Proposed Professional Information for PARACETAMOL BIOTECH IV (Clean Copy)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PARACETAMOL BIOTECH IV 10 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARACETAMOL BIOTECH IV contains 10 mg per mL paracetamol as active ingredient.

Each 100 mL vial contains 1 g paracetamol.

Sugar free.

Excipients with known effect:

Contains propylene glycol.

Contains sodium.

For the 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.

The pH of the solution is between 3.5 and 6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARACETAMOL BIOTECH IV is indicated for:

The short-term treatment (not exceeding 24 hours) of mild to moderate pain e.g. after dental procedures and minor orthopaedic procedures, and the 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.

Unintentional overdose can lead to serious liver damage and death. Health care providers are reminded that it is essential to follow both the weight-related dose recommendations and to consider individual patient risk factors for hepatotoxicity including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione) and dehydration (see sections 4.4, 4.2 and 4.9).

Adults and adolescents weighing more than 50 kg:

PARACETAMOL BIOTECH IV 1 g 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 in 24 hours.

Adolescents and adults weighing less than 50 kg and children weighing more than 33 kg (approximately 11 years old):

PARACETAMOL BIOTECH IV: 15 mg/kg per administration, i.e. 1,5 mL solution per kg. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 60 mg/kg (without exceeding 3 g in 24 hours).

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***
> 50 kg	1 g (i.e. 100 mL vial up to 4 times a day	4 hours	Must not exceed 4 g in 24 hours
> 33 kg and ≤ 50 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 3 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

Severe renal insufficiency:

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 4.4).

Hepatic impairment:

In patients with impaired hepatic function, 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 reserves of hepatic glutathione).
- Dehydration.

Method of administration

PARACETAMOL BIOTECH IV should be administered as a 15-minute intravenous infusion.

Careful monitoring to avoid air embolism is needed, notably at the end of the infusion, especially if a central venous catheter is used for the infusion.

Also see sections 6.2 and 6.6.

4.3 Contraindications

PARACETAMOL BIOTECH IV is contraindicated in:

- Situations where there is a hypersensitivity to paracetamol or to paracetamol hydrochloride (prodrug of paracetamol) or to any of the excipients of PARACETAMOL BIOTECH IV (see section 6.1).
- Cases of severe hepatocellular insufficiency or active liver disease including alcoholic hepatitis.

- Children weighing less than 33 kg (approximately 11 years old) as safety and efficacy have not been established.

4.4 Special warnings and precautions for use

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

Dosages of PARACETAMOL BIOTECH IV in excess of those recommended may cause severe liver damage.

Clinical symptoms and signs of liver damage are usually seen first after two days with a maximum usually after 4 – 6 days. Treatment with an antidote should be given as soon as possible as PARACETAMOL BIOTECH IV overdose may be fatal (see section 4.9).

In order to avoid the risk of overdose, ensure that the other medicines administered do not contain paracetamol.

PARACETAMOL BIOTECH IV 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.

PARACETAMOL BIOTECH IV 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.

Salicylates in prolonged treatments together with PARACETAMOL BIOTECH IV significantly

increased the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal diseases, and cancer of the urinary bladder. Do not exceed the recommended individual dosages for salicylates and PARACETAMOL BIOTECH IV (see section 4.5).

The anticoagulant effect could be increased when high doses of PARACETAMOL BIOTECH IV are used together with anticoagulants, such as warfarin (see section 4.5).

The risk of PARACETAMOL BIOTECH IV toxicity may be increased in patients receiving potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes (see section 4.5).

Patients suffering from alcoholism, hepatitis, recovering from any form of liver disease or malnutrition should not use excessive quantities of PARACETAMOL BIOTECH IV.

PARACETAMOL BIOTECH IV should be used with caution in patients suffering from renal disease, as prolonged excessive use of paracetamol can produce nephropathy. Paracetamol-induced renal function impairment may be sufficiently severe and could result in uraemia, especially with prolonged use of high doses. In patients with renal impairment with a creatinine clearance of 30 mL/minute or less the elimination of paracetamol is delayed, therefore a 6 hourly dose interval is recommended (see section 4.2).

PARACETAMOL BIOTECH IV should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert’s syndrome (familial hyperbilirubinaemia) (see sections 4.2 and 4.3).
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min) (see sections 4.2 and 5.2).
- Chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day) (see section 4.3).

- Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione).
- Dehydration, hypovolaemia.
- Glucose 6 phosphate dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia).

Store PARACETAMOL BIOTECH IV in a safe place out of reach of children.

Excipients:

PARACETAMOL BIOTECH IV contains 800 mg propylene glycol in each 100 mL vial. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the fetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis (see section 4.6).

