Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 10 mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for infusion contains 10 mg of paracetamol.
Each 10-mL bag of solution for infusion contains 100 mg paracetamol.
Each 50-mL bag of solution for infusion contains 500 mg paracetamol.
Each 100-mL bag of solution for infusion contains 1000 mg paracetamol.

Excipients with known effect:
Each 10-mL bag contains 25.2 mg, equivalent to 1.1 mmol of sodium.
Each 50-mL bag contains 126 mg, equivalent to 5.5 mmol of sodium.
Each 100-mL bag contains 252 mg, equivalent to 11 mmol of sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear solution
Colourless to slightly yellowish or reddish coloured solution.
Osmolality: 270-310 mOsmol/kg
pH: 5.5-6.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol 10 mg/mL solution for infusion is indicated for the short-term treatment of moderate pain, particularly post-surgery pain, and for the short-term treatment of fever, when the intravenous route is clinically justified by the urgent need to treat pain or hyperthermia and/or when other routes of administration cannot be used.

Paracetamol 10 mg/mL solution for infusion in 10-mL bag is indicated in newborns at term, infants and children weighing less than or equal to 10 kg.
Paracetamol 10 mg/mL solution for infusion in 50-mL bag is indicated in infants and children weighing more than 10 kg and less than or equal to 33 kg.
Paracetamol 10 mg/mL solution for infusion in 100-mL bag is indicated in adults, adolescents and children weighing more than 33 kg.

4.2 Posology and method of administration

Posology:

Dosing based on patient weight.

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of Paracetamol 10 mg/mL per administration based on upper weight limits of group (mL)*** **	**Maximum daily dose****
10-mL bag				

≤ 10 kg*	7.5 mg/kg	0.75 mL/kg	7.5 mL	30 mg/kg
50-mL bag				
> 10 kg to ≤ 33 kg	15 mg/kg	1.5 mL/kg	49.5 mL	60 mg/kg not exceeding 2 g
100-mL bag				
> 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).

** **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.

Do not administer more than 4 doses per 24 hours.

Renal impairment

In patients with renal insufficiency, the minimum interval between each administration must be modified according to the following scheme**:**

Creatinine clearance	Administration interval
Clcr ≥ 50 mL/min	4 hours
Clcr 10-50 mL/min	6 hours
Clcr < 10 mL/min	8 hours

Hepatic impairment

In adult patients with chronic liver failure or compensated active liver disease, hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low hepatic glutathione reserves), dehydration, Gilbert's disease or weighing less than 50 kg, the maximum daily dose must not exceed 3 g (see section 4.4).

Older patients

Dose adjustment is not required in the elderly. However, it should be taken into account that renal and/or hepatic insufficiency is more common in patients above 65 years of age (see section 5.2).

Method of administration

Intravenous use.

Precautions to be taken before handling or administering the medicinal product (see section 6.6):

Take care when prescribing and administering <NAME OF THE PRODUCT> 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.

The paracetamol solution is administered as a 15-minutes intravenous infusion.
The paracetamol solution may be diluted in 0.9 % sodium chloride or 5 % glucose solution up to a factor of 10. In this case, the diluted solution must be used within 2 hours of its preparation (including the time required for infusion). For instructions on dilution of the product before administration, see section 6.6.

Patients weighing ≤ 10 kg (10-mL bag):

- The 10-mL bag must not be hung as an infusion due to the small volume of the medicinal product to be administered in this population.
- The 10-mL bag must not be used for direct infusion. The volume to be administered should be withdrawn from the bag and should be given as is or diluted (in a volume from 1 to 9) in a 0.9 % sodium chloride solution or 5 % glucose solution and administered over 15 minutes.
- 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.

