SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Uni-Pharma 10 mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 10 mg paracetamol.

Each 100 ml bag solution for infusion contains 1000 mg paracetamol.

Excipients with known effect: Sodium 250 mg/100 ml.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to slightly yellowish solution.

pH: 4.5 – 6.0 during shelf-life

Osmolarity: approximately 290mOsmol/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol Uni-Pharma 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.

Paracetamol Uni-Pharma is indicated in adults, adolescents and children weighing more than 33 kg.

4.2 Posology and method of administration

Intravenous route.

The 100 ml bag 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 *Paracetamol Uni-Pharma* per administration based on upper weight limits of group (mL)****	**Maximum Daily Dose ***
> 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	1g	100mL	100mL	4g

*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).

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 Uni-Pharma* 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.

4.3 Contraindications

- Hypersensitivity to the active substance; 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).

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, check that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entails risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) 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).

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 gluthatione),
- dehydration

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.

This medicinal product contains approximately 10.9 mmol (or 250 mg) of sodium per 100ml of *Paracetamol Uni-Pharma*. To be taken into consideration by patients on a controlled sodium diet.

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 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),
- 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.

Breastfeeding

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, *Paracetamol Uni-Pharma* may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are Rare (>1/10,000, <1/1,000) or Very Rare (<1/10,000), these are described below:

System Organ Class	Rare >1/10,000, <1/1,000	Very rare <1/10,000
General disorders and administration site conditions	Malaise	Hypersensitivity reaction
Cardiac disorders	Hypotension	
Hepatobiliary disorders	Increased levels of hepatic transaminases	
Blood and lymphatic system disorders		Thrombocytopenia, Leucopenia, Neutropenia

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).

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 discontinuation of treatment.

Cases of erythema, flushing, 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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: nausea, vomiting, anorexia, pallor, abdominal pain.

Overdose, 7.5 g or more of paracetamol in a single administration in adults and 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 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 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: OTHER ANALGESICS AND ANTIPYRETICS,

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 of paracetamol is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of paracetamol 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 Cerebro Spinal 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 in 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.

Full term 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 h) than in adults. In neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table. Pharmacokinetic values as a function of age (standardized clearance, CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-1}) are presented 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 population estimate for CL

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 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

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

Preclinical data reveal no special hazard for humans beyond the information included in other sections of this 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

Hydroxypropylbetadex

Disodium Edetate

Sodium Chloride

Sodium Dihydrogen Phosphate Dihydrate (pH adjustment, E339)

Disodium Hydrogen Phosphate Dihydrate (pH adjustment, E339)

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C without overwrapping.

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.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Do not refrigerate or freeze.

Keep the bags in the outer carton to protect the product from light.

6.5 Nature and contents of container

100 ml polypropylene bags equipped with an infusion site, consisting of a polyolefin/styrene-block copolymer based tube. The tube is sealed with a chlorobutyl rubber stopper and an aluminium cap.

The bags are overwrapped with aluminium foil, metalized film or with a polyethylene-based multilayer film.

Packs of 1 x 100 ml, 10 x 100 ml, 20 x 100 ml or 50 x 100 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

There could be a potential presence of moisture between the bag and the outer packaging as a result of the sterilisation process. This does not impact the quality of the solution.

7 MARKETING AUTHORISATION HOLDER

Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

14th km National Road 1,

GR-145 64 Kifissia

Greece

8 MARKETING AUTHORISATION NUMBER(S)

PL 20989/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/05/2015

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07/06/2022