PARACETAMOL BIOTECH IV contains 200 mg sodium per vial, equivalent to 10 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on PARACETAMOL BIOTECH IV:

Probenecid could increase the plasma concentrations of PARACETAMOL BIOTECH IV by almost a 2-fold reduction in clearance of paracetamol. A decrease in PARACETAMOL BIOTECH IV dose may be considered with concomitant use.

The absorption of paracetamol may be accelerated when used together with metoclopramide.

Salicylamide may prolong the elimination half-life of paracetamol as contained in PARACETAMOL BIOTECH IV.

Salicylates in prolonged treatments together with paracetamol significantly increased the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal diseases, and cancer of the urinary bladder. The recommended individual doses for PARACETAMOL BIOTECH IV and the salicylates should not be exceeded.

Phenytoin administered concomitantly with PARACETAMOL BIOTECH IV 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.

Medicines that induce liver microsomal enzymes such as barbiturates or primidone could decrease the therapeutic effect of PARACETAMOL BIOTECH IV.

Concomitant use of PARACETAMOL BIOTECH IV and hepatic enzyme inducers should be used with caution as these medicines increase the risk of paracetamol induced hepatotoxicity. These

substances include, but are not limited to barbiturates, isoniazid, rifampicin, carbamazepine, anticoagulants, zidovudine, amoxicillin, clavulanic acid, ethanol or hepatotoxic medicines.

Effect of PARACETAMOL BIOTECH IV on other medicines:

PARACETAMOL BIOTECH IV may increase the chance of unwanted effects when administered with other medicines.

The anticoagulant effects may increase when high doses of PARACETAMOL BIOTECH IV are used together with anticoagulants, coumarin (e.g. warfarin) and/or indadione derivates. Increased monitoring of INR values should be conducted during the period of concomitant use, as well as 1 week after discontinuation of PARACETAMOL BIOTECH IV.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical experience of intravenous administration of paracetamol in pregnant women is limited.
Epidemiological data from the use of oral therapeutic doses of paracetamol did not result in any unwanted effects in pregnant women or on the health of the fetus/new-born infant.
Prospective data on pregnancies exposed to overdose 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 teratogenic or fetotoxic effects.
Nevertheless, PARACETAMOL BIOTECH IV should only be used during pregnancy after careful benefit/risk assessment, and the recommended dosage and duration must be strictly observed.
Also see “*Excipients*” in section 4.4.

Lactation

Paracetamol is excreted in breast milk in small quantities. Rash in nursing infants has been reported. Caution should be used when administering PARACETAMOL BIOTECH IV to women who are breastfeeding their babies.

4.7 Effects on ability to drive and use machines

PARACETAMOL BIOTECH IV should have no influence on the ability to drive and the use of machines. No unwanted effects which could influence the ability to drive and to operate machinery have been reported by patients using PARACETAMOL BIOTECH IV.

4.8 Undesirable effects

Blood and lymphatic system disorders:

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

Immune system disorders:

Less frequent: Hypersensitivity.

Endocrine disorders:

Less frequent: Pancreatitis.

Vascular disorders:

Less frequent: Hypotension.

Hepato-biliary disorders:

Less frequent: Hepatitis, increased levels of hepatic transaminases.

Frequency unknown: Hepatic necrosis, hepatic failure.

Renal and urinary disorders:

Less frequent: Renal colic, renal failure, sterile pyuria.

General disorders and administration site conditions:

Less frequent: Malaise.

Post-marketing experience

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

Immune system disorders:

Anaphylactic shock, anaphylaxis, hypersensitivity reaction, angio-oedema.

Cardiac disorders:

Tachycardia.

Gastrointestinal disorders:

Nausea, vomiting.

Hepato-biliary disorders:

Fulminant hepatitis, hepatic necrosis, hepatic failure.

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 conditions:

Administration site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of PARACETAMOL BIOTECH IV is important. It allows continued monitoring of the benefit/risk balance of PARACETAMOL BIOTECH IV. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**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. There is a risk of poisoning, particularly in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicine 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, anorexia and 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 administration of PARACETAMOL BIOTECH IV, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin or increased INR time. Clinical symptoms of liver damage are usually evident initially only after 2 days and reach a maximum after 4 to 6 days. Liver damage may lead to encephalopathy, coma and death.

