

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralink 10mg/ml Solution for Infusion

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.

Excipient with known effect: Sodium 0.076 mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear, slightly yellowish.

pH 5.5

Osmolarity 295 mOsm/litre

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- 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 50 ml vial is restricted to term new-born infants, infants, toddlers and children weighing less than 33 kg.

The 100 ml vial is restricted to adults, adolescents and children weighing more 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 Paralink (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	7.5mL	30 mg/kg

> 10 kg to ≤33kg	15 mg/kg	1.5mL/kg	49.5mL	60mg/kg not exceeding 2g
> 33 kg to ≤50kg	15 mg/kg	1.5mL/kg	75 mL	60mg/kg not exceeding 3g
>50kg with additional risk factors for hepatotoxicity	1g	100mL	100mL	3g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100mL	100mL	4g

* **Pre-term newborn infants:** No safety and efficacy data are available for pre-term newborn infants (see 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.

Elderly patients:
Dose adjustment is not required in the elderly (see section 5.2).

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). In 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 PARALINK 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 Paralink 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 Paralink 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 7.5ml per dose
- The user should be referred to the product information for dosing guidelines.

Text for the 50ml and 100ml 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 50ml vial:

Paralink of 50ml vial can also be diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Paralink into nine volumes diluent) In this case, use the diluted solution within the hour following its preparation (infusion time included).

Text for the 50ml and 100ml 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.

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

For instruction on special precautions for disposal of the product, see section 6.6.

4.3 Contraindications

- Hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients listed in section 6.1.
- in 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 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 be used as soon as this route of administration is possible.

In order to avoid the risk of overdose, it should be checked that no other medicines administered contain either paracetamol or propacetamol.

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, cytolytic hepatitis) are not usually seen until two days, and up to a maximum of 4–6 days, after administration. 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.

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).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100ml, i.e. essentially 'sodium free'.

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 in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.
- Salicylamide may prolong the elimination t½ of paracetamol.
- Caution should be taken with the concomitant intake of enzyme-inducing substances (see section 4.9).

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 the intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects in pregnancy or on the health of the foetus / newborn infant.

Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.

No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not show any malformation or foetotoxic effects.

Nevertheless, Paralink 10 mg/ml Solution for Infusion 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, Paralink 10 mg/ml Solution for Infusion 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. As with all paracetamol products, adverse reactions are rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000). They are described below:

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, Leucopenia, Neutropenia.
Cardiac disorders	Rare	Hypotension
Hepatobiliary disorders	Rare	Increased levels of hepatic transaminases
General disorders and administration site conditions	Rare Very rare	Malaise Hypersensitivity reaction
Skin and subcutaneous tissue disorders	Very rare	Serious skin reactions

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.

Very rare cases of serious skin reactions have been reported

Cases of erythema, flushing and tachycardia have been reported.

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 generally appear within the first 24 hours and comprise of: 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.

Emergency measures

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 i.v. or oral route, if possible before the 10th 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 return to normal in one to two weeks with full restitution of 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

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

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 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 is similar to that observed following infusion of 1 g and 2 g propacetamol (containing 500 mg 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 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.

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. Plasma half-life is 2.7 hours and total body clearance is 18 l/h.

New-born 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 hours) 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.h⁻¹ 70kg⁻¹)

Age	Weight (kg)	CL _{std} /F _{oral} (l.h ⁻¹ 70kg ⁻¹)
40 weeks PCA	3.3	5.9
3 months PNA	6	8.8
6 months PNA	7.5	11.1
1 year PNA	10	13.6
2 years PNA	12	15.6
5 years PNA	20	16.3
8 years PNA	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, 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).

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

Preclinical 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Hydrochloric acid, 37% (for pH-adjustment)
Mannitol
Sodium hydroxide 4% (for pH-adjustment)
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

Shelf life after first opening of the container

Use immediately after opening

50ml vial:

If diluted in 0.9% sodium chloride or 5% glucose, the solution should also be used immediately. However, if the solution is not used immediately, do not store for more than 1 hour (infusion time included).

6.4 Special precautions for storage

Keep the vial in the original carton in order to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container

50 ml and 100 ml colourless type II glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium flip-off cap.

50 ml pack sizes 10 (10x1) vial.

100 ml pack size: 1 vial, 10 (10 x 1) vials

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Ricesteele Manufacturing Ltd
Cookstown Estate
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0095/007/011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th September 2012

10 DATE OF REVISION OF THE TEXT

December 2015