CETAGESIC IV PAED

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 400,0 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 and plastic (LDPE)**, 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 Urticaria Acute generalised exanthematous pustulosis Toxic epidermal necrolysis Stevens-Johnson syndrome
General disorders and administration site condition	Administration site reaction

Reporting of suspected adverse reactions

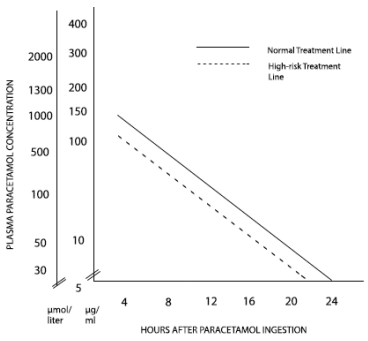
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, 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

Glass vial - 3 years (36 months)
Plastic (LDPE) - 2 years (24 months)

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 sterile, clear colourless type I glass vial with bromobutyl rubber stopper and purple aluminium seal and flip-off cap.
- 50 ml sterile, translucent white LDPE plastic Euro head bottle with cream-coloured latex rubber disc and transparent or opaque Snap-fit cap.
- 50 ml sterile, translucent white LDPE plastic nipple head bottle.

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. No: 011 848 3050

8. REGISTRATION NUMBER(S)

52/2.7/0445

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2022

PI 520445-2

CETAGESIC IV PAED

SKEDULERINGSTATUS

S3

1. NAAM VAN DIE MEDISYNE
CETAGESIC IV PAED 10 mg/ml oplossing vir infusie.

2. KWALITATIEWE AND KWANTITATIEVE SAMESTELLING
Elke ml bevat parasetamol 10 mg (500 mg / 50 ml)
Suikervry
Hulstowwe met bekende effek:
Bevat 2.47 mmol (56.85 mg) natrium per 50 ml oplossing vir infusie.
Bevat 400,0 mg propileenglukol per 50 ml oplossing vir infusie
Vir die volledige lys hulpstowwe, sien afdeling 6.1

3. FARMASEUTIESE VORM
Oplossing vir infusie.
'n Helder, kleurlose tot effens gelerige oplossing. Vry van vreemde stowwe.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
CETAGESIC IV PAED is aangedui in kinders 1 jaar of ouer, vir:
- korttermyn behandeling van ligte to matige pyn, bv. na 'n klein operasie.
- korttermyn behandeling van koors wanneer die orale roete nie geskik is nie.

4.2 Posologie en metode van toediening
Posologie
MOENIE DIE AANBEVOLE DOSIS OORSKRY NIE
Die voorgeskrewe dosis moet gebaseer wees op die pasiënt se gewig.
Onopsetlike oordosis kan lei tot ernstige lewerskade en dood (sien afdeling 4.9).
Gesondheidsorgverskaffers word daaraan herinner dat dit noodsaaklik is om beide die gewigsverwante dosisaanbevelings te volg en om individuele pasiënt minimum risikofaktore vir hepatotoksisiteit te oorweeg, insluitend hepatosellulêre ontoereikendheid, chroniese alkoholisme, chroniese wanvoeding (lae reserwes van lewerglutation) en dehidrasie (sien afdeling 4.4).
Beperk tot kinders wat meer as 10 kg weeg (ongeveer 1 jaar oud) maar minder as 33 kg (ongeveer 11 jaar oud).
Dosis:
15 mg/kg parasetamol voortoediening (d.w.s. 1,5 ml oplossing per kg) CETAGESIC IV PAED tot vier keer per dag. Die minimum interval tussen elke toediening moet minstens 4 ure wees. Die maksimum daaglikse dosis moet nie 60 mg/kg oorskry nie.

DOSERING IS GEBASEER OP PASIËNT GEWIG
DOSERING AANBEVELINGS WORD IN DIE TABEL HIERONDER AANGEBIED.

