SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

CETAGESIC IV PAED 10 mg/mL solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains paracetamol 10 mg (500 mg/ 50 mL)

Sugar-free

Excipients with known effect:

Contains 2.47 mmol (56.85 mg) sodium per 50 mL of solution for infusion.

Contains 400 mg propylene glycol per 50 mL of solution for infusion.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for Infusion.

A clear colourless to slightly yellowish solution. Free from foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CETAGESIC IV PAED is indicated in children 1 year of age and older, for:

- short-term treatment of mild to moderate pain e.g., following minor surgery.
- short-term treatment of fever when the oral route is unsuitable.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE

The prescribed dose must be based on the patient's weight.

Unintentional overdose can lead to serious liver damage and death (see section 4.9).

Healthcare providers are reminded that it is essential to follow both the weight-related dose recommendations and to consider individual patient minimum risk factors for hepatotoxicity including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration (see section 4.4).

Restricted to children weighing more than 10 kg (approximately 1 year of age) but less than 33 kg (approximately 11 years old).

Dosage:

15 mg/kg of paracetamol pre-administration (i.e., 1,5 mL solution per kg) of CETAGESIC IV PAED up to four times a day. The minimum interval between each administration must be at least 4 hours. The maximum daily dose must not exceed 60 mg/kg.

DOSING IS BASED ON PATIENT WEIGHT

DOSING RECOMMENDATIONS ARE PRESENTED IN THE TABLE BELOW.

Patient weight (non-oedematous weight)	**Paracetamol dose (10 mg/mL) per administration**	**Minimum interval between each administration**	**Maximum daily dose***
> 10 kg and ≤ 33 kg	15 mg/kg (i.e. 1,5 ml solution per kg) up to 4 times a day	4 hours	≤ 60 mg/kg Must not exceed 2 g in 24 hours

* The maximum daily dose takes into account all the medicines containing paracetamol.

The dosage should be calculated on non-oedematous weight.

Special populations:

Patients with renal impairment

It is recommended to leave a minimum interval of 6 hours between each administration in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see section 5.2).

Patients with hepatic impairment

In patients with impaired hepatic function, the dose must be reduced or the dosing interval prolonged. The maximum daily dose should not exceed 60 mg/kg/day (not exceeding 2 g/day) in the following situations:

Adults weighing less than 50 kg

Chronic or compensated active hepatic disease, especially those with mild to moderate hepatocellular insufficiency.

- Gilbert's syndrome (familial hyperbilirubinaemia)
- Chronic alcoholism
- Chronic malnutrition (low reserved of hepatic glutathione) and
- Dehydration

Method of administration

CETAGESIC IV PAED is to be administered as a 15-minute intravenous infusion. Before administration, the product should be visually inspected for any particulate matter and discolouration. It is intended for single use only. Once opened, the vial should be used immediately.

As CETAGESIC IV PAED is presented in glass vials, dose monitoring to avoid air embolism is needed, notably at the end of the infusion regardless of the route of administration but especially if a central venous catheter is used for the infusion.

Any unused solution should be discarded.

CETAGESIC IV PAED should not be mixed with other medicines (see section 6.2).

CETAGESIC IV PAED may be diluted up to one-tenth (one volume CETAGESIC IV PAED into nine volumes diluent) in a 0,9 % sodium chloride solution or a 5 % glucose solution. The volume of the diluted solution should take into account the total volume of fluid to be administered to the patient as well as the medical condition of the patient. When CETAGESIC IV PAED is diluted as recommended, the total volume of diluted solution to be administered must be infused within one hour of its preparation (infusion time included) (see section 6.6).

4.3 Contraindications

CETAGESIC IV PAED is contraindicated in:

- known hypersensitivity to paracetamol or to paracetamol hydrochloride (pro-drug of paracetamol) or to any of the excipients (see section 6.1).
- cases of severe hepatocellular insufficiency or decompensated active liver disease including alcoholic hepatitis (see section 4.4).

4.4 Special warnings and precautions for use

This product contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

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 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.
CETAGESIC IV PAED can cause serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions and use of the medicine should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
This medicine contains 56.85 mg sodium per 50 mL.
CETAGESIC IV PAED is considered high in sodium. This should be particularly taken into account for those on a low salt diet.
CETAGESIC IV PAED contains 8,0 mg propylene glycol in each mL, which is equivalent to 12 mg/kg per 1,5 mL (total daily dose for patients > 10 kg and ≤ 33 kg is 48 mg/kg propylene glycol.

CETAGESIC IV PAED should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia).
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min)
- Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia).
- Chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day).
- Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia (see section 4.2)

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease should not use excessive quantities of CETAGESIC IV PAED.
Use with caution in renal disease.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on CETAGESIC IV PAED:

- 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 half-life of paracetamol,
- Caution should be paid to the concomitant use of paracetamol and enzyme-inducing substances as these substances increase the risk of paracetamol induced liver injury. These substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, and ethanol,
- Phenytoin administered concomitantly with paracetamol may result in decreased paracetamol effectiveness and an increased risk of hepatotoxicity. Patients receiving phenytoin therapy should avoid large and/ or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity.
- Flucloxacillin: Caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with a risk factor for glutathione deficiency such as severe renal impairment, sepsis, malnutrition, and chronic alcoholism. Close monitoring is recommended in order to detect the appearance of acid base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

Effects of CETAGESIC IV PAED on other medicines:

- Paracetamol may increase the chance of unwanted effects where administered with other medicines.
- Anticoagulants: Concomitant use of paracetamol (4 g per day for at least 4 days) with concomitants including warfarin may lead to variations in 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 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/ new-born 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 should be used with caution during pregnancy. In this case, the recommended dosage and duration must be strictly observed.

