients weighing less will require smaller volumes.**

The minimum interval between each administration must be at least 4 hours. No more than 4 doses to be given in 24 hours.

The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours.

Elderly: Dose adjustment is not required in elderly people (see Pharmacokinetic properties).

Severe renal insufficiency: It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), to increase the minimum interval between each administration to 6 hours (see Pharmacokinetic properties).

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration.

The maximum daily dose must not exceed 3 g (see Special warnings and precautions for use).

Method of administration:

For IV infusion only.

The paracetamol solution is administered as a 15-minute intravenous infusion.

To remove solution, use a 0.8 mm needle (21-gauge needle) and vertically perforate the stopper at the spot specifically indicated.

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the infusion applies particularly for central route infusion, in order to avoid air embolism.

To be used with non-pyrogenic IV Administration set with aseptic technique.

Do not use, if found leaking upon squeezing or solution is not clear. Solution containing visible solid particles must not be used.

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to propacetamol hydrochloride (prodrug of paracetamol).
- In cases of severe hepatocellular insufficiency.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special Warnings:

Take care when prescribing and administering Paracetamol to avoid dosing errors due to confusion between milligram (mg) and millilitre (ml), which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

In order to avoid the risk of overdose, it should be checked that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entail risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of administration of the medicinal product with a peak seen usually after 4-6 days. Treatment with antidote should be given as soon as possible (see Overdose).

Paracetamol can cause serious skin reactions. Patients should be informed of early signs of serious skin reactions. The use of paracetamol should be discontinued if signs of rash or other symptoms of hypersensitivity appear.

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see Posology and method of administration).

Precautions for use:

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency, Gilbert's syndrome
- severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see Posology and method of administration and Pharmacokinetic properties)
- chronic alcoholism
- low reserves of hepatic glutathione as a result of chronic malnutrition, anorexia, bulimia or cachexia - dehydration.
- gluclose-6-phosphate dehydrogenase deficiency (may cause haemolytic anemia)

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5- oxoproline, is recommended.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml, that is to say essentially 'sodium free'.

INTERACTION WITH OTHER MEDICINAL PRODUCTS (DRUG INTERACTION)/ OTHER FORMS OF INTERACTION

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.
- Salicylamide may prolong the elimination half-life of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances including barbiturates, isoniazid, carbamazepine, rifampin, ethanol and others (see Overdose).
- Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see Special warnings and precautions for use)

PREGNANCY, LACTATION AND FERTILITY

Pregnancy: A large amount of data on pregnant women indicates neither malformities nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency

Lactation: After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol may be used in breast-feeding women.

Fertility: Not Known

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not Known

UNDESIRABLE EFFECTS

The following definitions apply to the incidence of the undesirable effects: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Vary Rare	Frequency not known (cannot be estimated from available data)
Blood and lymphatic system disorders				Thrombocytopenia, leukopenia, neutropenia	
Immune system disorders				Anaphylactic shock*, hypersensitivity reaction*	
Cardiac disorders					Tachycardia
Vascular disorders			Hypotension		
Hepatobiliary disorders			Hepatic transaminases increased		
Skin and subcutaneous tissue disorders				Serious skin reactions**, Rash*, Urticaria*	Erythema, pruritus, flushing
General disorders and administration	Reactions at injection site (pain and burning sensation)	Malaise			

OVERDOSE

Signs and Symptoms: There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly people, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain.

Overdose (7.5 g or more of paracetamol in a single administration in adults or 140 mg/kg of body weight in a single administration in children) causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

Treatment:

- Immediate hospitalisation
- Before beginning treatment, take a tube of blood for plasma paracetamol assay as soon as possible after the overdose.
- The treatment includes administration of the antidote, N-acetylcysteine (NAC) by the i.v. or oral route, if possible before the 10th hour. NAC can, however, give some degree of protection even after 10 hours, but in these cases, prolonged treatment is given.
- Symptomatic treatment
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of liver function. In very severe cases however, liver transplantation may be necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Analgesics; other analgesics and antipyretics;

ATC code: N02BE01

Pharmacodynamic properties

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Paracetamol provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

Paracetamol reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

Pharmacokinetic properties

Absorption: Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours. The bioavailability of paracetamol following infusion of 500 mg and 1 g is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15 minutes intravenous infusion of 500 mg and 1 g is about 15 µg/ml and 30 µg/ml respectively.

Distribution: The volume of distribution of paracetamol is approximately 1 l/kg. Paracetamol is not extensively bound to plasma proteins. Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/ml) were observed in the cerebrospinal fluid as and from the 20th minute following infusion.

Biotransformation: Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination: The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 l/h.

Special population

Renal insufficiency: In cases of severe renal impairment (creatinine clearance 10-30 ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), to increase the minimum interval between each administration to 6 hours (see Posology and method of administration).

Elderly: The pharmacokinetics and the metabolism of paracetamol are not modified in elderly people. No dose adjustment is required in this population.

Paediatric population: The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 hours) than in adults. In neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table - Age related pharmacokinetic values (standardised clearance, *CL_{std}/F_{oral} ($l.h^{-1}$ $70kg^{-1}$)

Age	Weight (kg)	CL_{std}/F_{oral} ($l.h^{-1}$ $70kg^{-1}$)
40 weeks PCA	3.3	5.9
3 months PNA	6	8.8
6 months PNA	7.5	11.1
1 years PNA	10	13.6
2 years PNA	12	15.6
5 years PNA	20	16.3
8 years PNA	25	16.3

STORAGE: Keep in a cool place, temperature not exceeding 30ºC. Do not freeze or refrigerate.
Keep out of reach of children.
Don't use Paracetamol IV Infusion after the expiry date printed on label and carton.

PRESENTATION:

Primary Packing: 100 ml LDPE Bottle.
Secondary Packing: Such a bottle is packed in a printed mono carton.

Manufactured by:
Puerto Life Sciences Pvt. Ltd.
Plot No.: A 206-207, Riico Industrial area
Ghiloth, Tehsil: Neemrana, Distt: Alwar,
Rajasthan-301705, India.

Marketed by:
VARENYAM®
Varenyam Healthcare Pvt. Ltd.
FF/SF, Sun Welkin Tower-H,Harni-Halol Road,
Vadodara-390022, Gujarat, India.