

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 10 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 10 mg paracetamol.

Each vial of 50 ml contains 500 mg paracetamol.

Each vial of 100 ml contains 1000 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear, colourless to slightly yellowish and free from visible particles.

Osmolality 270 to 310 mOsm/kg

pH: 4.5 – 6.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol 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.

Newborn infants, infants, toddlers and children (less than or equal to 33 kg)

Use 50 ml fill vial.

Adults, adolescents and children (above 33 kg)

Use 100 ml fill vial.

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 (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 ≤33 kg	15 mg/kg	1.5 mL/kg	49.5mL	60 mg/kg not exceeding 2g
> 33 kg to ≤50 kg	15 mg/kg	1.5 mL/kg	75 mL	60 mg/kg not exceeding 3g

Patient weight	Dose per administration	Volume per administration	Maximum volume per administration **	Maximum Daily Dose ***
>50 kg with additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	4 g

* **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 impairment 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.

Renal impairment:

In patients with renal impairment, the minimum interval between each administration should be modified according to the following schedule:

Creatinine clearance	Dosing interval
≥50 mL/min	4 hours
10-50 mL/min	6 hours
<10 mL/min	8 hours

Hepatic insufficiency

In patients with chronic or compensated active hepatic disease, hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration, Gilbert's syndrome, weighing less than 50 kg: The maximum daily dose must not exceed 3 g (see section 4.4).

Elderly Patients

No dose adjustment is usually required in geriatric patients.

Method of administration:

Take care when prescribing and administering Paracetamol to avoid dosing errors due to confusion between milligram (mg) and milliliter (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.

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

Patients weighing ≤ 10 kg:

- The glass vial of Paracetamol 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 and could be administered undiluted or diluted (from one to nine volumes diluent) in a 0.9% sodium chloride solution or 5% glucose solution and administered in 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. The volume administered to this weight group should never exceed 7.5ml per dose
- The user should refer to the dosage recommendations in the summary of product characteristics.

To remove solution, use a 0.8 mm needle (21gauge needle) must be use and the stopper vertically perforated at the spot specifically indicated.

As for all solutions for infusion presented in glass vials, 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.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Paracetamol is contraindicated:

- in patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- 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 milliliter (mL), which could result in accidental overdose and death (see section 4.2).
--

It is recommended to use a suitable analgesic oral treatment be used as soon as this administration route 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 the recommended entails 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 (See section 4.9).

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. that is to say essentially "sodium free".

Paracetamol can cause serious skin reactions. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity

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, Gilbert's syndrome,
- severe renal impairment (see sections 4.2 and 5.2),
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration.
- In 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.

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 of the paracetamol dose should be considered for concomitant treatment with probenecid,
- Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol,
- Caution should be paid to 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.
- 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 risk factors (see section 4.4).

4.6 Fertility, pregnancy and lactation**Pregnancy:**

Clinical experience of intravenous administration of paracetamol is limited.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals.

However, a large amount of data for oral use in 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 may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are rare ($>1/10000$, $<1/1000$) or very rare ($<1/10000$), they are described below:

Organ system	Rare $>1/10000$, $<1/1000$	Very rare $<1/10000$
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Platelet/blood		Thrombocytopenia, Leucopenia, Neutropenia.

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.

Very rare cases of serious skin reactions 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 HPRC Pharmacovigilance Website: www.hpra.ie

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, abdominal pain. Overdose, 7.5 g or more of paracetamol in a single administration in adults and 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 tube of blood 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 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 restitution of 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 effects

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 single administration and after repeated administration during 24 hours. The bioavailability of paracetamol following infusion of 500 mg and 1 g of 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 at the end of 15-minute intravenous infusion of 500 mg and 1 g of Paracetamol is about 15 micrograms/mL and 30 micrograms/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 micrograms/mL) were observed in the Cerebro Spinal Fluid as and from 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 in 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 (standardized clearance, *CL_{std}/F_{oral} (l.h⁻¹ 70 kg⁻¹), are presented below.

Age	Weight (kg)	CL _{std} /F _{oral} (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
-------------	----	------

*CL_{std} is the population estimate for CL

Special populations

Renal impairment

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, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance \leq 30 mL/min), to increase the minimum interval between each administration 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 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

Cysteine hydrochloride monohydrate (E920)
Disodium phosphate (E339)
Hydrochloric acid, concentrated (for pH adjustment) (E507)
Mannitol (E421)
Sodium hydroxide (for pH adjustment) (E524)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.
Chemical and physical in-use stability in the solutions listed in section 6.6 has been demonstrated for 48 hours at 20-25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not refrigerate or freeze.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml fill volume in 100 ml Type II clear glass vial with chlorobutyl rubber stopper and red color aluminium flip-off cap.
100 ml fill volume in 100 ml Type II clear glass vial with chlorobutyl rubber stopper and blue color aluminium flip-off cap.
Pack size: pack of 25 vials.

6.6 Special precautions for disposal and other handling

Use a 0.8 mm needle and vertically perforate the stopper at the spot specifically indicated.

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. Any unused solution should be discarded.

Paracetamol can be diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Paracetamol into nine volumes diluent). The diluted solution should be visually inspected and should not be used in presence of opalescence, visible particulate matters or precipitate.

No special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/049/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd December 2021

10 DATE OF REVISION OF THE TEXT

February 2023