1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Injection 1g/100ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg paracetamol
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Infusion

4. Clinical particulars

4.1 Therapeutic indications

Paracetamol injection 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 adapted 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.
Posology
Dosing based on patient weight (please see the dosing table here below)

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	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	75ml	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 (see section 5.2).
**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 (See section 5.2).
In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:
The maximum daily dose must not exceed 3 g.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

RISK OF MEDICATION ERRORS
Take care to avoid dosing errors due to confusion between milligram (mg) and millilitre (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 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 (See section 4.9). Text for the 50ml and 100ml vials:
As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see section 4.2).
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 and 5.2),
• 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 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).
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 Pregnancy and Lactation

Ask a health professional before use.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable 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).
Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).
Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.
Cases of erythema, flushing, pruritus and tachycardia have been reported.
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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics 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.
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 (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
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Cysteine hydrochloride monohydrate

Disodium phosphate dihydrate

Mannitol

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. Protect from light. Store in the original package. Do not refrigerate or freeze.

6.5 Nature and contents of container

No.	Items	Remarks
1	Glass bottle	Primary packing material
2	Halogenation butyl rubber stopper	Primary packing material
3	Aluminium-plastic cap	Secondary packing material
4	Label	Secondary packing material
5	Package insert	Secondary packing material
6	Paper carton	Secondary packing material

100ml/bottle, 1bottle/box

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

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