PARACETAMOL BIOTECH IV

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 10,0 mg per mL paracetamol as active ingredient.
Each 100 mL vial contains 1,0 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. Healthcare 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.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with PARACETAMOL BIOTECH IV must immediately be discontinued and appropriate treatment instituted.

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 breastfeeding
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/newborn 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.

Breastfeeding
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.

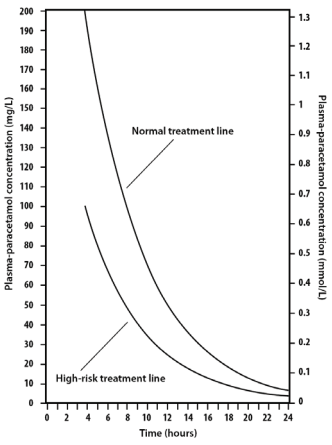
4.8 Undesirable effects
Blood and lymphatic system disorders
Less frequent: Thrombocytopenia, agranulocytosis, leucopenia, pancytopenia, neutropenia, anaemia.
Immune system disorders
Less frequent: Hypersensitivity.
Endocrine disorders
Less frequent: Pancreatitis.
Vascular disorders
Less frequent: Hypotension.
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, severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4).
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 1000 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 (C_{max}) 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
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10. DATE OF REVISION OF THE TEXT
20 July 2023

NAMIBIA:	
Reg. No. 23/2.7/0001	NS2

PI450443-3

PARACETAMOL BIOTECH IV

SKEDULERINGSTATUS

S3

1. NAAM VAN DIE MEDISYNE
PARACETAMOL BIOTECH IV 10 mg/mL oplossing vir infusie

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
PARACETAMOL BIOTECH IV bevat 10,0 mg per mL parasetamol as aktiewe bestanddeel.
Elke100 mL fles bevat 1,0 g parasetamol.
Suiker Vry.

Hulpstowwe met bekende effekte:
Bevat propileenglikol.
Bevat natrium.
Vir die volledige lys van Hulpstowwe, sien afdeling 6.1.

2. FARMASEUTIESE FORM
Oplossing vir infusie.
'n Helder, kleurlose tot effens gelerige oplossing, vry van vreemde stowwe.
Die pH van die oplossing is tussen 3,5 en 6.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
PARACETAMOL BIOTECH IV is aangedui vir:
Die korttermynbehandeling (nie meer as 24 uur) van ligte tot matige pyn bv. na tandheelkundige prosedures en geringe ortopediese prosedures, en die korttermynbehandeling van koors, wanneer die orale roete ongeskik is.

4.2 Posologie en metode van toediening
Posologie
MOENIE DIE AANBEVOLE DOSIS OORSKRY NIE.

Onopsetlike oordosis kan lei tot ernstige lewerskade en dood. Gesondheidsorgverskaffers word daaraan herinner dat dit noodsaaklik is om beide die gewigsverwante dosisaanbevelings te volg en om individuele pasiëntrisikofaktore vir hepatotoksisiteit te oorweeg, insluitend hepatosellulêre ontoereikendheid, chroniese alkoholisme, chroniese wanvoeding (lae reserwes van hepatiese glutatioon) en dehidrasie (sien afdelings 4.4, 4.2 en 4.9).

Volwassenes en adolessente wat meer as 50 kg weeg:
PARACETAMOL BIOTECH IV 1 g per toediening, dit wil sê een 100 mL flessie, tot vier keer per dag. Die minimum interval tussen elke toediening moet 4 uur wees. Die maksimum daaglikse dosis moet nie 4 g in 24 uur oorskry nie.

Adolessente en volwassenes wat minder as 50 kg weeg en kinders wat meer as 33 kg weeg (ongeveer 11 jaar oud):
PARACETAMOL BIOTECH IV: 15 mg/kg per toediening, dit wil sê 1,5 mL oplossing per kg. Die minimum interval tussen elke toediening moet 4 uur wees. Die maksimum daaglikse dosis moet nie 60 mg/kg oorskry nie (sonder om 3 g in 24 uur te oorskry).