Breastfeeding

After oral administration, paracetamol is excreted into breastmilk in small quantities. No undesirable effects on nursing infants have been reported.

Rash in nursing infants has been reported. Caution should be used when administering paracetamol to women who are breastfeeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following Adverse Drug Reactions (ADRs) can occur:

Blood and lymphatic system disorders

Less frequent: Thrombocytopenia, agranulocytosis, leucopenia, pancytopenia, neutropenia, anaemia

Cardiac disorders

Less frequent: Hypotension

Hepatobiliary disorders

Less frequent: Increased levels of hepatic transaminases, hepatitis, pancreatitis

Renal and urinary disorders

Less frequent: Renal colic, renal failure and sterile pyuria

General disorders and administration site condition

Frequent: reactions at injections site (pain and burning sensation)

Less frequent: Malaise, hypersensitivity reaction

Post-marketing experience:

The following adverse events have also been reported during post-marketing surveillance but the incidence rate (frequency) is not known.

Organ System	**Adverse event**
Immune system disorders	Anaphylactic shock
	Anaphylaxis
	Hypersensitivity reaction
	Angioedema
Blood and lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Nausea
	Vomiting
Hepatobiliary disorders	Fulminant hepatitis
	Hepatic necrosis
	Hepatic failure
	Increased hepatic enzymes

Skin and subcutaneous tissue disorders	Erythema Flushing Pruritus Rash Urticarial Acute generalised exanthematous pustulosis Toxic epidermal necrolysis Stevens-Johnson syndrome
General disorders and administration site condition	Administration site reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexiaand possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 mL dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**

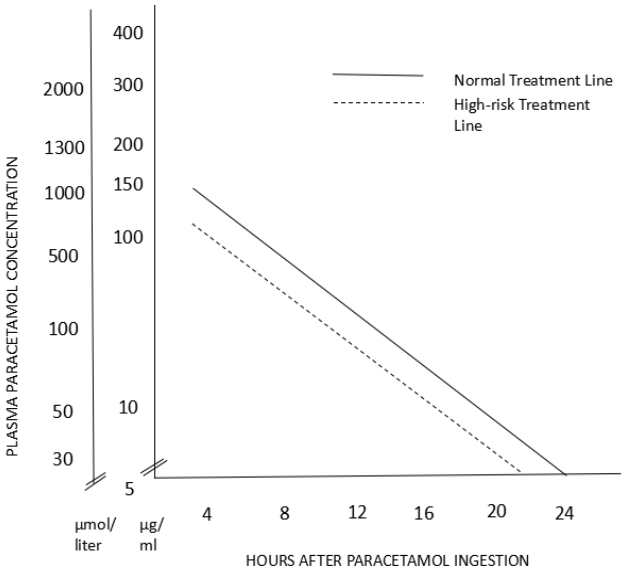
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.

For overdose with an extended/ modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity.

Monitor all patients with significant ingestion for at least ninety six hours.



Source: Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11th Ed

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	OTHER ANALGESICS AND ANTIPYRETICS
ATC Code:	N02BE01

Paracetamol has analgesic and antipyretic activities. The precise mechanism of the analgesic and antipyretic properties of paracetamol has not been established; it may involve central and peripheral actions.

5.2 Pharmacokinetic properties

Absorption

In adults, paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15 minutes intravenous infusion of 500 mg of paracetamol is about 15 µg/mL.

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 in adults, significant concentrations of paracetamol (about 1,5 µg/mL) were observed in the cerebrospinal fluid as and from 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

P450 to a reaction intermediate (N-acetyl benzaquinoneimine) 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 poisoning, 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 elimination half-life is 2,7 hours and total body clearance is 18 L/h.

Children

The pharmacokinetic parameters of paracetamol observed in 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. Total excretion of paracetamol and its metabolites is the same at all ages.

Special populations

Subjects with renal insufficiency

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), the elimination of paracetamol is 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, it is recommended to leave an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

Hepatic impairment

Paracetamol should be used with caution in patients with mild to moderate liver impairment and is contraindicated when there is active disease, particularly alcoholic hepatitis because of CYP

2E1 induction, which leads to increased formation of the hepatotoxic metabolite of paracetamol.

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.

Studies on loacal tolerance of paracetamol infusion in rats and rabbits showed good tolerability.

Absence of delayed contact hypersenistivity has been tested in guinaea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol

Citric Acid Monohydrate

Sodium Metabisulphite

Disodium Hydrogen Phosphate Dihydrate

Sodium Chloride

Water for Injection

6.2 Incompatibilities

CETAGESIC IV PAED should not be mixed with other medicines.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light.

Do not refrigerate or freeze.

Do not administer if visible particles are present.

Use immediately after opening. Discard remaining portion.

Keep out of reach of children.

6.5 Nature and contents of container

50 mL clear glass vials USP type I, closing with 32 mm bromobutyl rubber stoppers and sealed with 33 mm aluminium flip off seals.

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

Tel. nr: 011 848 3050

8. REGISTRATION NUMBER

52/2.7/0445

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 February 2022

10. DATE OF REVISION OF THE TEXT

28 September 2023