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

Biocon

Paracetamol Infusion IP (1.0% w/v)

PROLOP™ प्रोलोप

Composition:
Each mL contains:
Paracetamol IP 10 mg
Water for Injections IP q.s.

WARNING: Taking more than daily dose may cause serious liver damage or allergic reaction (e.g. swelling of the face, mouth and throat, difficulty in breathing , itching or rash)

PHARMACEUTICAL FORM
Solution for infusion

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic Group: Other analgesics and antipyretics

ATC code: N02BE01

Mechanism of Action
The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central actions 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 an antipyretic effect of at least 6 hours.

Pharmacokinetic Properties

Adults

Absorption

The pharmacokinetics of paracetamol is linear up to 2 g after a single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g is 10 mg/ml, similar to that observed following infusion of 1 g and 2 g paracetamol (corresponding to 500 mg and 1 g paracetamol, respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15 minutes intravenous infusion of 500 mg and 1 g of paracetamol 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 2 g of propacetamol (equivalent to 1 g paracetamol), significant concentrations of paracetamol (about 1.5 µg/ml) were observed in the cerebro-spinal fluid (CSF) from the 20th minute following infusion.

Metabolism

Paracetamol is metabolised mainly in the liver following 2 major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The later route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 (CYP 450) to a reactive intermediate N-acetyl-p-benzoquinone imine or NAPQI, 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.

At therapeutic doses, CYP3A4 (the major isoform P450 in human liver), contributes to the production of the cytotoxic metabolite. For very high supratherapeutic plasma concentrations (1500 mg/ml) of paracetamol, the 2E1 and 1A2 isoforms may also be involved.

Elimination

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

Neonates, Infants, and Children

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 h) than in adults. In neonates, the plasma half-life is longer than in infants ie, around 3.5 hours. Neonates, infants, and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Age related pharmacokinetic values (standardized clearance,*CL_{std}/F_{oral} ($L.h^{-1}$ 70 kg^{-1}), are presented below.

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

*CL_{std} is the population estimate for CL
[$]PCA- postconceptional age
[#]PNA-postnatal age

Special Populations

Renal insufficiency

In cases of severe renal impairment (creatinine clearance [CrCl] 10 to 30 ml/min), the elimination of paracetamol is slightly delayed, and the elimination half-life ranges 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 (CrCl⩽30 ml/min), to increase the minimum interval between each administration to 6 hours (see section **Posology and Method of Administration**.).

Elderly subjects

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population (see section **Posology and Method of Administration**).

Preclinical Safety Data
Preclinical data reveal no special hazard for humans. Studies on local tolerance of paracetamol in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

CLINICAL PARTICULARS

Therapeutic Indications
PROLOP™ is indicated for the short-term treatment of moderate pain, especially following surgery and for the 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
Intravenous route

Posology

Type of the Patient	Dose per Administration	Minimum Interval Between 2 Administrations (hours)	Maximum Daily Dose (MDD)
Adults and adolescents>50 kg	1 g	4	4 g
Children and adults (>33 to <50 kg)	15 mg/kg	4	60 mg/kg to 3 g
Children (>10 approximate 1 year old to <33 kg)	15 mg/kg	4	60 mg/kg to 2 g
New borns, infants, toddlers and children⩽ 10 kg (up to approximate 1 year old)	7.5 mg/kg	4	30 mg/kg

Severe renal insufficiency:

It is recommended, when giving paracetamol to patients with severe renal impairment (CrCl⩽30 ml/min), to increase the minimum interval between each administration to 6 hours (see section **Pharmacokinetic Properties**).

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration, the MDD must not exceed 3 g (see section **Posology and Method of Administration**).

Geriatric: No dosage adjustment is required in elderly patients.

Method of Administration
The paracetamol solution is administered as a 15 minute intravenous infusion.

Contraindications
Paracetamol is contraindicated in patients with:

- Hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- Severe hepatocellular insufficiency.
- Hepatic failure.

Special Warnings and Precautions for Use
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, check that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entails 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 2 days of drug administration with a peak seen usually after 4 to 6 days. Treatment with antidote should be given as soon as possible (see section **Overdose**).

