1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name: Paracetamol Infusion (10mg/ml) – Feverach

1.2 Strength: 10mg/ml

1.3 Pharmaceutical Dosage Form: Solution for infusion

2. QUALITATIVE AND QUANTITATIVE DECLARATION

Qualitative Composition:

Each ml contains

Paracetamol BP

Water for Injections BP

Quantitative Composition:

Each ml contains

Paracetamol BP 10 mg

Water for Injections BP q.s.

3. PHARMACEUTICAL FORM

Pharmaceutical form: Solution for infusion

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:

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

Patient weight	Dose per	Volume per	Maximum volume	Maximum Daily

	administration	**administration**	**of paracetamol, solution for infusion (10 mg/mL) per administration based on upper weight limits of group (mL)*** **	**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

Pre-term newborn infants: No safety and efficacy data are available for pre-term newborn infants

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.

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.

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:

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

Patients weighing ≤ 10 kg

- The glass bottle of Paracetamol infusion should not be hung as an infusion due to the small volume of the medicinal product to be administered in this population
- A 5 or 10 ml syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume. However, this should never exceed 7.5ml per dose
- The user should be referred to the product information for dosing guidelines.

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 bottle, 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 perfusion applies particularly for central route infusion, in order to avoid air embolism.

4.3 Contraindications:

• in patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients.

• in cases of severe hepatocellular insufficiency.

4.4 Special Warning and Precautions for use:

Warnings

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 may 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 drug administration with a peak seen usually after 4 - 6 days. Treatment with antidote should be given as soon as possible.

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 gluthatione),
- dehydration.

4.5 Interaction with other Medicinal Products 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 Fertility, Pregnancy and Lactation:

Pregnancy:

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. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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.

Nevertheless, Paracetamol Infusion 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 Infusion may be used in breast-feeding women.

4.7 Side Effects:

The frequency of adverse events listed below is defined using the following convention:

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).

Organ System	**Rare**	**Very rare**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Skin and subcutaneous		Very rare cases of serious skin

tissue disorders		reactions have been reported.
Platelet/blood		Thrombocytopenia Leucopenia, Neutropenia

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.8 Overdose:

There is a risk of poisoning, 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

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group : other 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 10 mg/ml Solution for 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 10 mg/ml Solution for Infusion reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

5.2 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 10 mg/ml Solution for 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 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the cerebrospinal fluid at and after the 20th minute following infusion.

Metabolism:

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 within 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.

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 sulphate conjugates than adults.

Table - Age related pharmacokinetic values (standardised clearance, *CLstd/Foral (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 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

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 sulphate 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 (see section 4.2. 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.

5.3 Preclinical Safety Data:

Nonclinical data reveal no special hazard for humans based on studies of safety Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of Paracetamol 10 mg/ml Solution for Infusion in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Sodium Metabisulphite
Di sodium Edetate
Disodium Hydrogen Phosphate Dihydrate
Mannitol,
Citric acid monohydrate,
Sodium hydroxide
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

6.4 Special Precautions for Storage:

Store below 30 C, Do not refrigerate or freeze. Protect from light. Keep out of reach of children

6.5 Nature and Contents of Container:

The product is packed in 100 ml clear glass bottle USP Type-II closed with 32 mm grey butyl rubber stopper with lock and 32 mm blue color flip off seal.

6.6 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.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Aculife Healthcare Pvt. Ltd.

8. MARKETING AUTHORIZATION NUMBER

G/28D/LVP/8