SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN:

Each 10 mL ampoule contains 100 mg paracetamol.

One mL of solution for infusion contains 10 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 PAEDIATRIC 100 mg B. BRAUN is indicated for term newborn infants, infants and toddlers weighing up to 10 kg for:

- the short-term treatment of mild to moderate pain e.g. following minor surgery
- the short-term treatment of fever, when the oral route is unsuitable.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN 10 ml ampoule is restricted to term newborn infants, infants and toddlers weighing up to 10 kg.

Unintentional overdose can lead to serious liver damage and death (see section 4.9). Healthcare providers are reminded that it is essential to follow both the weight-related dose recommendations and to consider individual patient minimum risk factors for hepatotoxicity, including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration (see section 4.2, Recommended dosage in patients with hepatic impairment).

DOSING IS BASED ON PATIENT WEIGHT

Maximum of 7,5 mg/kg of paracetamol per administration (i.e. 0,75 mL solution per kg) of PARACETAMOL PAEDIATRIC 100 mg B. BRAUN up to four times a day. The minimum interval between each administration must be at least 4 hours. The maximum daily dose must not exceed 30 mg/kg.

DOSING RECOMMENDATIONS ARE PRESENTED IN THE TABLE BELOW.

Patient weight (non - oedematous weight)	**Paracetamol dose (10 mg/ml) per administration**	**Minimum interval between each administration**	**Maximum daily dose***
10 ml ampoule			

≤ 10 kg**	7,5 mg/kg*** i.e. 0,75 ml solution per kg) up to 4 times a day	4 hours	≤ 30 mg/kg

* The maximum daily dose takes **into account all the medicines containing paracetamol.** **Preterm newborn infants: No safety and efficacy data are available for premature newborn infants (see also section 5.2)

***Patients weighing less will require smaller volumes.

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.

The dosage should be calculated on non-oedematous weight.

Recommended dosage in patients with renal impairment

It is recommended to leave a minimum interval of 6 hours between each administration in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see section 5.2).

Recommended dosage in patients with hepatic impairment

In patients with impaired hepatic function, the dose must be reduced or the dosing interval prolonged. The maximum daily dose should not exceed 30 mg/kg/day in the following situations:

- chronic or compensated active hepatic disease, especially those with mild to moderate hepatocellular insufficiency
- Gilbert's syndrome (familial hyperbilirubinaemia)
- chronic malnutrition (low reserves of hepatic glutathione)
- dehydration

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN is contraindicated in patients with severe hepatic impairment.

Method of administration

Take care when prescribing and administering PARACETAMOL PAEDIATRIC 100 mg B. BRAUN 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. Take care to ensure the dose is measured and administered accurately.

Intravenous use.

General

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN is to be administered as a 15-minute intravenous infusion.

Before administration, the product should be visually inspected for any particulate matter and discolouration. It is intended for single-use only. Once opened, the vial should be used immediately.

- Any unused solution should be discarded.
- PARACETAMOL PAEDIATRIC 100 mg B. BRAUN should not be mixed with other medicinal products.

Patients weighing 10 kg or less

- The volume to be administered should be withdrawn from the container 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 PAEDIATRIC 100 mg B. BRAUN into nine volumes diluent) and administered over 15 minutes (see section 6.6). Care must be taken to administer excessive fluid volumes of the diluent.

- The dose to be administered and the container 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.
- 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. **However, this should never exceed 7,5 mL per dose.**
- The user should be referred to the product information for dosing guidelines.

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

4.3 Contraindications

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN is contraindicated in:

- Known hypersensitivity to paracetamol or to paracetamol hydrochloride (pro-drug of paracetamol) or to any of the excipients listed in section 6.1.
- Cases of severe hepatocellular insufficiency or decompensated active liver disease.

4.4 Special warnings and precautions for use

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN Solution for Infusion contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

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).

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 proparacetamol. The dose may require adjustment (see section 4.2).

Doses of PARACETAMOL PAEDIATRIC 100 mg B. BRAUN in excess of 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 to 6 days. Treatment with antidote should be given as soon as possible (see section 4.9).

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN can cause serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions and use of the medicine should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia), (see section 4.2 and 5.2).
- Severe renal insufficiency (creatinine clearance ≤ 30 ml/ min) (see sections 4.2 and 5.2).
- Glucose 6 Phosphate Dehydrogenate (G6PD) deficiency (may lead to haemolytic anaemia).
- Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease should not use excessive quantities of PARACETAMOL PAEDIATRIC 100 mg B. BRAUN.

Use with caution in renal disease.

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN contains mannitol

Mannitol may have a mild laxative effect.

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per container, this is to say essentially 'sodium- free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on PARACETAMOL PAEDIATRIC 100 mg B. BRAUN

- *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, as contained in PARACETAMOL PAEDIATRIC 100 mg B. BRAUN.
- Caution should be paid to the concomitant use of PARACETAMOL PAEDIATRIC 100 mg B. BRAUN and enzyme-inducing substances as these substances increase the risk of paracetamol induced liver injury. These substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, and ethanol (see section 4.9).
- Phenytoin administered concomitantly with PARACETAMOL PAEDIATRIC 100 mg B. BRAUN may result in decreased paracetamol effectiveness and an increased risk of hepatotoxicity. Patients receiving phenytoin therapy should avoid large and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity.
- *Flucloxacillin* -caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with a risk factor for glutathione deficiency such as severe renal impairment, sepsis, malnutrition, and chronic alcoholism. Close monitoring is recommended in order to detect the appearance of acid base disorders, namely HAGMA, including the urinary 5-oxoproline.

Effect of PARACETAMOL PAEDIATRIC 100 mg B. BRAUN on other medicines

- PARACETAMOL PAEDIATRIC 100 mg B. BRAUN may increase the chance of unwanted effects when administered with other medicines.