4.3 Contraindications

- hypersensitivity to paracetamol or to propacetamol hydrochloride (paracetamol prodrug) or to any of the excipients listed in section 6.1.
- severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Special 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 oral analgesic treatment as soon as this route of administration is possible. In order to avoid the risk of overdose, check that other medicines administered do not contain either paracetamol or propacetamol. Doses higher than those recommended cause a risk of very severe liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are generally observed after 2 days following administration of treatment and usually peak after 4 to 6 days. Treatment with an antidote should be given as soon as possible (see section 4.9).

Hepatic disorders risk factors

Caution is advised in case of the following risk factors that may lower the threshold for liver toxicity. The dose should be adjusted and the maximum daily dose should not be exceeded in these patients:

- hepatocellular insufficiency, Gilbert disease
- severe renal insufficiency
- chronic alcoholism
- chronic malnutrition (low hepatic gluthatione reserves),
- dehydration,
- patients weighing less than 50kg
- deficiency in glucose-6-phosphatase dehydrogenase (which can cause hemolytic anemia)

Serious skin reactions

This medicinal product can cause serious skin reactions. Patients should be informed of the early signs of serious skin reactions and use of the drug should be discontinued at the first appearance of a rash or other sign of hypersensitivity.

Concomitant use with other medication

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Excipients with known effect
This medicinal product contains 25.2 mg of sodium per 10-mL bag, which is equivalent to 1.26 % of the WHO recommended maximum daily food intake of 2 g of sodium per adult.
This medicinal product contains 126 mg of sodium per 50-mL bag, which is equivalent to 6.3 % of the WHO recommended maximum daily food intake of 2 g of sodium per adult.
This medicinal product contains 252 mg of sodium per 100-mL bag, which is equivalent to 13 % of the WHO recommended maximum daily food intake of 2 g of sodium per adult.
The maximum daily dose of this product (corresponding for example to 4 bags of 100 mL) in an individual weighing more than 50 kg without additional risk factors for hepatotoxicity is equivalent to 50 % of the maximum daily dose recommended by the WHO for sodium.
This medicine is considered rich in sodium. This should be especially taken into account for those on a low-salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Precautions of use:

- Probenecide reduces the clearance of paracetamol by almost half inhibiting its conjugation to glucuronic acid. A reduction in the dose of paracetamol should be considered when combined with probenecide.
- Salicylamide may increase the elimination half-life of paracetamol.
- Particular care should be taken when taking enzyme inducers concomitantly. These substances include, but are not limited to, barbiturates, isoniazid, carbamazepine, rifampicin and ethanol (see section 4.9).
- The concomitant use of paracetamol (4 g per day for at least 4 days) and oral anticoagulants may lead to slight variations in INR. In this case, increased monitoring of INR is necessary during the period of concomitant use and one week after stopping paracetamol.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk 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.

Breast-feeding
Following oral administration, small quantities of paracetamol are excreted in breast milk. No adverse effects on infants have been reported. Paracetamol can therefore be used while breastfeeding.

4.7 Effects on ability to drive and use machines

Paracetamolhas no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

As with all medicinal products containing paracetamol, few side effects are expected at therapeutic doses. Adverse drug reactions are listed below by system organ class and frequency.
The frequency of undesirable effects is classified as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA-	**Rare > 1/10**	**Very rare < 1/10 000**	**Not known**

system organ class database	**000, < 1/1000**		
General disorders and administration site conditions	Malaise	Reaction at the administration site or even diffuse (pain and burningsensation)	
Skin and subcutaneous tissue disorders		Rash, urticaria, serious skin reactions*	Erythema, pruritus
Immune system disorders		Anaphylacticshock, hypersensitivity reaction*	
Cardiacdisorders			Tachycardia
Vascular disorders	Hypotension		Flushing
Hepatobiliary disorders	Increased levels of hepatic transaminases		
Blood and lymphatic system disorders		Thrombocytopenia, Leukopenia, Neutropenia	
Metabolism and nutrition disorders			High anion gap metabolic acidosis**

*Very rare cases of hypersensitivity reactions, serious skin reactions have been reported which require discontinuation of treatment.