Doseringsaanbevelings word in die tabel hieronder aangebied:

Pasiënt gewig (nie-edematiese gewig)	**Parasetamol dosering (10 mg/mL) per toediening**	**Minimum interval tussen elke toediening**	**Maksimum daaglikse dosis***
> 50 kg	1 g (d.w.s 100 mL fles tot 4 keer per dag	4 ure	Moet nie 4 g in 24 uur uur oorskry nie
> 33 kg en ≤ 50 kg	15 mg/kg (d.w.s 1,5 mL oplossing per kg) tot 4 keer per dag	4 ure	≤ 60 mg/kg Moet nie 3 g in 24 uur oorskry nie

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

Spesiale bevolkings
Ernstige nierontoereikhendheid:
Dit word aanbeveel om 'n minimum interval van 6 uur tussen elke toediening te laat by pasiënte met ernstige nierontoereikhendheid (kreatinienopruiming ≤ 30 mL/min) (sien afdeling 4.4).

Lewer inkorting:
By pasiënte met verswakte lewerfunksie moet die maksimum daaglikse dosis nie 60 mg/kg/dag (nie meer as 2 g/dag) oorskry nie in die volgende situasies:
• 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 reserwes van hepatiese glutatioon).
• Dehidrasie.

Metode van toediening
PARACETAMOL BIOTECH IV moet as 'n 15-minute binneaarse infusie toegedien word.
Noukeurige monitering om lugembolie te vermy is nodig, veral aan die einde van die infusie, veral as 'n sentrale veneuse kateter vir die infusie gebruik word.
Sien ook afdelings 6.2 en 6.6.

4.3 Kontraindikasies
PARACETAMOL BIOTECH IV is teenaangedui in:
• Situasies waar daar hipersensitiwiteit is vir parasetamol of vir parasetamolhidrochloried (voormiddel van parasetamol) of vir enige van die hulpstowwe van PARACETAMOL BIOTECH IV (sien afdeling 6.1).
• Gevalle van ernstige hepatosellulêre ontoereikendheid of aktiewe lewersiekte insluitend alkoholiese hepatitis.
• Kinders wat minder as 33 kg weeg (ongeveer 11 jaar oud) omdat veiligheid en doeltreffendheid nie vasgestel is nie.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Dit word aanbeveel om geskikte orale pynstillende behandeling te gebruik sodra hierdie toedieningsroete moontlik is.
Dosisse van PARACETAMOL BIOTECH IV wat groter is as dié wat aanbeveel word, kan ernstige lewerskade veroorsaak.
Kliniese simptome en tekens van lewerskade word gewoonlik eers na twee dae gesien met 'n maksimum gewoonlik na 4 – 6 dae.
Behandeling met 'n teenmiddel moet so gou as moontlik gegee word aangesien PARACETAMOL BIOTECH IV oordosis noodlottig kan wees (sien afdeling 4.9).
Om die risiko van oordosis te vermy, maak seker dat die ander medisyne wat toegedien word nie parasetamol bevat nie.
PARACETAMOL BIOTECH IV kan ernstige velreaksies veroorsaak soos akute veralgemeende eksantematiese pustulose (AGEP), Stevens-Johnson-sindroom (SJS) en toksiese epidermale nekrolise (TEN), wat noodlottig 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.

PARACETAMOL BIOTECH IV bevat parasetamol wat in oordosis noodlottig 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.

