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 50 ml bag contains 500 mg paracetamol.
Each 100 ml bag contains 1000 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear and slightly yellowish solution.

The solution is iso-osmotic and its pH is between 5.0 and 7.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol is indicated for:

- the short-term treatment of moderate pain, especially following surgery,
- 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 100 ml vial or bag is restricted to adults, adolescents and children weighing more than 33 kg.

The 50 ml vial or bag is restricted to term newborn infants, infants, toddlers and children weighing up to 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 10mg/ml solution for infusion per administration based on upper weight limits of group (mL)*** **	**Maximum Daily Dose****

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol 10mg/ml solution for infusion per administration based on upper weight limits of group (mL)***	Maximum Daily Dose**
≤ 10 kg*	7.5 mg/kg	0.75 mL/kg	7.5 mL	30 mg/kg
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 mL/kg	49.5 mL	60 mg/kg, not exceeding 2 g
> 33 kg to ≤ 50 kg	15 mg/kg	1.5 mL/kg	75 mL	60 mg/kg, not exceeding 3 g
> 50 kg and 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).
**__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 in patients with normal renal function (creatinine clearance ≥50 ml/min).

- The minimum interval between each administration in patients with severe renal insufficiency (creatinine clearance 10-50 ml/min) must be at least 6 hours.
- The minimum interval between each administration in patients with requiring haemodialysis (creatinine clearance <10 ml/min) must be at least 8 hours.
- The maximum daily dose must not exceed 3 g (see section 4.4) in adult patients with chronic or compensated active hepatic disease, hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration, Meulengracht Gilbert Syndrome, weighing less than 50 kg.
- No more than 4 doses to be given in 24 hours.

Method of administration:

Take care when prescribing and administering Paracetamol 10 mg/ml solution for infusion to avoid dosing errors due to confusion between milligram (mg) and millilitre (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. Take care to ensure the dose is measured and administered accurately.

For single use only. Any unused solution should be discarded.

Before administration, the product should be visually inspected for any particulate matter and discolouration.

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

Patient weighing ≤ 10 kg:

- The glass vial or bag of Paracetamol 10 mg/ml solution for infusion should not be hung as an infusion due to small volume of medicinal product to be administered in this population

- The volume to be administered should be withdrawn from the vial or bag and diluted in 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Paracetamol 10 mg/ml 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 7.5 mL per dose
- The user should be referred to the product information for dosing guidelines

For dilution of Paracetamol 10 mg/ml solution for infusion see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients
- Severe hepatocellular insufficiency (Child-Pugh >9)

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 millilitre (mL), which could result in accidental overdose and death (see section 4.2).

It is recommended to use a suitable analgesic oral treatment as soon as this route of administration is possible.

In order to avoid the risk of overdose, check that no other medicinal products administered do contain paracetamol or propacetamol hydrochloride.

Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of hepatic damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) 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).

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

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment, and sepsis or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin.

If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended.

The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

As for all solutions for infusion presented in vials or bags, close monitoring is needed notably at the end of the infusion to avoid air embolism (see section 6.6).

<u>Paracetamol should be used with particular caution under the following circumstances:</u>

- Abnormal Liver Function and Hepatocellular insufficiency (Child-Pugh ≤9)
- Hepatobiliary disorders
- Meulengracht Gilbert Syndrome (familial non-haemolytic jaundice)
- Severe renal insufficiency (creatinine clearance ≤30 ml/min), see sections 4.2 and 5.2
- Chronic alcohol abuse
- Chronic malnutrition (low reserves of hepatic glutathione)
- Total parenteral nutrition (TPN) use
- Use of enzyme inducers
- Use of hepatotoxic agents
- 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.
- Dehydration

Effects on laboratory tests

Paracetamol can affect tests for uric acid using phosphotungstic acid and blood sugar tests using glucose-oxidase-peroxidase.

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 half-life of paracetamol.
- The metabolism of paracetamol is impaired in patients taking enzyme-inducing medicinal products such as rifampicin, barbiturates, tricyclic antidepressants, isoniazid and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone).
- Isolated reports describe unexpected hepatotoxicity in patients taking alcohol or enzyme-inducing medicinal products (see section 4.9).
- Concurrent administration of paracetamol and chloramphenicol may prolong the action of chloramphenicol.
- Concurrent administration of paracetamol and AZT (zidovudine) enhances the tendency to neutropenia.
- Concurrent administration of paracetamol and oral contraceptives may reduce the elimination half-life of paracetamol.
- 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 due to pyroglutamic 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, However, a large amount of data from the use of oral therapeutic doses of paracetamol 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

Paracetamol Kabi has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following definition of frequency:

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 Frequency cannot be estimated from the available data

As with all paracetamol containing medicinal products, undesirable effects are rare or very rare. They are described in the following table:

System organ class	Common	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia, neutropenia, agranulocytosis	
Immune system disorders			Anaphylactic shock*, hypersensitivity reaction *), bronchospasm*	
Metabolism and nutrition disorders				High anion gap metabolic acidosis**
Cardiac disorders				Tachycardia
Vascular disorders		Hypotension		
Skin and subcutaneous tissue disorders			serious skin reactions***, rash*urticaria*	Erythema, flushing, pruritus
General disorders and administration site conditions	Administration site reaction (pain and burning sensation)	Malaise		
Investigations		Transaminases increased		

***** Very rare cases of hypersensitivity reactions in the form of anaphylactic shock, urticaria, skin rash have been reported and require discontinuation of treatment.
****** High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.
******* Very rare cases of serious skin reactions 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:
HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

At particular risk for hepatic damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are elderly patients, young children, patients with hepatic disorders, chronic alcoholism, chronic malnutrition and patients concurrently receiving medicinal products that lead to enzyme induction. In such cases, overdose may be fatal.

