Summary of Product Characteristics

1. Name of the Medicinal Product

Product Name: PARA-R

Generic Name: Paracetamol Infusion 1% w/v

Strength: Paracetamol: 1000mg/100ml (10mg/ml)

Pharmaceutical form: Solution for Infusion

2. Qualitative and quantitative composition Unit Dosage Composition:

Sr. No.	**Ingredients**	**Pharmacopoeial Standard**	**Label Claim** (Each 100ml contains)	**Required Std. Qty./ Bottle** (in mg)	**Reason for Inclusion**
1.	Paracetamol	BP	1000 mg	1000.00	Active
2.	Mannitol	BP	--	5000.00	Tonicity Agent
3.	Disodium Edetate	BP	--	10.000	Chelating Agent
4.	Disodium Hydrogen Phosphate Dihydrate	BP	--	0.375	Buffering Agent
5.	Hydrochloric Acid	BP	--	q.s.	For pH adjustment
6.	Water for Injections	BP	q.s.	q.s. to 100 ml	Vehicle

3. Pharmaceutical form

Solution for Infusion.

A clear, colourless solution.

The pH of the solution between 4.5 to 6.5.

4. Clinical particulars

4.1. Therapeutic indications

Paracetamol Infusion 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.

4.2. Posology and method of administration

For Intravenous use.

The 50 ml solution is used in newborn infants, infants, toddlers and children weighing less than 33kg.

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

Dosing based on patient weight.

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of paracetamol infusion (10 mg/ml) per administration based on upper weight limits of group (ml)**	**Maximum Daily Dose**
≤10 kg	7.5 mg/kg	0.75 ml/kg	7.5ml	30 mg/kg
> 10 kg to ≤33kg	15 mg/kg	1.5ml/kg	49.5ml	60mg/kg not

				exceeding 2g
> 33 kg to ≤50kg	15 mg/kg	1.5ml/kg	75 ml	60mg/kg not exceeding 3g
>50kg with additional risk factors for hepatotoxicity	1g	100ml	100ml	3g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100ml	100ml	4g

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.

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

The maximum daily dose must not exceed 3

g. Method of administration

Take care when prescribing and administering paracetamol infusion, 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.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to propacetamol hydrochloride (prodrug of paracetamol).

In cases of severe hepatocellular insufficiency.

4.4. Special warnings and special precautions for use Warnings

Take care to avoid dosing errors due to confusion between milligram (mg) and millilitre (ml), which result in accidental overdose and death.

It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration 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 those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of drug administration with a peak seen usually after 4-6 days. Treatment with antidote should be given as soon as possible.

Text for the 100ml bottle:

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion.

Precautions for use

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance ≤30 ml/min).
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration.
- This medicine contains less than 1 mmol sodium (23 mg) per 50ml vial and 100ml vial, that is to say essentially 'sodium-free'.

4.5. Interaction with other FPPs and other forms of interaction

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.

- Salicylamide may prolong the elimination t½ of paracetamol.
- Caution should be taken with the concomitant intake of enzyme-inducing substances. 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.

4.6. Use in Pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, 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.

Breast-feeding

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol 10 mg/ml Infusion may be used in breast-feeding women.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

As with all paracetamol products, adverse drug reactions are rare or very rare. They are described below:

Blood and lymphatic system disorders

Thrombocytopenia, leucopenia, neutropenia *Vascular disorders*

Hypotension

Hepatobiliary disorders

Increased levels of hepatic transaminases

Skin and subcutaneous tissue disorders

Serious skin reactions

General disorders and administration site conditions

Malaise, Hypersensitivity reaction

4.9. 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 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.

Emergency measures

Immediate hospitalisation.

Before beginning treatment, take a blood sample 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 return of normal liver function. In very severe cases, however, liver transplantation may be necessary.

5. Pharmacological properties

1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics and antipyretics, ATC Code: N02BE01

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

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

2. Pharmacokinetic properties Adults

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 500mg and 1 g of Paracetamol 10 mg/ml Solution for Infusion is similar to that observed following infusion of 1g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol Infusion is about 15µg/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 1g paracetamol, significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the cerebrospinal fluid at and after the 20th minute following infusion.

Biotransformation

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulfuric 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 within 24 hours, mainly as glucuronide (60-80%) and sulfate (20-30%) 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 i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulfate conjugates than adults.

Special populations 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 sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours.

Elderly subjects

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

3. Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of Paracetamol Infusion in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. Pharmaceutical particulars

6.1. List of excipients

Mannitol

Disodium Edetate

Disodium Hydrogen Phosphate Dihydrate

Hydrochloric Acid

Water for Injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except for dilution with 0.9% sodium chloride or 5% glucose solution.

6.3 Shelf life

24 months from date of manufacture.

6.4. Special precautions for storage

Store below 30°C. Protect from light & heat. Do not freeze.

5. Nature and contents of container

100 ml LDPE bottle packed in a poly pouch in a unit carton along with package insert.

6. Special precautions for disposal and other handling

Before administration, the product should be visually inspected for any particulate matter and discolouration. For single use only. Any unused solution should be discarded.
Keep the medicine out of reach of children.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Manufactured By:

R. K. Laboratories Pvt. Ltd.

V.P.O. – Manpura, Tehsil- Nalagarh,

Distt.- Solan (Himachal Pradesh)-174101 India.

8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0247

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

19th July, 2022

10. DATE OF REVISION OF THE TEXT