National Agency for Food & Drug Administration &

Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

AVIPOL (Paracetamol Injection)

Strength

Each ml contains		
Paracetamol	BP	150mg
Lignocaine Hydrochloride	BP	1% w/v
Benzyl Alcohol (as Preservative)	BP	1% w/v
Water for Injections	BP	q.s

Pharmaceutical dosage form: Intravenous Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch size: 120 Litres

Ingredients	Specification	Label Claim (mg)	Overage	Quantity added (kg) /batch
Paracetamol	BP	150mg	2%	18.360
Lignocaine Hydrochloride	BP	1% w/v	---	1.200
Benzyl Alcohol	BP	1% w/v	---	1.200 Lt
Propylene Glycol	BP	50% w/v	---	60.000 Lt
Water for Injections	BP	q.s	---	q.s to 120 Lt

BP : British Pharmacopoeia

3. PHARMACEUTICAL FORM

A Clear and colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Reduce fever

Provide relief from pain

Alleviate pain at the site of injection

4.2 Posology and method of administration

Adults: 2 to 4 ml every 4-6 hours or as directed by the Physician.

Children (Above 12 years / >33 kg): Upto 2 ml (300 mg) every 4 hours OR Upto 3 ml (450 mg) every 6 hours.

Infants and Children (From 2 - 12 years / < 33 kg): Upto 0.5 to 1 ml (75 mg - 150 mg) every 4 hours OR Upto 2 ml (300 mg) every 4 to 6 hours. Upto 7.5 mg to 10 mg/kg of body weight or as per Physician's discretion.

Method of administration: Intravenous Injection

4.3 Contraindications

- In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients.
- 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 milliliter (mL), which could result in accidental overdose and death

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 containing paracetamol are administered at the same time.

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 (See section 4.9 Overdose).

This medicinal product contains 4.32mmol sodium per dose. To be taken into consideration by 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) (see sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties),
- 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 Overdose).
- 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 show any malformation or 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 machines

Not relevant

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100 to 1/10); uncommon (≥ 1/1,000 to 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Organ System	**Rare**	**Very rare**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Skin and subcutaneous tissue disorders		Very rare cases of serious skin reactions have been reported.
Platelet/blood		Thrombocytopenia Leucopenia, Neutropenia

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

4.9 Overdose

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, 7.5 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.

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 10 mg/ml Solution for Infusion 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 10 mg/ml Solution for Infusion 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 500mg and 1 g of Paracetamol 10 mg/ml Solution for Infusion is similar to that observed following infusion of 1g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol 10 mg/ml Solution for Infusion 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.

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 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 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 (standardised clearance, *CLstd/Foral (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.

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

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

Studies on local tolerance of Paracetamol 10 mg/ml 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

S.No	Ingredients	Specification
1.	Benzyl Alcohol	BP
2.	Propylene Glycol	BP
3.	Water for Injection	BP

6.2 Incompatibilities: Not Applicable

6.3 Shelf life: 48 months from the data of manufacturing

6.4 Special precautions for storage: Store below 300 C. protect from direct sun light.

6.5 Nature and contents of container:

Avipol Injection is packed as 5x2mL, 20x5x2mL Type 1 amber coloured Ampoules.

6.6 Special precautions for disposal: Not Applicable

7. APPLICANT / MANUFACTURER:

APPLICANT:

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