Symptoms of overdose
Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain.

Overdose with 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 paediatric patients, leads to hepatic cell necrosis, which can cause complete and irreversible necrosis and subsequently hepatocellular insufficiency, metabolic acidosis and encephalopathy. This, in turn, can lead to coma, sometimes with fatal outcome. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin in combination with decreased prothrombin levels are observed, which may occur 12 to 48 hours after administration.

Clinical symptoms of hepatic damage are usually evident after two days, and reach a maximum after 4 to 6 days.

Treatment of overdose

- Immediate hospitalisation
- Before initiating treatment, and as soon as possible following the overdose, a blood sample for determination of plasma paracetamol levels should be taken.
- The treatment includes administration of the antidote, N-acetylcysteine (NAC) either by the intravenous or the oral route, if possible during the first 10 hours. N-acetylcysteine can also offer some degree of protection even after 10 hours, but in this case prolonged treatment will be required.
- Symptomatic treatment
- Liver function tests must be carried out at the beginning of treatment and repeated every 24 hours. Usually hepatic transaminases return to normal in one to two weeks with full recovery of normal liver function. In very severe cases, however, liver transplantation may be necessary.
- Haemodialysis can reduce the plasma paracetamol concentration, but the effects are limited.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides, ATC code: N02BE01

The precise analgesic and antipyretic mode of action of paracetamol has not been established. A central and peripheral effect is likely.

Paracetamol provides onset of pain relief within 5 to 10 minutes following administration. The peak analgesic effect is obtained within 1 hour and analgesia usually persists 4 to 6 hours.

Paracetamol reduces fever within 30 minutes following administration. The antipyretic effect persists for at least 6 hours.

5.2 Pharmacokinetic properties

Adults

Absorption
Following single and repeated administration during 24 hours paracetamol pharmacokinetics is linear up to 2 g.

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 a 15-minute intravenous infusion of 500 mg and 1 g of paracetamol is about 15 microgram/ml and 30 microgram/ml, respectively.

Distribution
The volume of distribution of paracetamol is approximately 1 l/kg. Paracetamol is not extensively bound to plasma proteins (about 10 %). Twenty minutes following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 microgram/ml) were observed in the cerebrospinal fluid.

Biotransformation
Paracetamol is mainly metabolised in the liver following two major hepatic pathways: conjugation with glucuronic acid and sulphuric acid. At doses that exceed the therapeutic dose, the latter route is rapidly saturated. A small fraction (less than 4 %) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, with normal dosing, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, in the event of massive overdose, 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.

Newborn infants, 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 hours) than in adults. In newborn infants, the plasma half-life is longer than in infants, i.e. around 3.5 hours. Newborn infants, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table: Age related pharmacokinetic values (standardised clearance, *CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-1})

Age	**Weight (kg)**	**CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-1})**
40 weeks (age post conception)	3.3	5.9
3 months (age postnatal)	6	8.8
6 months (age postnatal)	7.5	11.1
1 year (age postnatal)	10	13.6
2 years (age postnatal)	12	15.6
5 years (age postnatal)	20	16.3
8 years (age postnatal)	25	16.3

*CL_{std} is the population estimate for CL

Special population

Renal insufficiency
In severe renal impairment (creatinine clearance 10-50 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 lower in subjects with severe renal impairment than in healthy subjects. Therefore, when giving paracetamol to patients with severe renal impairment (creatinine clearance 10-50 ml/min), the minimum interval between each administration should be increased to 6 hours (see section 4.2).

Elderly
The pharmacokinetics and metabolism of paracetamol are not altered in elderly. No dose adjustment is required in this patient 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 solution for infusion 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.

Paracetamol was found to be noncarcinogenic in male rats as well as in male and female mice. Equivocal evidence of carcinogenic activity was noted for female rats based on an increased incidence of mononuclear cell leukemia.

A comparative review of the literature on paracetamol genotoxicity and carcinogenicity showed that genotoxic effects of paracetamol appear only at dosages above the recommended range resulting in severe toxic effects including pronounced liver and bone marrow toxicity. The threshold level for genotoxicity is not reached at therapeutic dosages of paracetamol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cysteine
Mannitol (E421)
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

Bag before opening
24 months
After first opening
Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature.
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, unless opening and storage have taken place in controlled and validated aseptic conditions.
If diluted in sodium chloride 9 mg/ml (0.9 %) solution or 50 mg/ml glucose (5 %) solution, the solution should also be used immediately.
However, if the diluted solution is not used immediately, do not store for more than 6 hours (infusion time included).

6.4 Special precautions for storage

Do not refrigerate or freeze.

For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

10 ml Type I glass ampoules, colourless.
50 ml and 100 ml Type II glass vials closed with bromobutyl stoppers and aluminium/plastic flip-off caps.
50 ml and 100 ml bagswith the primary film, administration port (infusion port) and addition port (injection port) consisting of a polyolefin housing and a transparent and /or aluminium overpouch and containing an oxygen scavenger. The bags are closed with polyisoprene stoppers and polypropylene caps.

Pack sizes:
10 ampoules
1 vial
10 vials
12 vials
20 vials
20 bags
50 bags
60 bags

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling

As for all solutions for infusion presented in, vials or bags, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of infusion route. This monitoring at the end of the infusion applies particularly for central route infusions, in order to avoid air embolism.

Compatibility

Paracetamol 10 mg/ml solution for infusion can be diluted in sodium chloride 9 mg/ml (0.9 %) solution or 50 mg/ml glucose (5%) solution up to one tenth (one volume Paracetamol 10 mg/ml solution for infusion into nine volumes diluent).

The diluted solution should be visually inspected and should not be used in the presence of opalescence, visible particulate matter or precipitate.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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