Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

SANMOL®
Paracetamol

2. Qualitative and quantitative composition

Each mL contains:
Paracetamol 10 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for Infusion
This solution is clear, odorless, colourless to not more intensive than BY7 standard colour

4. Clinical particulars

4.1 Therapeutic indications

Paracetamol infusion 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 50 mL bottle is restricted to toddlers and children weighing from 10 kg (approximately one year old) to 33 kg.
The 100 mL bottle is restricted to adults, adolescents, and children weighing more than 33 kg (approximately 11 years old).

Posology

- Adolescents and adults weighing more than 50 kg:

Paracetamol 1 g 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.

- Children weighing more than 33 kg (approximately 11 years old), adolescents, and adults weighing less than 50 kg:

Paracetamol 15 mg/kg per administration, i.e. 1.5 mL 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 (approximately 1 year old) and weighing less than 33 kg: Paracetamol 15 mg/kg per administration, i.e. 1.5 mL 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).
- 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.

Method of Administration

The Paracetamol solution is administered as a 15 minutes intravenous infusion. It can also be diluted in 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 proportion (infused time included). As for all solutions for infusion presented in glass bottle. It is reminded that a close monitoring is needed notably at the end of the infusion, regardless the administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid embolism.

4.3 Contraindications

- Hypersensitivity to Paracetamol or to Propacetamol hydrochloride (prodrug of Paracetamol) or to any of the excipient.
- Severe hepatocellular insufficiency.
- Patients with hepatic failure or active liver disease.

4.4 Special warnings and precautions for use

Warnings

Prolonged or frequent use is discouraged. It is recommended that a suitable analgesic oral treatment will 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 either paracetamol or propacetamol. The dose may require adjustment.

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 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)
- Chronic alcoholism
- Chronic malnutrition (low reserves of hepatic gluthatione)
- Dehydration

- Patients suffering from a genetically caused G-6-PD deficiency (favism), the occurrence of a haemolytic anaemia is possible due to the reduced allocation of glutathione following the administration of Paracetamol

4.5 Interaction with other medicinal products and other forms of interaction

- Probenecid causes an almost two-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.
- Caution should be paid to the concomitant intake of enzyme-inducing agents. These substances include but are not limited to: Barbiturates, Isoniazid, Anticoagulants, Zidovudine, Amoxicillin
+ Clavulanic acid, Carbamazepine, and Ethanol. Induction of metabolism of Paracetamol from enzyme inducers may result in an increased level of hepatotoxic metabolites.
- Concomitant use of Paracetamol (4000 mg per day for at least 4 days) with oral anticoagulants including Warfarin 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 one 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.

4.6 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.

Lactation

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

- Dizziness, headache, dystonia, nausea, vomiting, constipation

- Simple skin rash or urticaria to anaphylactic shock have been occurred and require discontinuation of treatment

- Malaise

- Hypersensitivity reaction

- Hypotension

- Increased level of hepatic transaminases

- Thrombocytopenia, leucopenia, neutropenia

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 requested to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

Symptoms

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. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.
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.

Treatment

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-acetylcysteine (NAC) by the intravenous 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 restitution 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 : Analgesics; Other analgesics and antipyretics; Anilides ATC Code : N02BE01

Mechanism of Action

The precise mechanism of the analgesic and antipyretic properties of Paracetamol has still to be established; it may involve central and peripheral actions.

Pharmacodynamic 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 1 g and 2 g propacetamol (containing 500 mg and 1 g

Paracetamol respectively). The maximal plasma concentration (C_{max}) 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 cerebrospinal fluid at and after the 20 minute following infusion.

Biotransformation:

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 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.

Newborn Infants, 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} ($l\times h^{-1}\times 70\ kg^{-1}$)*

Age	**Weight (kg)**	**CL_{std}/F_{oral} ($l\times h^{-1}\times 70\ kg^{-1}$)**
40 weeks post-conception	3.3	5.9
3 months postnatal	6	8.8
6 months postnatal	7.5	11.1
1 year postnatal	10	13.6
2 year postnatal	12	15.6
5 year postnatal	20	16.3
8 year postnatal	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.

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

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

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

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Metabisulfite
Mannitol
L-Histidine
Pyrogen Free Sodium Hydroxide
Hydrochloric Acid
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C, away from light Do not refrigerate or freeze

6.5 Nature and Content of container

Each bottle contains Paracetamol 1000 mg, filled in a clear glass vial (type II) of 100 mL, closed with a rubber stopper and sealed with a flip off seal both in diameter of 32 mm.

Each box comes with 1 bottle @ 100 mL

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. The product should be used immediately after opening and any unused solution should be discarded. If diluted in 0.9% Sodium chloride or 5% Glucose, the solution should be used immediately. However, if the solution is not used immediately, store below one hour (infusion time included).

7. Marketing Authorization Holder

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8. Marketing Authorization Number

H2014/CTD1514/384

9. Date of first authorization/renewal of the authorization

07/08/2014

10. Date of revision of the text

31/03/2026