Salisilate in langdurige behandelings saam met PARACETAMOL BIOTECH IV het die risiko van pynstillende nefropatie, nierpapillêre nekrose, eindstadium niersiektes en kanker van die blaas aansienlik verhoog. Moenie die aanbevole individuele dosisse vir salisilate en PARACETAMOL BIOTECH IV oorskry nie (sien afdeling 4.5).
Die antikoagulant effek kan verhoog word wanneer hoë dosisse PARACETAMOL BIOTECH IV saam met antikoagulante, soos warfarien, gebruik word (sien afdeling 4.5).
Die risiko van PARACETAMOL BIOTECH IV-toksisiteit kan verhoog word by pasiënte wat potensieel hepatotoksiese medisyne of medisyne ontvang wat lewermikrosomale ensieme induseer (sien afdeling 4.5).
Pasiënte wat aan alkoholisme, hepatitis ly, herstel van enige vorm van lewersiekte of wanvoeding moet nie oormatige hoeveelhede PARACETAMOL BIOTECH IV gebruik nie.
PARACETAMOL BIOTECH IV moet met omsigtigheid gebruik word by pasiënte wat aan niersiekte ly, aangesien langdurige oormatige gebruik van parasetamol nefropatie kan veroorsaak. Parasetamol-geïnduseerde nierfunksie inkorting kan ernstig genoeg wees en kan lei tot uremie, veral met langdurige gebruik van hoë dosisse. By pasiënte met nierversaking met 'n kreatinienopruiming van 30 mL/minuut of minder word die eliminasie van parasetamol vertraag, daarom word 'n dosisinterval van 6 uur aanbeveel (sien afdeling 4.2).

PARACETAMOL BIOTECH IV moet met omsigtigheid gebruik word in gevalle van:
• Hepatosellulêre ontoereikendheid, insluitend Gilbert se sindroom (familiële hiperbilirubinemie) (sien afdelings 4.2 en 4.3).
• Ernstige nierontoereikhendheid (kreatinienopruiming ≤ 30 mL/min) (sien afdelings 4.2 en 5.2).
• Chroniese alkoholisme, oormatige alkoholinname (3 of meer alkoholiese drankies elke dag) (sien afdeling 4.3).
• Anoreksie, bulimie of kakeksie, chroniese wanvoeding (lae reserwes van hepatiese glutatioon).
• Dehidrasie, hipovolemie.
• Glukose 6 fosfaat dehidrogenase (G6PD) tekort (kan lei tot hemolitiese anemie).
Bewaar PARACETAMOL BIOTECH IV op 'n veilige plek buite bereik van kinders.

Ernstige kutane nadelige reaksies (SCARs)
Ernstige kutane nadelige reaksies (SCARs) soos toksiese epidermale nekrolise (TEN), Steven Johnson se sindroom (SJS), akute veralgemeende eksantematiese pustulose (AGEP), geneesmiddeluitslag met eosinofilie en sistemiese simptome (DRESS) of geneesmiddel-geïnduseerde hipersensitiwiteitsindroom (DIHS)) en vaste geneesmiddel-uitbarstings (FDE) is aangemeld by pasiënte wat behandel is met medisyne wat parasetamol bevat. Indien 'n pasiënt SCARs ontwikkel, moet behandeling met PARACETAMOL BIOTECH IV onmiddellik gestaak word en toepaslike behandeling ingestel word.

Hulpstowwe:
PARACETAMOL BIOTECH IV bevat 800 mg propileenglikol in elke 100 mL fles. Mediese monitering is nodig by pasiënte met verswakte nier- of lewerfunksies omdat verskeie nadelige gebeurtenisse wat aan propileenglikol toegeskryf word, aangemeld is, soos nierdisfunksie (akute tubulêre nekrose), akute nierversaking en lewerdisfunksie.
Alhoewel daar nie getoon is dat propileenglikol reproduktiewe of ontwikkelingstoksisiteit by diere of mense veroorsaak nie, kan dit die fetus bereik en is dit in melk gevind. Gevolglik moet toediening van propileenglikol aan swanger of lakterende pasiënte in 'n geval oorweeg word per geval basis (sien afdeling 4.6).
PARACETAMOL BIOTECH IV bevat 200 mg natrium per flessie, gelykstaande aan 10 % van die WGO se aanbevole maksimum daaglikse inname van 2 g natrium vir 'n volwassene.