**High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor and abdominal pain, or patients may be asymptomatic.
Overdose, from 7.5 g paracetamol as a single dose in adults and 140 mg/kg of body weight in a single dose in children, can cause hepatic cytolysis which can lead to complete and irreversible necrosis resulting in hepatocellular insufficiency, metabolic acidosis, encephalopathy which may lead to coma and death.
Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactacte dehydrogenase and bilirubin are observed with increased prothrombin levels that may appear 12 to 48 hours after administration.
Risk of liver damage:

- fulminant hepatitis,
- liver failure,
- cholestatic hepatitis,
- cytolytic hepatitis

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
Some patients may be at increased risk of liver damage from paracetamol toxicity:
Risk factors include:

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving liver enzyme inducers
- Patients suffering from chronic alcoholism
- Patients suffering from chronic malnutrition

Clinical symptoms of liver damage are generally observed after two days and reach a maximum after 4 to 6 days.

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency management

- Immediate hospitalization.
- Before starting treatment, take a sample of blood to measure paracetamol plasma, as soon as possible after the overdose, if possible 4 hours post ingestion in the case of a single acute overdose.
- Treatment of overdose includes administration of the antidote N-acetylcysteine (NAC) intravenously or orally, if possible before the tenth hour. NAC can, however, provide some protection even after 10 hours, but in this case, the treatment should be prolonged.
- Symptomatic treatment should be implemented.
- Liver tests should be done initially and repeated every 24 hours.

Usually, liver transaminases return to normal after one or two weeks, with complete recovery of liver function. However, in very severe cases, a liver transplant may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANALGESICS AND ANTIPYRETICS,
ATC code: N02BE01
Mechanism of action
The precise mechanisms underlying the analgesic and antipyretic properties of paracetamol still need to be established but may involve both central and peripheral actions.

Pharmacodynamic effects
This medicinal product starts to relieve pain within 5 to 10 minutes post-dose. The peak of the analgesic effect is achieved in 1 hour and usually lasts for 4 to 6 hours.
Paracetamol reduces fever within 30 minutes post-dose and the duration of the antipyretic effect is at least 6 hours.

5.2 Pharmacokinetic properties

IN ADULTS

Absorption :
The pharmacokinetics of paracetamol are linear up to 2 g as a single dose and after repeated administrations over 24 hours.
The bioavailability of paracetamol following the infusion of 500 mg and 1 g of paracetamol is similar to that observed following the infusion of 1 g and 2 g of propacetamol (containing 500 mg and 1 g of paracetamol, respectively).

The peak plasma concentrations (C_{max}) of paracetamol observed at the end of the 15-minute intravenous infusion of 500 mg and 1 g of Paracetamol are approximately 15 µg/mL and 30 µg/mL, respectively.

Distribution :
The volume of distribution of paracetamol is approximately 1 l/kg.
Paracetamol is poorly bound to plasma proteins.
Following the infusion of 1 g paracetamol, significant concentrations of paracetamol (of approximately 1.5 µg/mL) were recovered in the cerebrospinal fluid only 20 minutes post-infusion.

Biotransformation :
Paracetamol is mainly metabolised by the liver following two major hepatic pathways: glucuronide conjugation and sulphate conjugation. This latter pathway is rapidly saturable at doses higher than the therapeutic doses. A small proportion (less than 4 %) is converted by cytochrome P 450 into a reactive intermediary (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in the urine following conjugation with cysteine and mercaptopuric acid. However, in a context of massive poisoning, the quantity of this toxic metabolite is increased.

Elimination :
Most metabolites of paracetamol are excreted in the urine. 90 % of the administered dose is excreted in the urine within 24 hours, mainly in the glucuronide conjugated (60-80 %) and sulphate conjugated (20-30 %) forms.
Less than 5 % are excreted unchanged.
The plasma half-life is 2.7 hours and total body clearance is approximately 18 l/h.

