DOCUMENT DETAILS

Document Number	SMPC-002
Document Name	Tasamol IV – Paracetamol 1000mg/100ml Solution for Infusion - SMPC
Department	Regulatory Affairs
Category	Summary of Medicinal Product Characteristics
Version No	01.00
Effective Date	25/Mar/2021
Next Review Date	N/A

SIGNATURES

ROLE	NAME	DESIGNATION	DEPARTMENT	DATE & TIME
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SUMMARY OF MEDICINAL PRODUCT CHARACTERISTICS	tasa pharma
Title:Tasamol IV – Paracetamol 1000mg/100ml Solution for Infusion - SMPC	
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Tasamol IV – Paracetamol 1000mg/100ml Solution for Infusion
Tasa Pharma Ltd

Active Ingredient
Paracetamol

1 Name of the medicinal product
Tasamol Paracetamol 10 mg/ml solution for infusion

2 Qualitative and quantitative composition
Each container contains 1000 mg paracetamol.
One ml contains 10 mg paracetamol
For the full list of excipients, see section 6.1.

3 Pharmaceutical form
Solution for infusion.
The solution is clear, colourless or pale brown colored solution.
pH: 5.0-6.5

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 use.
The product 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 (10 mg/ml) per administration based on upper weight limits of group (ml)**	Maximum Daily Dose *
> 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

***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.

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).
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).

Method of administration:

Take care when prescribing and administering Paracetamol 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.
Before administration, the product should be visually inspected for any particulate matter and discolouration.
For single use only.

As for all solutions for infusion, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the infusion applies particularly for central route infusions, in order to avoid air embolism.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to propacetamol hydrochloride (prodrug of paracetamol).
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 millilitre (ml), which could result in accidental overdose and death (see section 4.2).

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, it should be checked that no other medicines administered contain either paracetamol or propacetamol.

Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually seen after two days of drug administration with a peak seen after 4-6 days. Treatment with antidote should be given as soon as possible (See *section 4.9*).
This medicinal product contains less than 1mmol sodium (23mg) per 100ml of Paracetamol, i.e. essentially 'sodium free'.

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 glutathione),
- 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 in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.
- Salicylamide may prolong the elimination t½ of paracetamol.
- Caution should be taken with 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.

4.6 Fertility, 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.

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

Breastfeeding:

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

Not relevant.

4.8 Undesirable effects

As with all paracetamol products, adverse drug reactions are rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000). They are described below:

Organ System	Rare	Very rare
Blood and lymphatic system disorders		Thrombocytopenia Leucopenia, Neutropenia
Vascular disorders	Hypotension	
Hepatobiliary disorders	Increased levels of hepatic transaminases	
Skin and subcutaneous tissue disorders		Serious skin reactions
General disorders and administration site conditions	Malaise	Hypersensitivity reaction

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

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.

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 and abdominal pain.

Overdose, 7.5 g or more of paracetamol in a single administration in adults or 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, a blood sample for plasma paracetamol assay should be taken, 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 of 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 return of normal 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; *Anilides*
ATC Code: N02BE01

Mechanism of action
The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Phamacodynamic effects
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 a 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 1g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol is about 15µg/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 cerebrospinal fluid at and after the 20th 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 P_{450} 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 within 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.

Neonates, 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 new-born infants, the plasma half-life is longer than in infants i.e. round 3.5 hours. New-born 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} ($l.h^{-1}$ $70kg^{-1}$)

Age	Weight (kg)	CL_{std}/F_{oral} ($l.h^{-1}$ $70kg^{-1}$)
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 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 when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30 ml/min), the minimum interval between each administration should be increased to 6 hours (see section 4.2.).

Elderly:

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

Non-clinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of Paracetamol i.v. 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 Dihydrate
Hydrochloric acid – for pH adjustment
Sodium Hydroxide– for pH adjustment
Cysteine Hydrochloride Monohydrate
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Plastic bags: 24 months.
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

Plastic bags: Do not store above 30°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Polyolefin/ Styrene-block copolymer-based film bags of 100ml, provided with a Single Function Connector System (SFC) assembly, comprising of polypropylene port and a polypropylene cap assembled with rubber disc. Sealed with triple laminated pouch.
Pack size: 1 and 10 bags
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 Marketing authorisation holder

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