SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 10 mg/ ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One bottle with 100 ml contains 1000 mg paracetamol.

One bottle with 50 ml contains 500 mg paracetamol.

One ml contains 10mg paracetamol.

Excipients: Sodium 0.04mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, slightly yellowish solution.

The osmolality of the solution for infusion ranges between 285 and 315 mOsmol/kg.

The pH of the solution for infusion ranges between 5.0 and 6.0

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

Intravenous route.
The 100 ml bottle is restricted to adults, adolescents and children weighing more than 33 kg.
The 50 ml container is restricted to term newborn infants, infants, toddlers and children weighing less than 33 kg.

Posology:

Dosing based on patient weight (please see the following dosing table)

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

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

**** Maximum daily dose:** The maximum daily dose as presented in the table above is for patients that are not receiving any 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.

No more than 4 doses to be given in 24 hours.

Paediatric population
No safety and efficacy data are available for pre-term newborn infants (see section 5.2)

Patients with renal impairment
The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours.

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:

Precautions to be taken before handling or administering the medicinal product

Take care when prescribing and administering Paracetamol 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.

Patients weighing ≤10 kg:

- The bottle 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 bottle and diluted in a 9 mg/ml (0.9% w/v) sodium chloride solution or 50 mg/ml (5% w/v) glucose solution up to one tenth (one volume Paracetamol 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.

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

The paracetamol solution is administered as a 15-minute intravenous infusion.

Text for the 50ml:

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

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

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).

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

Text for the 50ml and 100ml:

As for all solutions for infusion, a close monitoring is needed notably at the end of the infusion (see section 4.2).

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.

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.

Paediatric population

Interaction studies have only been performed in adults

4.6 Fertility, pregnancy and lactation

Pregnancy:

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

Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects.

Nevertheless, Paracetamol should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Breast-feeding:

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 all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ system	Rare >1/10000, <1/1000	Very rare <1/10000
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Platelet/blood		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
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.

Management

- 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 i.v. 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 15μg/mL and 30μg/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 20^{th} 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 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.

Paediatric population
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. Age related pharmacokinetic values (standardized clearanc,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 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 impairment

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 $\leq$ 30 mL/min), to increase the minimum interval between each administration to 6 hours (see section 4.2. Posology and method of administration).

Older people

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 solution for infusion 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

Mannitol, Disodium Phosphate Anhydrous, Hydrochloric Acid (for pH-adjustment), Sodium Hydroxide (for pH-adjustment) and Water for Injections.

6.2 Incompatibilities

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

6.3 Shelf life

Unopened bottle: 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.

Text for the 50ml container:

If diluted in 9 mg/ml (0.9% w/v) sodium chloride or 50 mg/ml (5% w/v) 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

Do not store above 30°C.

Do not refrigerate or freeze.

Store the immediate packaging in the outer, aluminium overpackaging.

Following the opening of the overpackaging, the product must be used immediately.

6.5 Nature and contents of container

50ml and 100ml, plastic bottles of polypropylene, with a molded plastic cap, a rubber (type II) gasket and a pull ring or with plastic caps with embedded elastomers (twin ports). Each bottle is placed in a metalised protective plastic pouch

50ml and 100 ml bottle is available in packs of 1, 5, 10 and 12 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Text for the 50ml and 100ml bottles:

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

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

The diluted solution should be visually inspected and should not be used in presence of opalescence, visible particulate matters or precipitate.

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

7 MARKETING AUTHORISATION HOLDER

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Mitsi Building 3

Office 115, 1065 Nicosia, Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 24598/0028

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