Paracetamol Taro I.V. 10 mg/ml

Solution for Infusion
Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Taro I.V. 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg paracetamol.
One 50 ml vial contains 500 mg paracetamol.
One 100 ml vial contains 1000 mg paracetamol.

Excipients: Sodium 0.076 mg/ml
For a full list of excipients, see section 6.1 *List of excipients*.

3. PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear and colourless to slightly yellowish.

4. CLINICAL DATA

4.1 Therapeutical indications

Paracetamol Taro I.V. 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. As ready-to-use solution or after dilution.
Before administration, the product should be visually inspected for any particulate matter and discolouration. The content of one vial is for single use only.
The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg.
The 50 ml vial is restricted 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 Taro I.V. 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 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 *Pharmacokinetics properties*).
** **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 increase the minimum interval between each administration to 6 hours (See section 5.2 *Pharmacokinetics properties*).
In 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 *Special warnings and precautions during administration*).

Method of administration:

Take care when prescribing and administering **Paracetamol Taro I.V. 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.
Patients weighing ≤ 10 kg:

- The glass vial of **Paracetamol Taro I.V. 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 diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume **Paracetamol Taro I.V. 10 mg/ml** 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.

Text for the 50 ml and 100 ml vials:
To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.
Text for the 50 ml vial:
Paracetamol Taro I.V. 10 mg/ml of 50 ml vial can also be diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume **Paracetamol Taro I.V. 10 mg/ml** into nine volumes diluent). In this case, use the diluted solution within the hour following its preparation (infusion time included).
Text for the 50 ml and 100 ml vials:
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 Taro I.V. 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.
- Cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions during administration

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 *Posology and method of administration*).

- ❖ 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 medicines administered along with **Paracetamol Taro I.V. 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 - 6 days.
- ❖ Treatment with antidote should be given as soon as possible (See section 4.9 *Overdose*).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml of* Paracetamol Taro I.V. 10 mg/ml, *i.e. essentially "sodium free".

Text for the 50 ml and 100 ml vials:
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 *Posology and method of administration*).

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 cases of:

- Hepatocellular insufficiency, or active hepatic disease.
- Severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see sections 4.2 *Posology and method of administration* and 5.2 *Pharmacokinetic properties*).
- Chronic alcoholism.
- Chronic malnutrition (low reserves of hepatic gluthatione).
- 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 $t_{1/2}$ of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances (see section 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 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. Nevertheless, **Paracetamol Taro I.V. 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 in small quantities into breast milk. No undesirable effects on nursing infants have been reported. Consequently, **Paracetamol Taro I.V. 10 mg/ml** may be used in breast-feeding women.

4.7 Effects 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:

Organ system	Rare > 1/10000 to < 1/1000	Very rare < 1/10000	Isolated reports
General disorders	Malaise	Hypersensitivity reaction	
Cardiovascular disorders	Hypotension		
Hepatobiliary disorders	Increased levels of hepatic transaminases		
Blood and lymphatic system disorders			Thrombocytopenia Leucopenia Neutropenia

Very rare cases of hypersensitivity reactions ranging from dyspnea, 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 Taro I.V. 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 authorization 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

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 may 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 Taro I.V. 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 Taro I.V. 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 (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 1 gr 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 cerebrospinal 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 within 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 section 4.2 *Posology and method of administration*).

Elderly subjects:

The pharmacokinetic properties and the metabolism of paracetamol are not modified in elderly subjects. 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 the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

Diluted solution: chemical and physical in-use stability has been demonstrated for 1 hour at 25°C.

The diluted solution is for single use only. Any unused portion must be discarded after use.

Paracetamol Taro I.V. 10 mg/ml can be diluted in a 0.9% Sodium Chloride or 5% Glucose solution up to one tenth. In this case, store below 25°C and use the diluted solution within one hour following its preparation (infusion time included).

6.4 Special precautions for storage

Store below 25°C.

Store vials in the original carton in order to protect from light.

Do not refrigerate or freeze.

For storage conditions of the reconstituted, diluted medicinal product, see section 6.3 *Shelf life*.

6.5 Nature and Contents of Container

50 ml colourless type II glass vial closed with a bromobutyl stopper and sealed with an aluminium cap.

100 ml colourless type II glass vial closed with a bromobutyl stopper and sealed with an aluminium cap.

Pack size: pack of 10 vials.

6.6 Special precautions for disposal and other handling

Text for the 50 ml and 100 ml vials:

Use a 0.8 mm needle and vertically perforate the stopper at the spot specifically indicated.

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. Any unused solution should be discarded.

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

Any unused solution should be disposed of in accordance with local requirements.

7. MANUFACTURER:

Neogen N.V., Square Marie Curie, 20-1070 Anderlecht, Belgium.

8. LICENSE HOLDER:

Taro International Ltd., 14 Hakitor St., Haifa Bay Israel, 2624761.

9. REGISTRATION NUMBER

153.45.34119.00

The content of this leaflet was approved by the Ministry of Health in February 2015 and updated according to the guidelines of the Ministry of Health in December 2019.