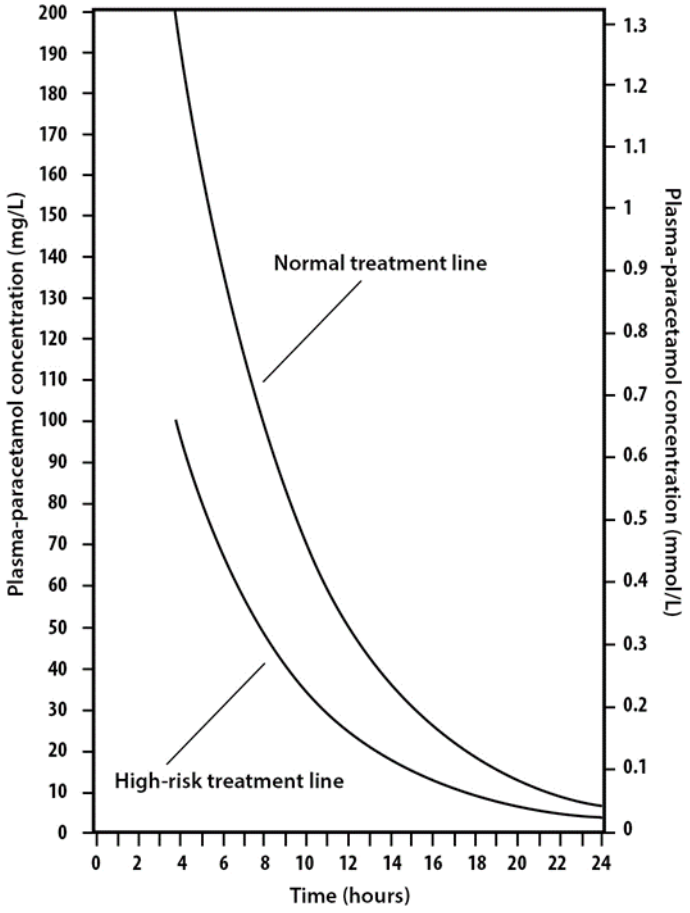
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment of paracetamol overdosage following IV administration of PARACETAMOL BIOTECH IV

As soon as possible after the suspected overdose, and before starting treatment, draw blood for a paracetamol plasma assay.

N-acetylcysteine (NAC) 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 the overdose may still be of benefit, especially if more than 150 mg/kg of paracetamol was administered. An initial dose of 150 mg/kg N-acetylcysteine in 200 mL dextrose 5 % w/v injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose 5 % w/v injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose 5 % w/v injection over the next sixteen hours. Sodium chloride 0,9 % w/v may be used where glucose 5 % w/v is unsuitable. **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.



Source: Martindale, The Complete Drug Reference, 36th Edition, page 109

Paracetamol overdose with IV Infusions

After an overdosage with an intravenous infusion, the standard nomogram used for determining treatment from paracetamol plasma concentrations following oral ingestion of an overdose of paracetamol, may not be appropriate. Paracetamol plasma concentrations more than 4 hours after intravenous injection may be lower than those predicted for the same oral dose at the same time point after 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.

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

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

Pharmacotherapeutic group: Other analgesics and antipyretics.

ATC code: N02BE01.

The mechanism of analgesic and antipyretic actions of paracetamol has not been fully determined. It may involve central and peripheral actions.

5.2 Pharmacokinetic properties

Absorption:

Paracetamol pharmacokinetics is linear up to 2 g after a single administration and after repeated administration during 24 hours. The maximal plasma concentration (Cmax) of 30 µg/mL paracetamol is observed after 15 minutes of an intravenous infusion of 1 g of paracetamol.

Distribution:

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of paracetamol to plasma proteins is variable. The volume of distribution is about 1 L/kg. Significant concentrations of paracetamol of about 1,5 µg/mL were observed in the cerebrospinal fluid after about 20 minutes of a 1 g paracetamol intravenous infusion.

Metabolism:

Paracetamol is metabolised in the liver by conjugation with glucuronic acid (60 %), sulphuric acid (35 %), and cysteine (± 3 %). A minor hydroxylated metabolite (N-acetyl-p-benzoquinone imine) is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidneys. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage. Neonates, infants and children up to 10 years excrete significantly more sulphate and less glucuronide conjugates than adults.

Elimination:

Paracetamol and its metabolites are mainly excreted in the urine.
Less than 5 % of the dose is excreted as unchanged paracetamol. Some 90 % to 100 % of the dose may be recovered in the urine as metabolites within the first 24 hours of administration. The plasma half-life of paracetamol is 2,7 hours for adults, 1,5 to 2 hours for infants and children and 3,5 hours in neonates. Total body clearance is 18 L/h at all ages.

Special populations

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 the 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) (see section 4.2).

Elderly subjects:

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects.

No dose adjustment is required in this population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Disodium hydrogen phosphate dihydrate

Propylene glycol

Sodium metabisulphite

Sodium chloride

Water for injection.

6.2 Incompatibilities

PARACETAMOL BIOTECH IV should not be mixed with other medicines.

6.3 Shelf life

Unopened vials:

36 months.

After first opening:

Use immediately.

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.

Discard remaining portion.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Before administration, the product should be visually inspected for any particulate matter and discolouration, e.g. yellowing. It is intended for single-use only. Once opened, the vial should be used immediately

Any unused solution should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBER

45/2.7/0443

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2015

10. DATE OF REVISION OF THE TEXT

03 December 2021