1. NAME OF THE MEDICINAL PRODUCT

Paracetamol – Fresenius 10 mg/ml

10 mg/ml solution for infusion.

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 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 - 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	15mg/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 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. 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 one of the excipients.
- In cases of severe hepatocellular insufficiency (Child-Pugh >9) or decompensated active liver disease.

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 milliliter (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 administration route is possible.

In order to avoid the risk of overdose, check that other medicines (including prescription and nonprescription) 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).

Paracetamol can cause serious skin reactions such as acute generalized 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 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:
- Abnormal Liver Function and Hepatocellular insufficiency (Child-Pugh ≤ 9).
- Hepatobiliary disorders.
- Meulengracht Gilbert Syndrome (familial non-hemolytic jaundice).
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min) (see sections 4.2 and 5.2).
- Chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day).
- anorexia, bulimia or cachexia.
- Chronic malnutrition (low reserves of hepatic gluthatione).
- 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 hemolytic anemia is possible due to the reduced allocation of glutathione following the administration of paracetamol.
- Dehydration, hypovolemia.

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 of the paracetamol dose should be considered for concomitant treatment with probenecid.
- Phenytoin administered concomitantly 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.
- Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol.
- The metabolism of paracetamol is impaired in patients taking enzyme-inducing medicinal products such as rifampicin, barbiturates, tricyclic antidepressants, 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.

4.6 Fertility, 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 pregnancies 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. Nevertheless, Paracetamol - Fresenius 10 mg/ml should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

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	Isolated reports[2]
General	Malaise	Hypersensitivity reaction	
Cardiovascular	Hypotension	Shock[2]	
Liver	Increased levels of hepatic transaminases		
Blood and the lymphatic system disorders[2]	Agranulocytosis, neutropenia[2]	Leucopenia Thrombocytopenia	
Neurological [2]		Neurological disorders[2]	Coma[2]
Renal/ Genitourinary[2]		Acute renal failure[2]	
Skin and subcutaneous tissue disorders[2]	Macular rash, injection site reaction[2] Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP)*	Maculopapular rash, pemphigoid reaction, pustular rash[2]	Lyell Syndrome[2]

* SJS, TEN and AGEP can be fatal and can occur with first-time use of Paracetamol or at any time while it is being taken.

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.
Post Market Adverse Effects for Propacetamol/ Paracetamol[2]

The following adverse events have also been reported during postmarketing surveillance, but incidence rate (frequency) is not known.

Organ System	Adverse Event
Blood and the lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Nausea Vomiting
General disorders and administration site conditions	Administration site reaction
Hepatobiliary disorders	Fulminant hepatitis Hepatic necrosis Hepatic failure Hepatic enzymes increased
Immune system disorders	Angioneurotic (Quincke's) edema Anaphylactic shock Anaphylaxis Hypersensitivity reactions (ranging from simple skin rash or urticaria to anaphylactic shock) have been reported and require the discontinuation of treatment
Skin and subcutaneous tissue disorders	Erythema, Flushing, Pruritus, Rash, Urticaria, Acute generalised exanthematous pustulosis

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

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 of overdose
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 i.v. 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.
- 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 mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Paracetamol 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 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 10 mg/ml 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 (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of Paracetamol 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 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 (standardised clearance, *CLstd/Foral
($l.h^{-1}$ 70 kg^{-1}).

Age	Weight (kg)	CLstd/Foral ($l.h^{-1}$ 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

*CLstd 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, it is recommended, when giving paracetamol to patients with severe renal impairment (see section 4.2), 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 (see section 4.2).

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 10 mg/ml in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

The effects of paracetamol in the diet of rats and mice was evaluated at 0, 600, 3000, and 6000 PPM for 2 years. 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

Vial before opening
24 months.

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

Medic-Trim Healthcare Ltd, Post Maabarot 4023000, Israel.

9. Registration numbers
153.99.34200.00 - 03

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in 6.2015.

מק"ט עלון: 160658010

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