Paracetamol should be used with caution in cases of:

- Hepatocellular insufficiency,
- Severe renal insufficiency (CrCl⩽30 ml/min) (see sections **Posology and Method of Administration** and **Pharmacokinetic Properties**),
- Chronic alcoholism,
- Chronic malnutrition (low reserves of hepatic gluthatione),
- Dehydration,
- Glucose-6-phosphate dehydrogenase deficiency (may lead to haemolytic anaemia).

Drug Interactions

- 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 ($t_{½}$)of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances such as anticonvulsants (barbiturates, carbamazepine, and phenytoin) as they may increase the clearance of paracetamol (see section **Overdose**).
- Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of international normalised ratio (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.
- Concomitant use of busulfan with paracetamol may result in reduced busulfan clearance.
- Concomitant use of diflunisal with paracetamol increases the paracetamol concentration, which may cause hepatotoxicity.

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Pregnancy and Lactation
Pregnancy: Category A
Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus/newborn infant. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects.

No signs of pre/postnatal toxicity were observed in rats treated with intravenous paracetamol at maternal exposures (based on area under concentration-time curve [AUC]) greater than 3 fold those anticipated at maximum clinical dose.

Nevertheless, paracetamol should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

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 with a caution.

Effects on Ability to Drive and Use Machines
Not known.

Undesirable Effects

Adverse Events in Adults - greater than 1% (observed in the clinical trials) were-

Neurological: dizziness, headache, dystonia

Gastrointestinal: vomiting, dry mouth, diarrhoea, constipation, nausea, dyspepsia, enlarged abdomen, gastrointestinal disorder NOS

Haematological: anaemia, post-operative haemorrhage

Hepatobiliary: gamma glutamyl transpeptidase (GT) increase, serum glutamic pyruvic transaminase (SGPT) increase

Psychiatric: insomnia

Skin and appendage: injection site pain, injection site reaction, post-operative site reaction, pruritus.

Respiratory: alveolitis, coughing

Endocrine/metabolic: hyperglycemia, hypokalemia

General: fatigue, fever, oedema-peripheral and chest pain

Adverse Events in Children - greater than 1% (observed in the clinical trials)
Skin and appendage: injection site pain

Neurological: hypotonia

Gastrointestinal: nausea, vomiting, abdominal pain, eructation

Body as a whole: fever

Post market adverse drug reactions for propacetamol/paracetamol are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ System	Rare (>1/10000, <1/1000)	Very Rare (<1/10000)
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	-
Liver	Increased levels of hepatic transaminases	-
Platelet/blood	Neutropenia, leucopenia,	-
Neurological	-	Neurological disorders, coma
Renal/genitourinary	-	Acute renal failure
Skin and appendage	Macular rash, injection site reaction	Maculo-popular rash, pemphigoid reaction, pustular rash

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment. Isolated reports of thrombocytopenia have been observed. Cases of erythema, flushing, pruritus, and tachycardia have been reported.

Overdose
There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, 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 and 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 (aspartate amino transferase [AST], alanine amino transferase [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 2 days, and reach a maximum after 4 to 6 days.

Emergency measures

- 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 intravenous or oral route, if possible before the 10th hour. However, NAC given even after 10 hours provides some degree of protection, but in these cases prolonged treatment is recommended.
- 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 1 to 2 weeks with full restitution of liver function. In very severe cases, however, liver transplantation may be necessary.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Paracetamol should not be mixed with other medicinal products.

Shelf Life : Please refer carton/label

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Storage and Precautions
Store below 30°C. Protect from light. Do not freeze.
Keep out of reach of children.
Keep the container in the outer packaging.
For single use only.

Special Precautions for Disposal and Other Handling
Before administration, the product should be visually inspected for any particulate matter and discoloration. Any unused solution should be discarded.

Nature and Contents of Container
Product is presented in a 100mL sterile non-pyrogenic single dose low density polyethylene container manufactured by FFS technology. The intact bottle is labeled with a product label and is provided a nozzle cap. Labeled bottle is further wrapped within a BOPP film and packed in unit carton.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

Leaflet revised on **June 2020**

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**.

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