- *Oral anticoagulants* - concomitant use of paracetamol, as in PARACETAMOL PAEDIATRIC 100 mg B. BRAUN, (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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not relevant

Breastfeeding

Not relevant

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Tabulated adverse reactions

System Organ Class	**Less frequent**	**Frequency not known** (cannot be estimated from the available data)
Blood and lymphatic system disorders	Thrombocytopenia, Agranulocytosis, Leucopenia, Pancytopenia, Neutropenia, Anaemia	—

Immune system disorders	Hypersensitivity reaction	Anaphylactic shock, Anaphylaxis, Angio-oedema
Cardiac disorders	—	Tachycardia
Vascular disorders	Hypotension	Flushing
Hepatobiliary disorders	Increased levels of hepatic transaminases, Hepatitis, Pancreatitis	—
Renal and urinary disorders	Renal colic, Renal failure, Sterile Pyuria	
Gastrointestinal disorders		Nausea, Vomiting
Skin and subcutaneous tissue disorders	Serious skin reactions	Pruritus, Erythema, Acute generalised exanthematous pustulosis, Toxic epidermal necrolysis, Stevens-Johnson syndrome
General disorders and administration site conditions	Malaise	Administration site reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://primaryreporting.who-umc.org/ZA.

4.9 Overdose

Prompt treatment is essential. In the event of an overdosage consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to PARACETAMOL PAEDIATRIC 100 mg B. BRAUN toxicity is increased in patients who have taken repeated high doses (greater than 5 - 10 g/day) of paracetamol for several days. 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, AIDS and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Overdosing may be fatal in these cases.

Symptoms

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.

Liver damage may become apparent 12 to 48 hours or later after administration, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time/INR. Liver damage may lead to encephalopathy, coma and death.

Overdose with a single administration of 7,5 g or more of paracetamol in adults or 140 mg/kg of body weight in children, causes cytolytic hepatitis likely to induce complete and irreversible hepatic necrosis, resulting in acute or fulminant hepatic failure, 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.

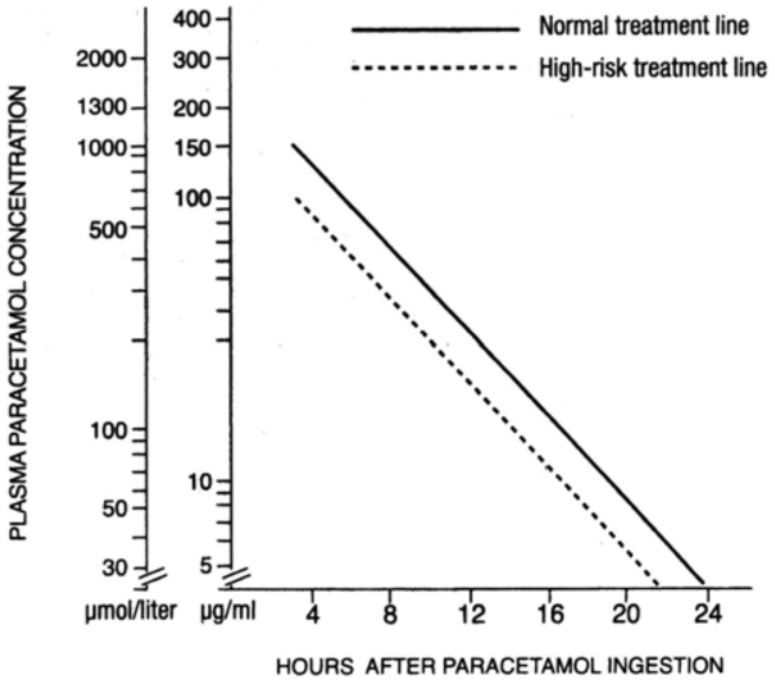
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment

Immediate hospitalisation.

Before beginning treatment, take a blood sample for plasma paracetamol assay, as soon as possible after the overdose.

N-acetylcysteine (NAC) should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage; although treatment up to 36 hours after ingestion may still be of benefit especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.** Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.



Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed.

Those whose plasma paracetamol levels are above the "normal treatment line", should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the "high risk treatment line". *(Refer to paracetamol nomogram above)*.

Prothrombin index correlates best with survival.

Monitor all patients with significant ingestion for at least 96 hours.

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. PHARMOCOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological classification: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

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 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 maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg of paracetamol is about 15 µg/ ml.

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.

Paediatric population:

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 new-born infants, the plasma half-life is longer than in infants i.e. around 3,5

hours. New-born 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 ≤ 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 to leave an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance ≤ 30 ml/ min), (see section 4.2).

Hepatic impairment:

Paracetamol should be used with caution in patients with mild to moderate liver impairment and is contraindicated when there is active disease, particularly alcoholic hepatitis because of

CYP 2E1 induction, which leads to increased formation of the hepatotoxic metabolite of paracetamol (see section 4.3).

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

Not applicable

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 PAEDIATRIC 100 mg B. BRAUN must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened:

24 months at 25 ºC.

After first opening

The infusion should commence immediately after dilution of the solution using suitable administration device

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 at or below 25 ºC. Do not refrigerate or freeze.

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

Ampoule of low-density polyethylene: 10 mL

Pack size: 20 x 10 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

PARACETAMOL PAEDIATRIC 100 mg B. BRAUN 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. HOLDER OF CERTIFICATE OF REGISTRATION

B. Braun Medical (Pty) Ltd,

253 Aintree Avenue

Hoogland Ext 41.

Northriding

Randburg, 2194

8. REGISTRATION NUMBER(S):

47/2.7/9001

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

23 August 2022

10. DATE OF REVISION OF THE TEXT

N/A