Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Pividoc (paracetamol infusion 1% w/v) 1 g/ 100 ml intravenous infusions

2. Qualitative and quantitative composition

Qualitative:
Active Substance: Paracetamol BP
INN Name: Paracetamol; Acetaminophen

Quantitative:
1 ml of Paracetamol Infusion contains 10.0 mg of Paracetamol BP.
1 LDPE bottle of 100.0 ml of Paracetamol Infusion contains 1 g of Paracetamol BP

Refer to section 6.1 for full list of excipients

3. Pharmaceutical form

A clear, colorless solution**.**

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

Method of Administration: Intravenous Route The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg.

Posology:

Adolescents and adults weighing more than 50 kg: Paracetamol 1g per administration, i.e. one 100 ml vial, 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)

Term newborns infants, infants, toddlers and children weighing less than 10 kg (up to approximately 1 year old): Paracetamol 7.5 mg/kg per administration, i.e. 0.75 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 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 6 hours.

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration: The maximum daily dose must not exceed 3 g.

4.3 Contraindications

Paracetamol Infusion is contraindicated:
- In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- In cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

In order to avoid the risk of overdose, check that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entails risk for very serious liver damage. Clinical symptoms and signs 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. As for all solutions for infusion, a close monitoring is needed notably at the end of the infusion.

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.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol Infusion may react with the following list of drugs:

- 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 $t_{1/2}$ of paracetamol.

- Caution should be paid to the concomitant intake of enzyme-inducing substances.

- 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.

- 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 high risk factors.

4.6 Pregnancy and Lactation

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

Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects.

Nevertheless, Paracetamol 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 infusion may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant**.**

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ system	**Rare** **>1/10000, <1/1000**	**Very rare** **<1/10000**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic Transaminases	
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.

Post marketing experience when paracetamol is used concomitantly with flucloxacillin; generally, in the presence of risk factors (see section 4.4)

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, 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 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 hospitalization.

- Before beginning treatment, take a tube of blood for plasma paracetamol assay, 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 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
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 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 Infusion reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

Mechanism of Action
Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory effects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that acetaminophen indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that acetaminophen selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2.

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 infusion 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 concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of Paracetamol infusion 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 Cerebro Spinal Fluid as and from the 20th minute following 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 metabolized

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.

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 (standardized clearance,* CL_{std}/F_{oral}($l*h^{-1}$ 70 kg^{-1}), are presented below.

Age	**Weight (kg)**	**CL_{std}/F_{oral} ($l*h^{-1}$ 70 kg^{-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.

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

Studies on local tolerance of Paracetamol 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

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

6.2 Incompatibilities

Paracetamol Infusion should not be mixed with other medicinal products.

6.3 Shelf-Life

2 years.

6.4 Special Precautions for storage

Store in cool place or at controlled room temperature below 30˚C. Avoid freezing and exposure to light.

6.5 Nature and Content of container

Paracetamol Infusion (1% w/v) is available in 100 ml LDPE bottle.

The container closure system consists of a LDPE bottle manufactured by FFS (FORM FILL & SEAL) technology. It is a one-piece container with no use of Rubber stopper and Seal. The secondary packing materials consist of label, wrap film, carton, insert and corrugated box.
For single use only.

6.6 Special precautions for disposal and other handling

Use a 0.8 mm needle and vertically perforate the stopper at the spot specifically indicated.

Before administration, the product should be visually inspected for any particulate matter and discoloration. 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. g Authorization Holder

7. Marketing Authorization Holder

Doctor Pharma Kenya Limited
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8. Marketing Authorization Number

CTD8417

9. Date of first authorization/renewal of the authorization

10/02/2023

10. Date of revision of the text

08/05/2025