Pasiënt gewig (nie-edematiese gewig)	Parasetamol dosis (10 mg/ml) per toediening	Minimum interval tussen elke dosis	Maksimum daaglikse dosis*
> 10 kg en ≤ 33 kg	15 mg/kg (bv. 1,5 ml oplossing per kg) tot en met 4 maal per dag	4 ure	≤ 60 mg/kg Moet nie 2 g in 24 uur oorskry nie

* Die maksimum daaglikse dosis neem alle medisyne wat parasetamol bevat in ag.
Die dosis moet bereken word volgens nie-edematiese gewig.

Spesiale populasies:
Pasiënte met nierversaking
Dit word aanbeveel om 'n minimum interval van 6 ure tussen elke toediening te laat by pasiënte met ernstige nierinkorting (kreatinienopruiming ≤ 30 ml/min) (sien afdeling 5.2).

Pasiënte met lewerinkorting
By pasiënte met verswakte lewerfunksie moet die dosis verminder word of die doseringsinterval verleng word. Die maksimum daaglikse dosis moet nie 60 mg/kg/dag (nie meer as 2 g/dag) in die volgende situasies oorskry nie:
Volwassenes wat minder as 50 kg weeg
Chroniese of gekompenseerde aktiewe lewersiekte, veral dié met ligte tot matige hepatosellulêre ontoereikendheid.
• Gilbert se sindroom (familiële hiperbilirubinemie)
• Chroniese alkoholisme
• Chroniese wanvoeding (lae reserwe van hepatiese glutation) en
• Dehidrasie

Metode van toediening
CETAGESIC IV PAED moet as 'n 15-minute binneaarse infusie toegedien word. Voor toediening moet die produk visueel geïnspekteer word vir enige deeltjies en verkleuring. Dit is slegs bedoel vir eenmalige gebruik. Sodra dit oopgemaak is, moet die flessie onmiddellik gebruik word.
Aangesien CETAGESIC IV PAED **in glas en plastiek (LDPE)** aangebied word, is dosismonitering nodig om lugembolie te vermy, veral aan die einde van die infusie, ongeag die toedieningsroete, maar veral as 'n sentrale veneuse kateter vir die infusie gebruik word.
Enige ongebruikte oplossing moet weggegooi word.
CETAGESIC IV PAED moet nie met ander medisyne gemeng word nie (sien afdeling 6.2).
CETAGESIC IV PAED kan tot een tiende verdun word (een volume CETAGESIC IV PAED in nege volumes verdunningsmiddel) in 'n 0,9 % natriumchloriedoplossing of 'n 5 % glukoseoplossing. Die volume van die verdunde oplossing moet die totale volume vloeistof wat aan die pasiënt toegedien moet word sowel as die mediese toestand van die pasiënt in ag neem. Wanneer CETAGESIC IV PAED verdun word soos aanbeveel, moet die totale volume verdunde oplossing wat toegedien moet word binne een uur na voorbereiding (infusietyd ingesluit) toegedien word (sien afdeling 6.6).

4.3 Kontraindikasies
CETAGESIC IV PAED is teenaangedui in:
- bekende hipersensitiwiteit vir parasetamol of parasetamol hidrochloried (pro-geneesmiddel van parasetamol) of vir enige van die hulpstowwe (sien afdeling 6.1).
- gevalle van ernstige hepatosellulêre ontoereikendheid of gedekompenseerde aktiewe lewersiekte insluitend alkoholiese hepatitis (sien afdeling 4.4).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Hierdie produk bevat parasetamol wat in oordosis dodelik kan wees. In die geval van oordosis of vermoedelike oordosis en nieteenstaande die feit dat die persoon asimptomaties kan wees, moet die naaste dokter, hospitaal of gifsentrum onmiddellik gekontak word.

