1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed on following page

1. NAME OF THE MEDICINAL PRODUCT

PARASAM IV INFUSION (Paracetamol Intravenous Infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg Paracetamol.

Each 100 ml contains 1000 mg Paracetamol.

Excipients

For excipients: see 6.1

3. PHARMACEUTICAL FORM

Solution for Infusion

A clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It 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 use

100 ml: restricted to adults, adolescents and children weighing more than 33 kg.

50 ml: restricted to newborn infants, infants and children weighing less than 33 kg.

Posology:

Adults and adolescents weighing more than 50 kg:

1 g of Paracetamol per administration, i.e. one 100 ml bottle, up to four times a day.

The minimum interval between each administration must be 4 hours.

The maximum daily dose must not exceed 4 g.

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.

Children weighing more than 33 kg (approx. 11 years old), adolescents and adults weighing less than 50 kg

15 mg/kg of Paracetamol per administration, i.e. 1.5 ml of solution per kg, up to four times a day. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 60 mg/kg (without exceeding 3 g).

Children weighing more than 10 kg (approx. 1 year old) and less than 33 kg:

15 mg/kg of Paracetamol per administration, i.e. 1.5 ml of solution per kg, up to four times a day.

The minimum interval between each administration must be 4 hours.

The maximum daily dose must not exceed 60 mg/kg (without exceeding 2 g).

Full-term newborn infants, infants and children weighing less than 10 kg (approx. 1 year old):

7.5 mg/kg of Paracetamol per administration, i.e. 0.75 ml of solution per kg, up to four times a day.

The minimum interval between each administration must be 4 hours.

The maximum daily dose must not exceed 30 mg/kg.

No safety and efficacy data are available for premature neonates.

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 at least 6 hours.

Method of administration

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

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

For single use only.

It is possible to dilute the Paracetamol solution with a 0.9% sodium chloride solution or a 5% glucose solution up to one tenth. 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 propacetamol hydrochloride (prod rug of Paracetamol) or to any of the excipients
- in patients with severe hepatocellular insufficiency

4.4. Special warnings and precautions for use

Warnings

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

Doses higher than those recommended entail the risk of very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, liver insufficiency, cholestatic hepatitis, and cytolytic hepatitis) are usually seen first after two days with a maximum usually after 4 to 6 days. Treatment with antidote must be given as soon as possible.

This medicinal product contains 79 mg sodium per 100 ml. This has to be taken into consideration for patients on a controlled sodium diet.

Precautions for use

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency
- severe renal insufficiency (creatinine clearance 30 ml/min
- chronic alcoholism
- chronic malnutrition (low reserves of hepatic glutathione)
- dehydration

4.5. Interactions 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 half-life of paracetamol.

Particular care must be exercised when enzymatic inductors are administered concomitantly.

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.

4.6. Pregnancy and lactation

Pregnancy

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

Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.

No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not shown any malformation or foetotoxic effects.

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

Lactation

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effect 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

None known.

4.8. Undesirable effects

As with all medicines containing paracetamol, adverse drug reactions are rare (> 1/10 000, < 1/1000) or very rare (< 1/10 000). These are described below.

Organ System	Rare > 1/10 000, < 1/1000	Very Rare < 1/10 000
General	Malaise	Hypersensitivity Reaction

Organ System	Rare > 1/10 000, < 1/1000	Very Rare < 1/10 000
Cardiovascular	Hypotension	
Hepatic	Increased levels of hepatic transaminases	
Platelets/blood		Thrombocytopenia Leucopenia Neutropenia

Pain or burning sensation at the injection site have been reported, which may result from the rate at which the infusion is administered and which is not necessarily resolved by decreasing infusion rate.

Erythema, flushing, pruritus and tachycardia have been reported in some cases.

Hypersensitivity reactions ranging from a simple skin rash or urticaria to anaphylactic shock, requiring discontinuation of treatment have been reported in very rare cases.

4.9. Overdose

There is a risk of liver damage (including fulminant hepatitis, liver insufficiency, 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. Overdose may be fatal in these cases

Symptoms generally appear within 24 hours and include: nausea, vomiting, anorexia, pallor and 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, encephalopathy which may lead to a 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 blood sample for plasma paracetamol assay as soon as possible after the overdose.
- Treatment for an overdose includes the oral or intravenous administration of the antidote Nacetylcysteine (NAC), if possible before the 10th hour. However NAC may give some degree of protection even after 10 hours, and prolonged treatment should be given in this case.
- 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 the liver function. In very severe cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: ANALGESICS AND ANTIPYRETICS,

ATC Code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established and 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 pharm kinetics 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 (containing 500 mg and 1 g of paracetamol respectively).

The maximum 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 of paracetamol, significant concentrations of paracetamol (about 1.5 µg/ml) were observed in the cerebrospinal fluid 20 minutes after 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 poisoning, 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 to 80%) and sulphate (20 to 30%) conjugates.

Less than 5% is eliminated unchanged.

Plasma half-life is 2.7 hours and total body clearance approximately 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 newborn infants, the plasma half-life is longer than in infants

i.e. around 3.5 hours. Newborn 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} ($I.h^{-1}$ $70kg^{-1}$) are described below:*

Age	Weight (kg)	CLstd/Foral (I.h-1 70kg-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 precautions

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, when giving paracetamol to patients with severe renal impairment (creatinine clearance 30 mL/min), the minimum interval between each administration should be increased to at least 6 hours.

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

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric Acid monohydrate

Mannitol

Di-sodium Hydrogen Phosphate Anhydrous

Sodium Bisulphite

Water for Injection

6.2. Incompatibilities

Paracetamol Infusion should not be mixed with other medicinal products.

6.3. Shelf life

24 months

After opening, this product should be used immediately

6.4. Special precautions for storage

Store below 30°C. Do not refrigerate or freeze. Protect from light

Keep medicines out of reach of children.

6.5. Nature and contents of container

Primary Packing: 100 ml solution packed in Plastic Bottles

Secondary Packing: Bottles overwrapped with polypropylene film roll and packed in carton with leaflet

6.6. Instruction for disposal

Before use, ensure that the container is undamaged and the contents clear in appearance.

After use, discard any remaining solution.

7. MARKETING AUTHORISATION HOLDER

SAM PHARMACEUTICAL LIMITED

8/9, Oyadiran Estate, Yaba, Lagos, Nigeria

8. MARKETING AUTHORISATION NUMBER

B4-9112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/10/2018

10. DATE OF REVISION OF THE TEXT

June-2023