1. **Name of the medicinal product**

Bramol Infusion

2. **Qualitative and quantitative composition**

Bramol Infusion

Each 100ml contains:
Paracetamol------1000mg

For a full list of excipients, see section 6.1

3. **Pharmaceutical form**

Solution for infusion.
The solution is clear, colorless to almost colorless.

4. **Clinical particulars**

4.1 Therapeutic indications

Bramol 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

Intravenous use.
The 50 ml vial is restricted to term 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.

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of paracetamol, solution for 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	1 g	100mL	100mL	4g

hepatotoxicity				

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

*** Pre-term newborn infants:** No safety and efficacy data are available for pre-term newborn infants (see section 5.2).

****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.

Method of Administration

Take care when prescribing and administering paracetamol, solution for infusion. ensuring the proper dose is communicated and dispensed. Take care to ensure the dose is measured and administered accurately.

Method of administration

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

Patients weighing ≤ 10 kg:

• The glass vial/bag of paracetamol, solution for infusion, should not be hung as an infusion due to the small volume of the medicinal product to be administered in this population

• The volume to be administered should be withdrawn from the vial/bag and diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume paracetamol, solution for infusion, into nine volumes diluent) and administered over 15 minute

• 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

4.3 Contraindications

• in patients with hypersensitivity to paracetamol or to any of the excipients.

• in cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Warnings

RISK OF MEDICATION ERRORS

Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death (see section 4.2).

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 no other medicines containing paracetamol are administered at the same time.

Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage are not usually seen until two days, and up to a maximum of 4-6 days, after administration. Treatment with antidote should be given as soon as possible (See section 4.9 Overdose).

This medicinal product contains 4.32mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Precautions for use

Paracetamol should be used with caution in cases of :

• hepatocellular insufficiency,

• severe renal insufficiency (creatinine clearance ≤30 mL/min) (see sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties),

• chronic alcoholism,

• chronic malnutrition (low reserves of hepatic glutathione),

• 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 (see section 4.9 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Clinical experience of the intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects in pregnancy or on the health of the foetus / newborn infant.

Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.

No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not show any malformation or foetotoxic effects.

Nevertheless, Paracetamol 10 mg/ml Solution for 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 10 mg/ml Solution for Infusion may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

Organ System	**Rare**	**Very rare**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic	

	transaminases	
Skin and subcutaneous tissue disorders		Very rare cases of serious skin reactions have been reported.
Platelet/blood		Thrombocytopenia Leucopenia, Neutropenia

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).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 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

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

Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Hydrochloric acid 1M (for pH-adjustment)
Mannitol
Sodium hydroxide 1M (for pH-adjustment)
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 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.

6.4 Special precautions for storage

Store below 30°C. away from light. Do not refrigerate or freeze.

6.5 Nature and contents of container

100ml amber glass USP type II vial sealed with rubber stopper and flip off seal, further packed in bleach board carton with hanger, envelop and insert.

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 authorisation holder

Brookes Pharma (Private) Limited

58-59, Sector No. 15, Korangi Industrial

Area, Karachi-749008.

Marketing authorisation number(s)

089175

9. Date of first authorisation/renewal of the authorisation

25/06/2018