1. NAME OF THE MEDICINAL PRODUCT

Paracetamol – Fresenius 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 10 mg paracetamol.
Each 50 ml vial contains 500 mg paracetamol.
Each 100 ml vial contains 1000 mg paracetamol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravenous infusion.

4. CLINICAL DATA

4.1. Therapeutical Indications

Paracetamol – Fresenius 10 mg/ml 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 route.
The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg.
The 50 ml vial is adapted to term newborn infants, infants, toddlers and children weighing less 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 - Fresenius 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	7.5 mL	30 mg/kg
>10 kg to ≤33 kg	15 mg/kg	1.5 mL/kg	49.5 mL	60 mg/ kg, not exceeding 2g
>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	1 g	100 mL	100 mL	3 g

risk factors for hepatotoxicity				
>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. 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.**

*****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 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 3 g (See section 4.4).

Method of administration:

Take care when prescribing and administering Paracetamol – Fresenius 10 mg/ml 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.

The paracetamol solution is administered as a 15-minute intravenous infusion.
For single use only. Any unused solution should be discarded.

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

Paracetamol – Fresenius 10 mg/ml 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 - Fresenius 10 mg/ml into nine volumes diluent).

Patients weighing ≤10 kg:
· The glass vial of Paracetamol – Fresenius 10 mg/ml 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 over 15 minutes. Use the diluted solution within the hour following its preparation (infusion time included).
· 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.

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.

4.3. Contraindications

Paracetamol – Fresenius 10 mg/ml is contraindicated in patients with:

- Hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the product's excipients listed in section 6.1.
- Cases of severe hepatocellular insufficiency.

4.4. Special Warnings and Precautions during Administration

Warnings

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

❖ In order to avoid the risk of overdose, one should check that the other medicinal products administered along with Paracetamol – Fresenius 10 mg/ml do not contain paracetamol or propacetamol.

❖ Doses higher than the recommended ones entails risk for hepatic injury, including the risk of severe hepatotoxicity and death. Do not exceed the maximum recommended daily dose of paracetamol. Clinical symptoms and signs of liver damage 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 4.9 Overdose).

Precautions during Administration

❖ Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.
Anyone who develops a skin rash or reaction while using paracetamol should stop the drug and seek medical attention right away. Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.
Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

Precautions for use

Paracetamol should be used with caution in the following cases:

❖ Hepatocellular insufficiency, or active hepatic disease

❖ serious renal insufficiency (creatinine clearance ≤ 30 ml/min) (See 4.2 Dosage and Way of Administration and 5.2 Pharmacokinetic Properties)
❖ chronic alcoholism,
❖ chronic malnutrition (low levels of hepatic glutathione)
❖ Severe hypovolemia (e.g., due to dehydration or blood loss)

4.5. Drug Interactions 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 t1/2 of paracetamol.
❖ Caution should be paid to the concomitant intake of enzyme-inducing substances (See 4.9 Overdose).

Effects of other Substances on Paracetamol
Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of paracetamol and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of paracetamol.

Chronic oral paracetamol use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) values in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of Paracetamol – Fresenius 10 mg/ml in patients on oral anticoagulants, increased monitoring of INR values should be conducted in such circumstances.

4.6. Pregnancy and Lactation

Pregnancy:
Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant. Prospective data on pregnant women exposed to overdoses did not show an increase in malformation risk.
Reproductive studies with the intravenous form of paracetamol have not been performed in animals.
However, studies with the oral route did not show any malformation of foetotoxic effects.

Lactation:
After oral administration, paracetamol is excreted in small quantities into breast milk. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol – Fresenius 10 mg/ml may be used in breast-feeding women.

4.7. Effect on the ability to drive or use machinery
No such effect has been reported.

4.8. Adverse Reactions
As all paracetamol products, adverse reactions are rare (>1/10000 to <1/1000) or very rare (<1/10000). These are described below:

Organic system	**Rare (>1/10000 to <1/1000)**	**Very rare (<1/10000)**	**Isolated reports**
General disorders	Malaise	Hypersensitivity Reactions	
Cardiovascular disorders	Hypotension		
Hepatobiliary disorders	Increased levels of hepatic transaminas		
Blood and lymphatic system disorders			Thrombocytopenia Leucopenia Neutropenia

Very rare cases of hypersensitivity reactions ranging from dyspnoea, hypotension and skin rash or urticaria to anaphylactic shock have been reported. Clinical signs include swelling of the face, mouth and throat, respiratory distress, urticaria, rash and pruritis. Discontinue Paracetamol – Fresenius 10 mg/ml immediately if symptoms associated with allergy or hypersensitivity occur.
Isolated reports of thrombocytopenia have been observed.
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. 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/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9. Overdose
In acute paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma paracetamol levels > 300 mcg/ml at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/ml or < 37.5 mcg/ml at 12 hours after ingestion.
There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly patients and young children, patients with liver disease, in cases of chronic alcoholism, patients with chronic malnutrition and patients receiving enzyme inducers. Overdosing can be fatal in these cases.
Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, abdominal pain, diaphoresis, and general malaise.

Overdose of 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.

Emergency measures
- Immediate hospitalization.
- 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 IV 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 peak after 4 to 6 days and return to normal in one to two weeks, with full restitution of liver function. In very rare cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

Therapeutical Category: Analgesic and Antipyretic
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 – Fresenius 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 – Fresenius 10 mg/ml reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

5.2. Pharmacokinetic Properties
Adults:
Absorption:
The pharmacokinetic properties of paracetamol are linear up to 2 gr after a single administration and after repeated administration, during 24 hours.
The maximum plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 1 g paracetamol is approximately 30 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 gr paracetamol, significant concentrations of paracetamol (approx. 1.5 μg/ml) were observed in the cerebro spinal fluid, as and from the 20th minute following infusion.
Metabolism:

Paracetamol is metabolized 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 metabolized 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.
Mean plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Newborns, 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 neonates, the plasma half-life is longer than in infants, i.e. around 3.5 hours. Newborns, infants and children up to 10 years old excrete significantly less glucuronide and more sulphate conjugates than adults. Total excretion of paracetamol and its metabolites is the same for all ages.

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, 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 4.2 Posology and Method of Administration).
Elderly subjects:
The pharmacokinetic properties and the metabolism of paracetamol are not modified in elderly patients. No dose adjustment is required in this population.

5.3. Pre-clinical data relative to safety
Preclinical data reveal no special hazard for humans beyond the information included in other sections of this SPC.

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

Vial before opening

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

After first opening

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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 1 hour (infusion time included).

6.4 Special precautions for storage

Store below 25 ºC.

Do not refrigerate or freeze.

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

6.5 Nature and contents of container

50 ml and 100 ml Type II glass vials closed with halobutyl stoppers and aluminium/plastic flip-off caps.

Pack sizes:

1 vial
10 vials
12 vials
20 vials

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 glass vials, 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 – Fresenius 10 mg/ml 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 – Fresenius 10 mg/ml 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. MANUFACTURER
Fresenius Kabi Austria GmbH
Plant Graz, Hafnerstrasse 36 A-8055 Graz, Austria.
Or
Fresenius Kabi Germany GmbH
Plant Friedberg, Freseniusstrasse 1, D-61169
Friedberg, Germany.

8. MARKETING AUTHORISATION HOLDER
Neopharm (Israel) 1996 LTD Hashiloach 6,
POB 7063 Petach Tiqva 4917001

9. REGISTRATION NUMBER
153-99-34200

Revised in June 2022 according to MOHs guidelines