SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

THERMODOL (Paracetamol Infusion 1.0% w/v)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 100 ml contains:
Paracetamol BP……..... 1000 mg
Water for Injections BP…… q.s.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM:

Clear, colourness to pale yellow liquid filled in LDPE bottle.

4. CLINICAL PARTICULARS:

4.1. Therapeutic Indications:

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 100 ml vial 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.

Body weight or age	**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**
Pre-term Newborn	No safety efficacy data are available for pre-term newborn infants			
Term newborn infants, infants, toddlers and children weighing up to 10 kg (up to approximately 1-year-old)	The use of 100 ml vial is not recommended in this group of patients			
Children weighing more than 10 kg (Approx. 1-year-old) and up to 33kg	The use of 100 ml vial is not recommended in this group of patients			
Children weighing more than 33kg (Approx. 11	15 mg/kg	1.5 ml/kg	75 ml	60 mg/kg not exceeding 3g

years old), **adolescents and adults weighing upto 50kg**				
>50kg with additional risk factors for hepatotoxicity	1g	100 mL	100 mL	3g
>50kg and no additional risk factor for hepatotoxicity	1g	100 mL	100 mL	4g

Method of Administration

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

Patients weighing ≤10 kg:

- The bottle of Paracetamol, 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- The volume to be administered should be withdrawn from the bottle diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one tenth (one volume Paracetamol, solution for infusion, into nine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 7.5 ml per dose.
- The user should be referred to the product information for dosing guidelines.

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.

As for all solutions for infusion presented in LDPE bottles, 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:

- In patients with hypersensitivity to Paracetamol or to any other excipient.
- In cases of severe hepatocellular insufficiency.

4.4. Special warnings and precautions for use:

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 no other medicines administered do not contain Paracetamol. Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage are not usually seen until two days, and up to a maximum of 4-6 days, after administration. Treatment with antidote should be given as soon as possible.

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. Interation with other medicinal products and other forms of interactions:

- 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.
- Concomitant use of Paracetamol (4g per day for at least 4days) 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 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 show any malformation of foetotoxic effects.

Nevertheless, Paracetamol 10 mg/ml Solution for infusion should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Lactation

After oral administration. Paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol 10 mg/ml solution for infusion may be used in breast-feeding women.

4.7. Effects on ability to drive and use machine:

Not relevant

4.8. Undesirable effects:

As with all products containing Paracetamol, the adverse reactions are rare (≥1/10000, <1/1000) or very rare (<1/10000) and are listed below:

Organ system	Rare ≥1/10000, <1/1000	Very rare <1/10000
General	**Malaise**	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased hepatic transaminase levels.	
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 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. Over dosage:

There is a risk of poisoning, 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 7.5g 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, take a blood sample for plasma Paracetamol assay, as soon as possible after the overdose. The treatment includes administration of the antidote, N-acetyl cysteine (NAC) by the i.v. or oral route, if possible before the 10^{th} hour. NAC can however, give some degree of protection even after 10 hours, but in these cases prolonged treatment should be administered.

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. Pharmacodynamics 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 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 in IV route. 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 concentrations (Cmax) of Paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1g of Paracetamol is approximately 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 1.5μg/ mL) were observed in the cerebrospinal fluid as and from the 20 minute following post-infusion.

Metabolism
Paracetamol is metabolized 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.

<u>New borns, infants and children</u>
The pharmacokinetic parameters of Paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life, which is slightly shorter (1.5 to 2 h) than in adults. In new-borns, the plasma half-life is longer than in infants at around 3.5 hours. New borns, infants and children up to 10 years excrete significantly less glucuronide and more Sulfate conjugates than adults. Total excretion of Paracetamol and its metabolites is the same for all ages.

<u>Special populations:</u>
Renal insufficiency
In cases of severe renal insufficiency (creatinine clearance 10-30 mL/min), the elimination of Paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. The elimination rate for the glucuronide and sulphate conjugates is three-times slower in subjects with severe renal insufficiency than in healthy subjects. Therefore, when Paracetamol is administered to patients with severe renal insufficiency (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours.

<u>Elderly patients</u>

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 in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been confirmed in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Mannitol BP, Disodium Hydrogen Phosphate Dihydrate BP, Hydrochloric Acid BP, Water for Injections BP.

6.2. Incompatibilities

Paracetamol should not be mixed with other medicinal products.

6.3. Shelf Life

24 Months

6.4. Special precautions for storage

Store protected from light & moisture, at a temperature not exceeding 30ºC. Do not freeze.

6.5. Nature and contents of container

100 ml in LDPE bottle packed in a monocarton along with packaging insert.

6.6. Special precaution for disposal

Before administration, the product should be inspected visually for any particles and colour changes. 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.

7. MARKETING AUTHORIZATION HOLDER

Unosource Pharma Ltd.
503-504, 5th Floor Hubtown Solaris
N.S. Phadke Marg, Andheri (East) MumbaI-400069, India

8. MARKETING AUTHORISATION NUMBER(S)

05245/5432/NMR/2017

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

07-08-2020

10. DATE OF REVISION OF THE TEXT

07-07-2023