SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol B. Braun 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution for infusion contains 10 mg paracetamol.

Each 10 ml ampoule contains 100 mg paracetamol
Each 50 ml bottle contains 500 mg paracetamol.
Each 100 ml bottle contains 1000 mg paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear and colourless to slightly pinkish-orangish. Perception may vary.
Theoretical Osmolarity 305 mOsm/l
pH 4.5 – 5.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol B. Braun 10 mg/ml 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

The 100 ml bottle 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 (see section 6.6) 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 per administration**	**Volume per administration**	**Maximum volume of Paracetamol B. Braun 10 mg/ml per administration based on upper weight limits of group (ml)*****	**Maximum <u>daily</u> dose****
≤ 10 kg*	7.5 mg/kg	0.75 ml/kg	7.5 ml	30 mg/kg

50 ml bottle

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol B. Braun 10 mg/ml per administration based on upper weight limits of group (ml)***	Maximum daily dose**
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 ml/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 B. Braun 10 mg/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 3 g
> 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

*Preterm newborn infants:
No safety and efficacy data are available for premature newborn infants (see also 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.

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 (See section 5.2).

Adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:
The maximum daily dose must not exceed 3000 mg (see section 4.4).

Method of administration

Take care when prescribing and administering Paracetamol B. Braun 10 mg/ml 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.

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

Patients weighing ≤10 kg:

- In case of non- availability of the 10 ml ampoule, the 50 ml bottle of Paracetamol B. Braun 10 mg/ml might be used but should not be hung as an infusion due to the small volume of the medicinal product to be administered in the population. The volume to be administered should be withdrawn from the ampoule and diluted in a sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution or a combination of both solutions up to one tenth (one volume Paracetamol B. Braun 10 mg/ml into nine volumes diluent) and administered over 15 minutes. See also section 6.6
- 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
- The user should be referred to the product information for dosing guidelines.

Paracetamol B. Braun 10 mg/ml can be diluted in a 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution or a combination of both solutions up to one tenth (one volume Paracetamol B. Braun 10 mg/ml into nine volumes diluent). In this case, use the diluted solution within the hour following its preparation (infusion time included).

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

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

Before administration, the product should be visually inspected for any particulate matter and discolouration. Only to be used if solution is clear, colourless or slightly pinkish-orangish (perception may vary) and the container and its closure are undamaged.

As for all solutions for infusion presented in containers with air space inside, 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 infusion applies particularly for central route infusions, in order to avoid air embolism.

4.3 Contraindications

- Hypersensitivity to paracetamol, propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients listed in section 6.1.
- 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).

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 (see section 4.2).

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, cyto-

lytic 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).

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
- 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.

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.

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** (see section 4.9).
- 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 due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, 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 B. Braun 10 mg/ml may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As with all paracetamol products, adverse drug reactions are rare (≥1/10000 to <1/1000) or very rare (<1/10000). 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 the lymphatic system disorders	-	Thrombocytopenia, Leucopenia, Neutropenia	-
Immune system disorders	-	Hypersensitivity reaction (1, 3)	-
Metabolism and nutrition disorders			High anion gap metabolic acidosis
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.

Description of selected adverse reactions
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.

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

Reporting 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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 10^{th} 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:
Analgesics; Other analgesics and antipyretics; Anilides
ATC Code: N02BE01

Mechanism of action

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

Pharmacodynamic effects

Paracetamol B. Braun 10 mg/ml 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 B. Braun 10 mg/ml 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 B. Braun 10 mg/ml is similar to that observed following infusion of 1 g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of Paracetamol B. Braun 10 mg/ml is about 15 µg/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 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.

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 h) 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} ($l \times h^{-1} \times 70\ kg^{-1}$)

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

pairment (creatinine clearance ≤ 30 ml/min), the minimum interval between each administration should be increased to 6 hours (see section 4.2).

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 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

Mannitol
Sodium citrate dihydrate
Acetic acid glacial (for pH adjustment)
Water for injections

6.2 Incompatibilities

Paracetamol B. Braun 10 mg/ml must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened:
The expiry date of the product is indicated on the packaging materials.

After first opening The infusion should commence immediately after connecting the container to the giving set.

After dilution
Chemical and physical in use stability (including infusion time) in the solutions listed in section 6.6 has been demonstrated for 48 hours at 23 °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.

6.4 Special precautions for storage

Store below 25 °C.

Keep the container in the outer carton in order to protect from light.

For storage conditions after first opening and after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottles of low-density polyethylene; contents: 50 ml, 100 ml
Ampoules of low-density polyethylene; content: 10 ml.
Pack size: 20 x 10 ml, 10 × 50 ml, 10 × 100 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Paracetamol B. Braun 10 mg/ml can be diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion or 50 mg/ml (5%) glucose solution for infusion or a combination of both solutions up to one tenth. For shelf life after dilution see section 6.3.

7. MANUFACURER

B.Braun Melsungen AG
Carl-Braun-Str.1, D-34212, Melsungen, Germany

8. REGISTRATION HOLDER

Lapidot Medical Import and Marketing Ltd.
8 Hashita street, Industrial park, Caesarea 3088900, ISRAEL

9. MARKETING AUTHORISATION NUMBER

153-65-34064-00

Revised in July 2025.