4.5 Interaksie met ander medisyne en ander vorme van interaksie
Effek van ander medisyne op PARACETAMOL BIOTECH IV:
Probenesied kan die plasmakonsentrasies van PARACETAMOL BIOTECH IV verhoog met byna 'n 2-voudige vermindering in opruiming van parasetamol. 'n Verlaging in PARACETAMOL BIOTECH IV dosis kan oorweeg word met gelyktydige gebruik.
Die absorpsie van parasetamol kan versnel word wanneer dit saam met metoklopramied gebruik word.
Salisilamied kan die eliminasie-halfleeftyd van parasetamol verleng soos bevat in PARACETAMOL BIOTECH IV.
Salisilate in langdurige behandelings saam met parasetamol het die risiko van pynstillende nefropatie, nierpapillêre nekrose, eindstadium niersiektes en kanker van die urinêre blaas aansienlik verhoog. Die aanbevole individuele dosisse vir PARACETAMOL BIOTECH IV en die salisilate moet nie oorskry word nie.
Fenitoïen wat gelyktydig met PARACETAMOL BIOTECH IV toegedien word, kan lei tot verminderde 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 glutatioontekorte soos ernstige nierversaking, sepsis, wanvoeding en chroniese alkoholisme. Noukeurige monitering word aanbeveel om die voorkoms van suurbasis-afwykings, naamlik HAGMA, op te spoor, insluitend die soek van urinêre 5-oksoprolien.
Medisyne wat lewermikrosomale ensieme, soos barbiturate of primidoon bevat, kan die terapeutiese effek van PARACETAMOL BIOTECH IV verminder.
Gelyktydige gebruik van PARACETAMOL BIOTECH IV en lewerensiem induseerders moet met omsigtigheid gedoen word aangesien hierdie medisyne die risiko van parasetamol geïnduseerde hepatotoksisiteit verhoog. Hierdie stowwe sluit in, maar is nie beperk nie tot barbiturate, isoniasied, rifampisien, karbamasepien, antikoagulante, sidovudien, amoksisillien, klavulaansuur, etanol of hepatotoksiese medisyne.

Effek van PARACETAMOL BIOTECH IV op ander medisyne:
PARACETAMOL BIOTECH IV kan die kans op ongewenste effekte verhoog wanneer dit saam met ander medisyne toegedien word.
Die antikoagulant-effekte kan toeneem wanneer hoë dosisse PARACETAMOL BIOTECH IV saam met antikoagulante, kumarien (bv. warfarien) en/of indadioonderivate gebruik word. Verhoogde monitering van INR-waardes moet uitgevoer word gedurende die tydperk van gelyktydige gebruik, sowel as 1 week na staking van PARACETAMOL BIOTECH IV.

6. Vrugbaarheid, swangerskap en borsvoeding
Swangerskap
Kliniese ervaring van binneaarse toediening van parasetamol by swanger vroue is beperk.
Epidemiologiese data van die gebruik van orale terapeutiese dosisse parasetamol het geen ongewenste effekte by swanger vroue of op die gesondheid van die fetus/pasgebore baba tot gevolg gehad 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 teratogene of fetotoksiese effekte getoon nie.
Nietemin, PARACETAMOL BIOTECH IV moet slegs tydens swangerskap gebruik word na noukeurige voordeel/risiko-bepaling, en die aanbevole dosis en duur moet streng nagekom word.
Sien ook "Hulpstowwe" in afdeling 4.4.

Borsvoeding
Parasetamol word in klein hoeveelhede in borsmelk uitgeskei. Uitslag by sogende babas is aangemeld. Omsigtigheid moet gebruik word wanneer PARACETAMOL BIOTECH IV toegedien word aan vroue wat hul babas borsvoed.

4.7 Effekte op die vermoë om te bestuur en masjiene te gebruik
PARACETAMOL BIOTECH IV behoort geen invloed te hê op die vermoë om te bestuur en die gebruik van masjiene nie. Geen ongewenste effekte wat die vermoë om te bestuur en masjinerie gebruik kan beïnvloed, is aangemeld deur pasiënte wat PARACETAMOL BIOTECH IV gebruik nie.

