Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

BRAVEMOL INTRAVENOUS INFUSION
Paracetamol Injection 10mg/ml

2. Qualitative and quantitative composition

Each ml contains:
Paracetamol BP.....1gm

Excipients of known effect: Mannitol

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for infusion.
A clear colourless solution

4. Clinical particulars

4.1 Therapeutic indications

Bravemol Intravenous Infusion is indicated for:

- 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.

4.2 Posology and method of administration

Intravenous use.
The 100 ml bag is restricted to adults, adolescents and children weighing more than 33 kg The 50 ml bottle is restricted to toddlers and children weighing more than 10 kg and up to 33 kg.
The 10 ml ampoule is restricted to term newborn infants, infants and toddlers weighing up to 10 kg.
Posology
The dose to be administered and the bottle size to be used depend exclusively on the patient`s weight. The volume to be administered must not exceed the determined dose. If applicable the desired volume must be diluted in a suitable solution for infusion prior to administration or a syringe driver must be used.
Dosing based on patient weight (please see the dosing table here below)

10 ml ampoule				
Patient weight	Dose pe administration	Volume pe administration	Maximum volume o Paracetamol (10mg/ml per administration base on upper weight limits o group (ml)***	Maximum daily dose

≤ 10 kg*	7.5 ml/kg	0.75 ml/kg	7.5 ml	30 mg/kg

50ml bottle				
Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol (10mg/ml) per administration based on upper weight limits of group (ml)***	Maximum daily dose
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 mg/kg	49.5 ml	60 mg/kg not exceeding 2 g

100 ml bottle				
Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol (10mg/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 3g
> 50 kg with additional risk factors for hepatotoxicity	1g	100 ml	100 ml	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1g	100 ml	100 ml	4 g

*** Preterm newborn infants:**
No safety and efficacy data are available for premature newborn infants
**** 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.
The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours.
No more than 4 doses to be given in 24 hours.
Severe renal insufficiency:
It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), to reduce the dose and increase the minimum interval between each administration to 6 hours.
Adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:
The maximum daily dose must not exceed 3000 mg.

Method of administration
Intravenous use.
The paracetamol solution is administered as a 15-minute intravenous infusion.

4.3 Contraindications

- Hypersensitivity to paracetamol, propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients.
- Cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. It is recommended that a suitable analgesic oral treatment will 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. The dose may require adjustment.
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.
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
- patients suffering from a genetically caused G-6-PD deficiency (favism), the occurrence of a haemolytic anaemia is possible due to the reduced allocation of glutathione following the administration of paracetamol.

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 container , i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

- **Probenecid** causes an almost two-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 half-life of paracetamol.
- Caution should be taken with the concomitant intake of **enzyme-inducing substances**.
- Concomitant use of paracetamol (4 000 mg 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.

4.6 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.

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.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

As with all paracetamol products, adverse drug reactions are rare (≥ 1/10 000 to <1/1 000) or very rare (<1/10 000). They are described below:

System Organ Class		Rare (≥ 1/10000 to <1/1000)	**Very rare** (<1/10000)	**Not known** (cannot be estimated from the available data)
Blood and lymphatic system disorders		---	Thrombocytopenia, Leucopenia, Neutropenia	---
Immune system disorders		---	Hypersensitivity reaction (1, 3)	---
Cardiac disorders		---	---	Tachycardia (2)
Vascular disorders		Hypotension	---	Flushing (2)

Hepatobiliary disorders		Increased levels of hepatic transaminases	---	---
Skin and subcutaneous tissue disorders		---	serious skin reactions (3)	Pruritus (2), Erythema (2)
General disorders and administration site conditions		Malaise	---	---

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

(2) Isolated cases

(3) Very rare cases of serious skin reactions have been reported.

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

Symptoms

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. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.

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 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 intravenous 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 restitution 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

Mechanism of action

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

Pharmacodynamic effect

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 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 intravenous administration of a single dose and after repeated administration during 24 hours.
The bioavailability of paracetamol following infusion of 500 mg and 1 g paracetamol 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 (C_{max}) of paracetamol observed after intravenous infusion of 500 mg and 1 g paracetamol over 15 minutes is approximately 15 µg/ml and 30 µg/ml respectively.

Distribution

The volume of distribution for paracetamol is approximately 1 L/kg.
Paracetamol does not bind extensively to plasma proteins.
Following infusion of 1 g paracetamol, significant concentrations of paracetamol (approximately 1.5 µg/mL) were observed in cerebrospinal fluid after 20 minutes post-infusion.

Metabolism

Paracetamol is mainly metabolised in the liver via two main hepatic pathways: glucuronic acid conjugation and sulfuric acid conjugation. The latter route is rapidly saturable at doses exceeding 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 via 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. The plasma half-life is 2.7 hours and total body clearance is 18 L/h

Newborns, 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, which is slightly shorter (1.5 to 2 h) than in adults. In new-borns, the plasma half-life is longer than in infants at around 3.5 hours. Newborns, infants and children up to 10 years excrete significantly less glucuronide and more sulfate conjugates than adults. Total excretion of paracetamol and its metabolites is the same for all ages.

*Table. Age related pharmacokinetic values (standardized clearance,*CLstd/Foral (l.h-1 70 kg 1), are presented below.*

Age	*Weight (kg)*	*CLstd/Foral ($l.h^{-1}$ 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*

*CLstd is the population estimate for CL

Special populations:

Renal insufficiency

In cases of severe renal insufficiency (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. The elimination rate for the glucuronide and sulphate conjugates is three-times slower in subjects with severe renal insufficiency than in healthy subjects. Therefore, when paracetamol is administered to patients with severe renal insufficiency (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours.

Elderly patients

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

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.
Studies on local tolerance of paracetamol in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been confirmed in guinea pigs.

6. Pharmaceutical Particulars

6.1 List of Excipients

1.	Cysteine Hydrochloric Monohydrate	BP
2.	Disodium Phosphate Dehydrate	BP
3.	Mannitol	BP
4.	Sodium metabisulphite	BP
5.	*Sodium Hydroxide	BP
6.	* Hydrochloric Acid	BP
7.	Activated charcoal	BP
8.	Water for Injection	BP

6.2 Incompatibilities

It should not be mixed with other medicinal products.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store at a temperature below 30°C. Protect from light. Do not freeze.

6.5 Nature and Content of container

A clear colourless solution filled and sealed in 100 ml USP Type 1 Flint Glass Vial.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

PHARMA SPECIALITIES LIMITED

8. Marketing Authorization Number

H2015/CTD2537/149/R1

9. Date of first authorization/renewal of the authorization

2025 September 15

10. Date of revision of the text

2025 September 15