Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 10 mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 10.00 mg for 1 ml of solution for infusion:
One 100-ml bag contains 1000 mg paracetamol.
One 50-ml bag contains 500 mg paracetamol.
One 10-ml bag contains 100 mg paracetamol.

Excipients-contains Sodium 2.52 mg/ml
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol is indicated in the short-term treatment of moderate pain, particularly post-surgery pain, and in 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.

4.2 Posology and method of administration

Intravenous use.
100-ml bag: for use in adults, adolescents and children weighing more than 33 kg only.
50-ml bag: for use in newborns, infants and children weighing less than 33 kg.
10-ml bag: for use in newborns, infants and children weighing less than 10 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 (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
>10kg 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	1g	100 ml	100 ml	3 g
>50 kg and no additional risk factors for hepatotoxicity	1g	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.
The minimum interval between each administration in patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min) must be at least 6 hours.
No more than 4 doses to be given in 24 hours.

In adult patients, in case of hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low hepatic glutathione reserves) or dehydration, the total dose of paracetamol per day should not exceed 3 g (see section 4.4).

Method of administration

Take care when prescribing and administering Paracetamol 10 mg/ml 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.

The paracetamol solution is administered as a 15-minute 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).

Patients weighing ≤10kg:
- The bag of Paracetamol 10 mg/ml Solution for Infusion 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 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

Paracetamol is contraindicated:

• In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (paracetamol prodrug) or to any of the excipients,
• In patients with severe hepatocellular failure.

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 millilitre (ml), which could result in accidental overdose and death (see section 4.2).

Appropriate oral analgesia is recommended as soon as this route of administration can be used.
To avoid any risk of overdose, the absence of paracetamol or propacetamol from the composition of other concomitant medicinal products must be checked.
Doses higher than those recommended cause a risk of very severe liver damage. The symptoms and clinical signs of liver damage (including fulminant hepatitis, hepatic insufficiency, cholestatic hepatitis, cytolytic hepatitis) are generally observed after 2 days and normally reach their peak within 4 to 6 days. Treatment with an antidote should be administered as soon as possible (see section 4.9).
This medicine contains 252 mg of sodium per 100ml 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.
PARACETAMOL CARELIDE 10 mg / ml, solution for infusion is considered to be rich in sodium. This should be especially taken into account for those on a low salt diet.

Precaution for use
• in patients with hepatocellular failure,
• in patients with severe renal insufficiency (creatinine clearance ≤30 ml/min (see sections 4.2 and 5.2),
• in patients suffering from chronic alcoholism,
• in patients suffering from chronic malnutrition (low liver gluthatione levels),
• in dehydrated patients.
• in patients weighing less than 50 kg (see section 4.2)

4.5 Interaction with other medicinal products and other forms of interaction

Probenecide almost halves the clearance of paracetamol by inhibiting glucuronic acid conjugation. A reduction in the dose of paracetamol should be considered when combined with probenecide.
Salicylamide may increase the elimination half-life of paracetamol.
Particular caution should be exercised when combining paracetamol with enzyme inducing agents (see section 4.9).
The concomitant use of paracetamol (4 g per day for at least 4 days) and oral anticoagulants may cause mild variations in the INR. In this case, increased surveillance of the INR is required during concomitant administration and for one week after paracetamol discontinuation.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical experience with the intravenous administration of paracetamol is limited. However, epidemiological data on the use of therapeutic oral doses of paracetamol have not demonstrated any adverse effects on pregnancy or on the health of the foetus or newborn infant.
Reproductive studies in animals have not been conducted using the intravenous dosage form.
However, studies performed using the oral route have not demonstrated any malformative or foetotoxic effects.
Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, Paracetamol should only be used during pregnancy following a careful assessment of the risk/benefit ratio. In this case, the recommended dosage and duration of treatment must be strictly complied with.

Lactation
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

Not applicable.

4.8 Undesirable effects

As with all paracetamol-containing medicinal products, side effects are rare (> 1/10,000, < 1/1,000) or very rare (< 1/10,000). These are described below:

MedDRA- system organ class database	Rare > 1/10 000, < 1/1000	Very rare < 1/10 000
General disorders and administration site conditions	Malaise	
Immune system disorders		Hypersensitivity reaction
Vascular disorders	Hypotension	
Hepatobiliary disorders	Increased levels of hepatic transaminases	
Blood and lymphatic system disorders		Thrombocytopenia, Leukopenia, Neutropenia

Very rare cases of pain reaction and burning sensation at injection site even diffuse have been reported.

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

Cases of erythema, hot flushes, pruritus and tachycardia have been reported.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

The risk of liver damage (including fulminant hepatitis, hepatic insufficiency, cholestatic hepatitis, cytolytic hepatitis) is particularly high in elderly subjects, young children, patients with liver damage, in patients suffering from chronic alcoholism, in patients suffering from chronic malnutrition, and in patients receiving enzyme inducing agents. In these cases, poisoning can be fatal.

Symptoms generally appear within 24 hours and include: nausea, vomiting, anorexia, pallor and abdominal pain.

An overdose, as from a dose of 7.5 g paracetamol as a single dose in adults and 140 mg/kg body weight as a single dose in children, causes hepatic cytolysis that may lead to complete and irreversible necrosis, giving rise to hepatocellular failure, metabolic acidosis and encephalopathy that may progress to coma and a fatal outcome.

At the same time, elevated levels of liver transaminases (ASAT, ALAT), lactate dehydrogenase and bilirubin are observed, and a reduction in the prothrombin time may appear within 12 to 48 hours post-dose.

The clinical symptoms of liver damage are generally observed after two days, reaching their peak within 4 to 6 days.

Emergency Management
• Immediate admission to a hospital.
• Before initiating treatment, a tube of blood should be collected for the plasma assay of paracetamol, as soon as possible after the overdose.

• Treatment of the overdose includes administration of the antidote N-acetylcysteine (NAC) via the intravenous or oral route, if possible within 10 hours of the overdose. However, NAC may provide a degree of protection even after 10 hours, but in this case prolonged treatment is administered.
• Symptomatic treatment.
• Liver function tests must be performed at the start and then every 24 hours.
• Liver transaminase levels usually return to normal within one or two weeks, with a complete recovery of liver function. However, in very severe cases, a liver transplant may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANALGESICS AND ANTIPYRETICS, ATC code: N02BE01

The precise mechanisms underlying the analgesic and antipyretic properties of paracetamol still need to be established but may involve both central and peripheral actions.
Paracetamol 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 2g 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 1g paracetamol, significant concentrations of paracetamol (of approximately 1.5 µg/ml) were recovered in the cerebrospinal fluid only 20 minutes post-infusion.

Metabolism
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 precautions

Patients with 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 therefore recommended to allow an interval of at least 6 hours between doses in patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see section 4.2).

Elderly subjects
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 and 1N sodium hydroxide (for pH adjustment), water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

After dilution: the physicochemical stability of the solution diluted in 0.9% sodium chloride or 5% glucose was demonstrated for 2 hours (including the infusion time).
However, from a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.
After opening the overwrapping: immediate use is recommended. However, the stability of the product after it has been removed from the overwrapping has been demonstrated for 24 hours.
Regarding storage conditions for the diluted 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

Precautions for handling in patients ≤ 10 kg: see section 4.2.

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 or yellowing. 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.

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.

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
69007 LYON
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

July 2023