Wees versigtig om doseringsfoute te vermy as gevolg van verwarring tussen milligram (mg) en milliliter (mL), wat kan lei tot toevallige oordosis en dood.
Dit word aanbeveel om 'n geskikte pynstillende orale behandeling te gebruik sodra hierdie toedieningsroete moontlik is.
Om die risiko van oordosis te vermy, maak seker dat ander medisyne wat toegedien word nie parasetamol of propasetamol bevat nie.
Dosis hoër as die aanbevole hou risiko vir baie ernstige lewerskade in. Kliniese simptome en tekens van lewerskade (insluitend fulminante hepatitis, lewerversaking, cholestatiese hepatitis, sitolitiese hepatitis) word gewoonlik die eerste keer gesien na twee dae van geneesmiddeltoediening met 'n piek wat gewoonlik na 4 - 6 dae gesien word. Behandeling met teenmiddel moet so gou as moontlik gegee word.
CETAGESIC IV PAED kan ernstige velreaksies veroorsaak soos akute veralgemeende eksantematiese pustulose (AGEP), Stevens-Johnson -sindroom (SJS) en toksiese epidermale nekrolise (TEN), wat dodelik kan wees. Pasiënte moet ingelig word oor die tekens van ernstige velreaksies en die gebruik van die medisyne moet gestaak word by die eerste verskyning van veluitslag of enige ander teken van hipersensitiwiteit.
Hierdie medisyne bevat 56,85 mg natrium per 50 ml.
CETAGESIC IV PAED word as hoog in natrium beskou. Dit moet veral in ag geneem word vir diegene op 'n lae sout dieet.
CETAGESIC IV PAED bevat 8,0 mg propileenglikol in elke ml, wat gelykstaande is aan 12 mg/kg per 1,5 ml (totale daaglikse dosis vir pasiënte > 10 kg en ≤ 33 kg is 48 mg/kg propileenglikol).

CETAGESIC IV PAED moet met omsigtigheid gebruik word in gevalle van:
• Hepatosellulêre ontoereikendheid, insluitend Gilbert se sindroom (familiêre hiperbilirubinemie).
• Ernstige nierinkorting (kreatinienopruiming ≤ 30 ml/min)
• Glukose 6 Fosfaat Dehidrogenase (G6PD) tekort (kan lei tot hemolitiese anemie).
• Chroniese alkoholisme, oormatige alkoholinname (3 of meer alkoholiese drankies elke dag).
• Anoreksie, bulimie of kakeksie, chroniese wanvoeding (lae reserwes van hepatiese glutation).
• Dehidrasie, hipovolemie (sien afdeling 4.2)
Pasiënte wat aan hepatitis of alkoholisme ly, of wat van enige vorm van lewersiekte herstel, moet nie oormatige hoeveelhede CETAGESIC IV PAED gebruik nie.
Gebruik met omsigtigheid in niersiekte.

4.5 Interaksie met ander medisyne en ander vorme van interaksie
Effekte van ander medisyne op CETAGESIC IV PAED:
• Probenesied veroorsaak 'n byna 2-voudige vermindering in opruiming van parasetamol deur die konjugasie daarvan met glukuroonsuur te inhibeer. 'n Verlaging van die dosis parasetamol moet oorweeg word vir gelyktydige behandeling met probenesied,
• Salisilamied kan die eliminasie-halfleeftyd van parasetamol verleng,
• Omsigtigheid moet gegee word aan die gelyktydige gebruik van parasetamol en ensiem-induserende stowwe aangesien hierdie stowwe die risiko van parasetamol-geïnduseerde lewerbesering verhoog. Hierdie stowwe sluit in, maar is nie beperk nie tot: barbiturate, isoniasied, antikoagulante, sidovudien, amoksisillien + klavulansuur, en etanol,
• Fenitoïen wat saam met parasetamol toegedien word, kan lei tot verlaagde parasetamol-effektiwiteit en 'n verhoogde risiko van hepatotoksisiteit. Pasiënte wat fenitoïenterapie ontvang, moet groot en/of chroniese dosisse parasetamol vermy. Pasiënte moet gemonitor word vir bewyse van hepatotoksisiteit.
• *Flukloksasillien:* Omsigtigheid word aangeraai wanneer parasetamol gelyktydig met Flukloksasillien toegedien word as gevolg van die verhoogde risiko van hoë anioongaping metaboliese asidose (HAGMA), veral by pasiënte met 'n risikofaktor vir glutationtekorte soos ernstige nierinkorting, sepsis, wanvoeding en chroniese alkoholisme. Noukeurige monitering word aanbeveel om die voorkoms van suurbasisafwykings, naamlik HAGMA, op te spoor, insluitend die soek van urinêre 5-oksoprolien.