FULL-TERM NEWBORNS, INFANTS AND CHILDREN

The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those obtained in adults, except for the plasma half-life which is slightly shorter (1.5-2 hours). In newborns, the plasma half-life is longer than in infants, i.e. around 3.5 hours. Newborns, infants and children up to 10 years of age excrete significantly fewer glucuronide conjugated derivatives and more sulphate conjugated derivatives than adults.

Table. Pharmacokinetic values as a function of age (standardised clearance CL^{std}/F^{oral} ($l.h^{-1}$ 70 kg^{-1}) are shown below.

Age	Weight (kg)	CL^{std}/F^{oral} (l.h-1 70 kg-1)
40 weeks of pregnancy	3.3	5.9
3 months	6	8.8
6 months	7.5	11.1
1 year	10	13.6
2 years	12	15.6
5 years	20	16.3
8 years	25	16.3

*$CL^{std}$is the estimated CL for the population.

SPECIAL POPULATION

Renal insufficiency
In patients with severe renal insufficiency (creatinine clearance: 10-30 mL/min), paracetamol excretion is slightly delayed, the elimination half-life ranging from 2 to 5.3 h. The excretion rates of glucuronide and sulphate conjugates is three times slower in patients with severe renal insufficiency than in healthy subjects.
It is recommended to increase the interval between doses in patients with renal insufficiency (see section 4.2).

Elderly
The pharmacokinetics and metabolism of paracetamol remain unchanged in the elderly. No dose adjustment is required in this patient population.

5.3 Preclinical safety data

Preclinical data have not indicated any specific risks other than those referred to in other sections of the SPC.
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.
Local safety studies in rats and rabbits demonstrated a good safety of Paracetamol 10 mg/ml Solution for Infusion.
The absence of delayed contact hypersensitivity was verified in guinea pigs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sodium hydroxide 1N (for pH adjustment)
Water for injections.

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products other than those mentioned in section 6.6.

6.3 Shelf life

2 years.
After opening the overwrapping: immediate use is recommended.
Chemical and physical in-use stability has been demonstrated for 24 hours at 15 °C to 25 °C.
After dilution, chemical and physical in-use stability of the solution diluted in 0.9 % sodium chloride or 5 % glucose has been demonstrated for 2 hours (including the infusion time).

From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze. For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10-ml overwrapped polyolefin bags equipped with a collection site.
50- and 100-ml overwrapped polyolefin bags equipped with an infusion site.
50- and 100-ml overwrapped polyolefin bags equipped with a collection site and an infusion site.
10-ml bags: boxes containing 1, 10, 15, 20 or 50 bags.
50-ml bags: boxes containing 1, 5, 10, 40, 45, 50 or 60 bags.
100-ml bags: boxes containing 1, 5, 10, 40, 45, 50 or 55 bags.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use in the paediatric population:
Precautions for handling in patients ≤ 10 kg: see section 4.2.

Handling instructions for healthcare professionals:

- The expiry date should be checked.
- Check that the bag has no leak, and discard any damaged or partially used bags, or, for 50- and 100-mL bags, those where the hanging hole is not opened.
- The overwrap should be removed from the bag after checking it is undamaged.
- Once opened, it should be used immediately.
- Before being administered, the product must be visually inspected to detect any particles.
- For single use only.
- Any unused solution must be discarded.
- The solution diluted in 0.9 % sodium chloride or 5 % glucose solution must be visually inspected again and should not be used if it is opalescent, or contains visible particles or a precipitate.

For 50- and 100-mL bags:
Do not vent and do not connect in series with other infusions.
The protection should be removed from the infusion site.

The infusion set should be connected to the bag.

7 MARKETING AUTHORISATION HOLDER

Laboratoire Aguettant
1 Rue Alexander Fleming
Lyon
69007
France

8 MARKETING AUTHORISATION NUMBER

PA1968/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2011

10 DATE OF REVISION OF THE TEXT

March 2025