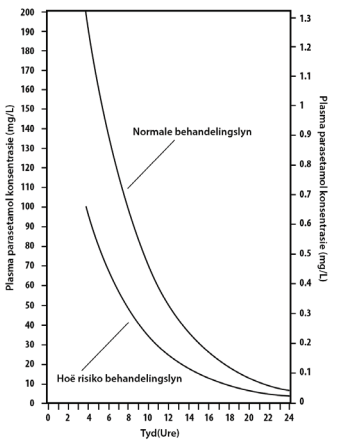
4.8 Ongewenste effekte
Bloed- en limfstelselafwykings
Minder gereeld: Trombositopenie, agranulositose, leukopenie, pansitopenie, neutropenie, anemie.
Immuunstelselafwykings
Minder gereeld: Hipersensitiwiteit.
Endokriene afwykings
Minder gereeld: Pankreatitis.
Vaskulêre afwykings
Minder gereeld: Hipotensie.
Hepato-galafwykings
Minder gereeld: Hepatitis, verhoogde vlakke van hepatiese transaminase.
Frekwensie onbekend: Hepatiese nekrose, lewerversaking.
Nier- en urinêre afwykings
Minder gereeld: Renale koliek, nierversaking, steriele pyurie.
Algemene afwykings en toedieningsplektoestande
Minder gereeld: Malaise.
Na-bemarking ervaring
Die volgende nadelige gebeurtenisse is ook gerapporteer tydens na-bemarking toesig, maar die frekwensie is nie bekend nie.
Immuunstelselafwykings
Anafilaktiese skok, anafilakse, hipersensitiwiteitsreaksie, angio-edeem.
Hartafwykings
Tagikardie.
Gastrointestinale afwykings
Naarheid, braking.
Hepato-galafwykings
Fulminante hepatitis, hepatiese nekrose, lewerversaking.
Vel- en subkutane weefselafwykings
Eriteem, blosing, pruritus, uitslag, urtikaria, ernstige kutane nadelige reaksies (SCARs) soos toksiese epidermale nekrolise (TEN), Stevens Johnson se sindroom (SJS), akute veralgemeende eksantematiese pustulose (AGEP), geneesmiddeluitslag met eosinofilie (en sistemiese simptome) DRESS) of geneesmiddel-geïnduseerde hipersensitiwiteitsindroom (DIHS) en vaste geneesmiddel-uitbarstings (FDE) (sien afdeling 4.4).
Algemene afwykings en toedieningsplektoestande
Toedieningsplek reaksies.

Rapportering van vermoedelike nadelige reaksies
Rapportering van vermoedelike nadelige reaksies na goedkeuring van PARACETAMOL BIOTECH IV is belangrik. Dit laat voortgesette monitering van die voordeel/risiko-balans van PARACETAMOL BIOTECH IV toe. Gesondheidsorgverskaffers word gevra om enige vermoedelike nadelige reaksies by SAHPRA aan te meld via die **"Adverse Drug Reactions Reporting Form"**, aanlyn gevind 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 effektief te wees. Bewyse van lewerskade word dikwels uitgestel tot nadat die tyd vir effektiewe behandeling verstryk het.
Vatbaarheid vir parasetamol toksisiteit is verhoog by pasiënte wat herhaalde hoë dosisse (meer as 5 - 10 g/dag) parasetamol vir 'n paar dae geneem het. Daar is 'n risiko van vergiftiging, veral in kroniese alkoholisme, kroniese lewersiekte, VIGS, wanvoeding, en met die gebruik van medisyne wat lewer mikrosomale oksidasie veroorsaak soos barbiturate, isoniasied, rifampisien, fenitoïen en karbamasepien.
Simptome van parasetamol oordosis 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 toediening van PARACETAMOL BIOTECH IV sigbaar word, aanvanklik deur verhoging van die serumtransaminase- en melksuurdehidrogenase-aktiwiteit, verhoogde serumbilirubienkonsentrasie en verlenging van die protrombien of verhoogde INR-tyd. Kliniese simptome van lewerskade is gewoonlik eers duidelik na 2 dae en bereik 'n maksimum na 4 tot 6 dae.
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 disritmieë is aangemeld.