Effekte van CETAGESIC IV PAED op ander medisyne:
• Parasetamol kan die kans op ongewenste effekte verhoog wanneer dit saam met ander medisyne toegedien word.
• *Antistolmiddels:* Gelyktydige gebruik van parasetamol (4 g per dag vir ten minste 4 dae) met gepaardgaande middels insluitend warfarien kan lei tot variasies in INR-waardes. In hierdie geval moet verhoogde monitering van INR-waardes uitgevoer word gedurende die tydperk van gelyktydige gebruik sowel as vir 1 week nadat parasetamol-behandeling gestaak is.

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap
Kliniese ervaring van binneaarse toediening van parasetamol is beperk. Epidemiologiese data van die gebruik van orale terapeutiese dosisse parasetamol dui egter op geen ongewenste uitwerking op die swangerskap of op die gesondheid van die fetus / pasgebore baba nie.
Voornemende data oor swangerskappe wat aan oordosis blootgestel is, het nie 'n toename in misvormingsrisiko getoon nie.
Reproduktiewe studies met die binneaarse vorm van parasetamol is nie by diere uitgevoer nie. Studies met die orale roete het egter geen misvorming van fetotoksiese effekte getoon nie.
Nietemin moet parasetamol met omsigtigheid tydens swangerskap gebruik word. In hierdie geval moet die aanbevole dosis en duur streng nagekom word.

Borsvoeding
Na orale toediening word parasetamol in klein hoeveelhede in borsmelk uitgeskei. Geen ongewenste effekte op sogende babas is aangemeld nie.
Uitslag by sogende babas is aangemeld. Omsigtigheid moet gebruik word wanneer parasetamol toegedien word aan vroue wat borsvoed.

4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik
Nie van toepassing nie.

4.8 Ongewenste effekte
Die volgende nadelige geneesmiddelreaksies (ADR's) kan voorkom:
Bloed- en limfstelselafwykings
Minder gereeld: Trombositopenie, agranulositose, leukopenie, pansitopenie, neutropenie, anemie
Hartafwykings
Minder gereeld: Hipotensie
Hepatobiliêre afwykings
Minder gereeld: Verhoogde vlakke van hepatiese transaminases, hepatitis, pankreatitis
Nier- en urinêre afwykings
Minder gereeld: Renale koliek, nierversaking en steriele pyurie
Algemene versteurings en toedieningsplek toestand
Gereeld: reaksies by die inspuitplek (pyn en brandende sensasie)
Minder gereeld: Malaise, hipersensitiwiteitsreaksie

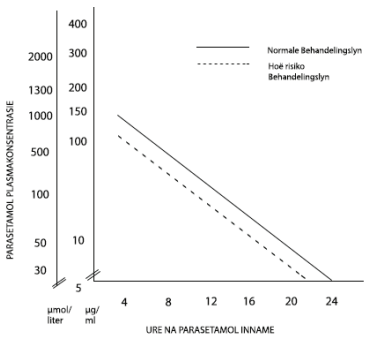
Na-bemarking ervaring:
Die volgende nadelige gebeurtenisse is ook gerapporteer tydens na-bemarking toesig, maar die voorkomssyfer (frekwensie) is nie bekend nie.

Orgaan Sisteem	Nadelige gebeurtenis
Immuunsisteem afwykings	Anafilaktiese skok Anafilakse Hipersensitiwiteitsreaksie Angioedeem
Bloed en limfatiese sisteem afwykings	Trombositopenie
Hartafwykings	Tagikardie
Gastrointestinaleversteurings	Naarheid braking
Hepatobiliêre afwykings	Fulminante hepatitis Hepatiese nekrose Lewerversaking Verhoogde lewerensieme
Vel en subkutane weefsel versteurings	Eriteem Gloede Pruritus Uitslag Urtikaria Akute algemene eksantematose pustulose Toksiese epidermale nekrolyse Stevens-Johnson sindroom
Algemene versteurings en toedieningsplek toestand	Toedieningsplek reaksie

