Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 10 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg paracetamol
One 50 ml vial contains 500 mg paracetamol.
One 100ml vial contains 1000 mg paracetamol.
Excipient with known effect: Sodium 0.076 mg/ml
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear, slightly yellowish and particle free.
pH 5.5
Osmolarity 295 mOsm/litre

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paracetamol 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

The 50 ml vial is restricted to term newborn 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

The dose to be administered and the bottle 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.
Dosing based on patient weight (please see the dosing table here below).

50ml vial

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of paracetamol, solution for infusion (10 mg/mL) per administration based on upper weight limits of**	**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

100ml vial

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of**	**Maximum Daily Dose**

			paracetamol, solution for infusion (10 mg/mL) per administration based on upper weight limits of group (mL)* **	**
> 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.

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).

Hepatocellular insufficiency:
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).

Method of administration:

Take care when prescribing and administering paracetamol, solution for infusion, to avoid dosing errors due to confusion between milligram (mg) and millilitre (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.
The paracetamol solution is administered as a 15-minute intravenous infusion.

Patients weighing ≤ 10 kg:

- The glass vial/bag of Paracetamol 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 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution or a combination of both solutions up to a maximum dilution of one tenth (one volume Paracetamol into nine volumes diluent) and administered over 15 minute. See also section 6.6.
- 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.

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:

Paracetamol of 50ml vial can also be diluted in a 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution or a combination of both solutions up to a maximum dilution of one tenth (one volume Paracetamol into nine volumes diluent) In this case, use the diluted solution within hours following its preparation (infusion time included).

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

For single use only. Any unused solution should be discarded.

Before administration, the product should be visually inspected for any particulate matter and discolouration. Only to be used if solution is clear, colourless or slightly yellowish (perception may vary) and the container and it's closure are undamaged.

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 infusion applies particularly for central route infusions, in order to avoid air embolism.

4.3 Contraindications

Paracetamol is contraindicated:
- in patients with 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

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).

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. The dose may require adjustment (see section 4.2)

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).

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

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:
- 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.
- patients suffering from a genetically caused G-6-PD deficiency (favism), the occurrence of a haemolytic anaemia is possible due to the reduced allocation of glutathione following the administration of paracetamol.

In patients with depleted glutathione status such as sepsis, malnourishment, alcohol abuse, renal and hepatic disorders, the use of paracetamol can increase the risk of liver failure and/or metabolic acidosis (see section 4.2).

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

4.5 Interaction with other medicinal products and other forms of interactions

- 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.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin
  as concurrent intake has been associated with high anion gap metabolic acidosis,
  especially in patients with risks factors (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy:
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity.
Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Clinical experience of the intravenous administration of paracetamol is limited.
No reproductive studies with the intravenous form of paracetamol have been performed in animals.

Lactation:
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol 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 with all paracetamol products, adverse reactions are rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data). They are described below:

Organ system	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not know (cannot be estimated from the available data)
Blood and lymphatic system disorders		Thrombocytopenia, Leucopenia, Neutropenia.	
Immune system disorders		Hypersensitivity reaction (1)	
Cardiac disorders			Tachycardia (2)
Vascular disorders	Hypotension		Flushing (2)
Hepatobiliary disorders	Increased levels of hepatic transaminases		
Skin and subcutaneous disorders		Serious skin reactions (3)	Pruritus (2) Erythema (2)
General disorders and administration site conditions	Malaise		

1. Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment
2. Isolated cases
3. Very rare cases of serious skin reactions have been reported

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitroing of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance.
Website: www.hpra.ie

4.9 Overdose

Symptoms
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.

Treatment

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.

Use of acetylcysteine is also beneficial in the treatment of paracetamol-induced metabolic acidosis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 yet 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 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 1g 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.

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.

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} ($l.h^{-1}$ 70 kg^{-1})

Age	**Weight (kg)**	**CL_{std} /F_{oral} ($l.h^{-1}$ 70 kg^{-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

Non-clinical 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.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for dilution with 0.9% sodium chloride solution or 5% glucose solution.

6.3 Shelf life

Unopened: 2 years
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.

For the 50 ml vial:
Chemical and physical in-use stability of the product after dilution in 9 mg/ml sodium chloride solution (0.9%) or 50 mg/ml glucose solution (5%) has been demonstrated for 4 hours (infusion time included) at 30°C.

6.4 Special precautions for storage

Store below 30°C.
Do not refrigerate or freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

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 cap.

Pack sizes
50 ml: 10 (10 x 1) vials
100 ml: 1 vial, 10 (10 x 1) or 12 (12 x 1) vials

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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

For single use only. Any unused solution should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/218/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010
Date of last renewal: 30th January 2013

10 DATE OF REVISION OF THE TEXT

May 2022