Aanmelding van vermoedelike nadelige reaksies
Dit is belangrik om vermoedelike nadelige reaksies aan te meld na goedkeuring van die medisyne. Dit laat voortgesette monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word gevra om enige vermeende nadelige reaksies by SAHPRA aan te meld via die **"6.04 Adverse Drug Reactions Reporting Form"**, wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
Vinnige behandeling is noodsaaklik. In die geval van 'n oordosis, raadpleeg onmiddellik 'n dokter, of neem die persoon direk na 'n hospitaal.
'n Vertraging in die aanvang van behandeling kan beteken dat teenmiddel te laat gegee word om doeltreffend te wees. Bewyse van lewerskade word dikwels uitgestel tot nadat die tyd vir effektiewe behandeling verstryk het.
Gevoeligheid vir parasetamol-toksisiteit word verhoog by pasiënte wat herhaalde hoë dosisse (meer as 5-10 g/dag) parasetamol vir 'n paar dae geneem het, in chroniese alkoholisme, chroniese lewersiekte, VIGS, wanvoeding, en met die gebruik van middels wat lewer mikrosomale oksidasie soos barbiturate, isoniasied, rifampisien, fenitoïen en karbamasepien.
Simptome van oordosis parasetamol in die eerste 24 uur sluit bleekheid, naarheid, braking, anoreksie en moontlik abdominale pyn in. Ligte simptome gedurende die eerste twee dae van akute vergiftiging, weerspieël nie die potensiële erns van die oordosis nie.
Lewerskade kan 12 tot 48 uur of later na inname sigbaar word, aanvanklik deur verhoging van die serumtransaminase- en melksuurdehidrogenase-aktiwiteit, verhoogde serumbilirubienkonsentrasie en verlenging van die protrombientyd. Lewerskade kan lei tot enkefalopatie, koma en dood.
Akute nierversaking met akute tubulêre nekrose kan ontwikkel selfs in die afwesigheid van ernstige lewerskade. Abnormaliteite van glukosemetabolisme en metaboliese asidose kan voorkom. Kardiale aritmieë is aangemeld.

Behandeling vir oordosis parasetamol:
Alhoewel bewyse beperk is, word dit aanbeveel dat enige volwasse persoon wat 5 - 10 gram of meer parasetamol (of 'n kind wat meer as 140 mg/kg gehad het) binne die voorafgaande vier uur ingeneem het, die maag deur spoeling (braking kan voldoende wees vir kinders) en 'n enkeldosis van 50 g geaktiveerde houtskool gegee via die spoelbuis. Inname van hoeveelhede parasetamol kleiner as dit kan behandeling vereis by pasiënte wat vatbaar is vir parasetamolvergiftiging (sien hierbo). In pasiënte wat stuperose of komatose is, moet endotrageale intubasie maagspoeling voorafgaan om aspirasie te vermy.
N-asetielsisteïen moet so gou moontlik toegedien word aan alle gevalle van vermoedelike oordosis, verkieslik binne agt uur na oordosering, alhoewel behandeling tot 36 uur na inname steeds voordelig kan wees, veral as meer as 150 mg/kg parasetamol geneem is. 'n Aanvangsdosis van 150 mg/kg N-asetielsisteïen in 200 ml dekstrose-inspuiting **binneaars** toegedien oor 15 minute, gevolg deur 'n infusie van 50 mg/kg in 500 ml dekstrose-inspuiting oor die volgende vier uur, en dan 100 mg/kg in 1 000 ml dekstrose-inspuiting oor die volgende sestien uur.
Die volume binneaarse vloeistof moet vir kinders aangepas word.
Alhoewel die orale formulering nie die behandeling van keuse is nie, kan 140 mg/kg opgelos in water aanvanklik toegedien word, gevolg deur 70 mg/kg elke vier uur vir sewentien dosisse.
'n Plasma parasetamolvlak moet vier uur na inname bepaal word in alle gevalle van vermoedelike oordosis. Vlakke wat voor vier uur gedoen word, kan misleidend wees. Pasiënte wat die risiko loop van lewerskade, en dus voortgesette behandeling met N-asetielsisteïen benodig, kan geïdentifiseer word volgens hul 4-uur plasma parasetamol vlak. Die plasmaparasetamolvlak kan teen tyd sedert inname in die nomogram hieronder geteken word. Die nomogram moet slegs gebruik word met betrekking tot 'n enkele akute inname.
Diegene wie se plasma-parasetamolvlakke bo die "normale behandelingslyn" is, moet herhaaldelik voortgaan met N-asetielsisteïenbehandeling met 100 mg/kg IV oor sestien uur herhaaldelik tot herstel. Pasiënte met verhoogde vatbaarheid vir lewerskade soos hierbo geïdentifiseer, moet behandeling voortgaan indien konsentrasies bo die "hoërisiko behandelingslyn is". Protrombien-indeks korreleer die beste met oorlewing.
Vir oordosis met 'n verlengde/gemodifiseerde vrystelling voorbereiding is die waarde van die nomogram onbekend. Aangesien daar geen inligting is oor die plasmavlakke van parasetamol na 'n oordosis van verlengde/gemodifiseerde vrystelling parasetamolpreparate nie, moet alle pasiënte met vermoedelike of bekende oordosis met sulke preparate N-asetielsisteïen ontvang. Weens 'n gebrek aan data vir formulerings met verlengde/gewysigde vrystelling, mag 'n vlak onder die "behandelingslyn" van die nomogram nie die moontlikheid van toksisiteit uitsluit nie. Monitor alle pasiënte met beduidende inname vir ten minste ses en negentig uur.



Bron: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed

5. FARMAKOLOGIESE EIENSKAPPE
Kategorie en klas: A 2.7 Antipiretika of antipiretiese en anti-inflammatoriese pynstillers.

5.1 Farmakodinamiese eienskappe

Farmakoterapeutiese groep:	ANDER PYNSTILLERS EN ANTIPIRETIKA
ATC Kode:	N02BE01

Parasetamol het pynstillende en koorswerende werking. Die presiese meganisme van die pynstillende en antipiretiese eienskappe van parasetamol is nie vasgestel nie; dit kan sentrale en perifere aksies behels.

5.2 Farmakokinetiese eienskappe
Absorpsie
By volwassenes is parasetamol se farmakokinetika lineêr tot 2 g na enkeltoediening en na herhaalde toediening gedurende 24 uur.
Die maksimum plasmakonsentrasie (Cmax) van parasetamol waargeneem aan die einde van 15 minute binneaarse infusie van 500 mg parasetamol is ongeveer 15 µg/ml.

Verspreiding
Die verspreidingsvolume van parasetamol is ongeveer 1 l/kg.
Parasetamol word nie ekstensief aan plasmaproteïene gebind nie.
Na infusie van 1 g parasetamol by volwassenes, is beduidende konsentrasies parasetamol (ongeveer 1,5 µg/ml) in die serebrospinale vloeistof waargeneem vanaf die 20ste minuut na infusie.

Biotransformasie
Parasetamol word hoofsaaklik in die lewer gemetaboliseer volgens twee groot hepatiese weë: glukuronsuurkonjugasie en swaelsuurkonjugasie. Laasgenoemde roete is vinnig versadigbaar by dosisse wat die terapeutiese dosisse oorskry. 'n Klein fraksie (minder as 4 %) word deur sitochroom P450 gemetaboliseer na 'n reaksie-tussenproduk (N-asetielbensakinonimien) wat, onder normale gebruikstoestande, vinnig ontgif word deur verminderde glutation en in die uriene uitgeskei word na konjugasie met sisteïen en merkapturiensuur. Tydens massiewe vergiftiging word die hoeveelheid van hierdie giftige metaboliet egter verhoog.

Uitskeiding
Die metaboliete van parasetamol word hoofsaaklik in die uriene uitgeskei. 90 % van die toegediende dosis word binne 24 uur uitgeskei, hoofsaaklik as glukuronied (60-80 %) en sulfaat (20-30 %) konjugate. Minder as 5 % word onveranderd uitgeskei.
Plasma-eliminasie-halfleeftyd is 2,7 ure en totale liggaamsopruiming is 18 l/h.

Kinders
Die farmakokinetiese parameters van parasetamol wat by kinders waargeneem word, is soortgelyk aan dié wat by volwassenes waargeneem word, behalwe vir die plasmahalfleeftyd wat effens korter is (1,5 tot 2 ure) as by volwassenes.
Totale uitskeiding van parasetamol en sy metaboliete is dieselfde vir alle ouderdomme.

Spesiale bevolkings
Pasiënte met nierinkorting
In gevalle van ernstige nierinkorting (kreatinienopruiming ≤ 30 ml/min), word die eliminasie van parasetamol vertraag, die eliminasie-halfleeftyd wissel van 2 tot 5,3 ure. Vir die glukuronied- en sulfaatkonjugate is die eliminasietempo 3 keer stadiger by proefpersone met ernstige nierversaking as by gesonde proefpersone. Daarom word dit aanbeveel om 'n interval van ten minste 6 ure tussen toedienings te laat by pasiënte met ernstige nierversaking (kreatinienopruiming ≤ 30 ml/min).

Lewerinkorting
Parasetamol moet met omsigtigheid gebruik word by pasiënte met ligte tot matige lewerinkorting en is teenaangedui wanneer daar aktiewe siekte is, veral alkoholiese hepatitis as gevolg van CYP 2E1-induksie, wat lei tot verhoogde vorming van die hepatotoksiese metaboliet van parasetamol.

Bejaarde pasiënte
Die farmakokinetika en die metabolisme van parasetamol word nie by bejaarde proefpersone gewysig nie. Geen dosisaanpassing is nodig in hierdie populasie nie.

5.3 Prekliniese veiligheidsdata
Prekliniese data toon geen spesiale gevaar vir mense buiten die inligting wat in ander afdelings ingesluit is nie.
Studies oor plaaslike verdraagsaamheid van parasetamol-infusie by rotte en konyne het goeie verdraagsaamheid getoon. Afwesigheid van vertraagde kontakhipersenistiwiteit is by proefkonyne getoets.

6.1 Lys van hulpstowwe
Propileenglukol
Sitroensuur monohidraat
Natrium Metabisulfiet
Dinatriumwaterstoffosfaatdihidraat
Natriumchloried
Water vir inspuiting

6.2 Onverdraagsaamheid
CETAGESIC IV PAED moet nie met ander medisyne gemeng word nie.

6.3 Raklewe
Glasflessie - 3 jaar (36 maande)
Plastiek (LDPE) - 2 jaar (24 maande)

6.4 Spesiale voorsorgmaatreëls vir berging
Bewaar teen of benede 30 °C. Beskerm teen lig.
Moet nie verkoel of vries nie.
Moet nie toedien as sigbare deeltjies teenwoordig is nie.
Gebruik onmiddellik na oopmaak. Gooi oorblywende gedeelte weg.
Hou buite bereik van kinders.

6.5 Aard en inhoud van houer
• 50 ml steriele, helder kleurlose tipe 1 glasflessie met bromobutielrubberprop en pers aluminiumseël en afdraaidop.
• 50 mL steriele, deurskynende wit LDPE-plastiek Euro-kopbottel met roomkleurige latexrubberskyf en deursigtige of ondeursigtige Snap-fit doppie.
• 50 ml steriele, deurskynende wit LDPE-plastiek tepelkopbottel.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Gebruik 'n 0,8 mm-naald en deurdring die prop vertikaal op die plek wat spesifiek aangedui is.
Voor toediening moet die produk visueel geïnspekteer word vir enige deeltjies en verkleuring. Slegs vir eenmalige gebruik. Enige ongebruikte oplossing moet weggegooi word.
Die verdunde oplossing moet visueel geïnspekteer word en moet nie gebruik word in die teenwoordigheid van opale vorming, sigbare deeltjies of neerslag nie.

7. HOUER VAN SERTIFIKAAT VAN REGISTRASIE
Biotech Laboratories (Edms.) Bpk
Grondvloer Blok K West Central Park
16de Weg 400, Randjespark
Halfweghuis
Midrand 1685
Tel. nr: 011 848 3050

8. REGISTRASIE NOMMER(S)
52/2.7/0445

9. DATUM VAN EERSTE REGISTRASIE /HERNUWING VAN DIE REGISTRASIE
24 Januarie 2022

PI 520445-2