Behandeling van oordosis parasetamol na IV toediening van PARACETAMOL BIOTECH IV
So gou as moontlik na die vermoedelike oordosis, en voor die aanvang van behandeling, trek bloed vir 'n parasetamol plasma-toets.
N-asetielsisteïen (NAC) moet so gou moontlik by alle gevalle van vermoedelike oordosis toegedien word, verkieslik binne agt uur na oordosis, alhoewel behandeling tot 36 uur na die oordosis steeds voordelig kan wees, veral as meer as 150 mg/kg parasetamol toegedien is. 'n Aanvangsdosis van 150 mg/kg N-asetielsisteïen in 200 mL dekstrose 5 % w/v inspuiting **binneaars** toegedien oor 15 minute, gevolg deur 'n infusie van 50 mg/kg in 500 mL dekstrose 5 % m/v inspuiting oor die volgende vier uur, en dan 100 mg/kg in 1000 mL dekstrose 5 % w/v inspuiting oor die volgende sestien uur natriumkloried 0,9 % w/v mag gebruik word waar glukose 5 % w/v nie geskik is nie. **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.



Bron: Martindale, The Complete Drug Reference, 36ste Uitgawe, bladsy 109

Parasetamol oordosis met binneaarse infusies
Na 'n oordosis met 'n binneaarse infusie, is die standaard nomogram wat gebruik word vir die bepaling van behandeling met parasetamol plasmakonsentrasies na orale inname van 'n oordosis parasetamol, moontlik nie gepas nie. Parasetamol plasmakonsentrasies meer as 4 uur na binneaarse inspuiting kan laer wees as dié wat voorspel word vir dieselfde orale dosis op dieselfde tydstip na inname.
Diegene wie se plasma-parasetamolvlakke bo die "normale behandelingslyn is", moet herhaaldelik voortgaan met N-asetielsisteïenbehandeling met 100 mg/kg binneaars 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.

Monitor alle pasiënte met beduidende oordosis vir ten minste ses en negentig uur.

Behandeling is simptomaties en ondersteunend.

5. FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
Kategorie en klas: A2.7 Antipiretika of antipiretiese en anti-inflammatoriese pynstillers.
Farmakoterapeutiese groep: Ander pynstillers en koorswerende middels.
ATC-kode: N02BE01.Die meganisme van pynstillende en antipiretiese aksies van parasetamol is nie volledig bepaal nie. Dit kan sentrale en perifere aksies behels.

5.2 Farmakokinetiese eienskappe
Absorpsie:
Parasetamol farmakokinetika is lineêr tot 2 g na 'n enkele toediening en na herhaalde toediening gedurende 24 uur. Die maksimum plasmakonsentrasie (C_{max}) van 30 µg/mL parasetamol word waargeneem na 15 minute van 'n binneaarse infusie van 1 g parasetamol.
Verspreiding:
Parasetamol word relatief eenvormig deur die meeste liggaamsvloeistowwe versprei. Binding van parasetamol aan plasmaproteïene is veranderlik. Die verspreidingsvolume is ongeveer 1 L/kg. Beduidende konsentrasies parasetamol van ongeveer 1,5 µg/mL is in die serebrospinale vloeistof na ongeveer 20 minute van 'n 1 g parasetamol binneaarse infusie.
Metabolisme:
Parasetamol word in die lewer gemetaboliseer deur konjugasie met glukuronsuur (60 %), swaelsuur (35 %) en sisteïen (± 3 %). 'n Klein gehidroksileerde metaboliet (N-asetiel-p-bensokinoonimien) word gewoonlik in baie klein hoeveelhede deur sitochroom P450 isoënsieme (hoofsaaklik CYP2E1 en CYP3A4) in die lewer en niere geproduseer. Dit word gewoonlik ontgift deur vervoeging met glutatioon, maar kan ophoop na parasetamol oordosis en weefselskade veroorsaak. Pasgeborenes, babas en kinders tot 10 jaar skei aansienlik meer sulfaat en minder glukuroniedkonjugate uit as volwassenes.
Eliminasie:
Parasetamol en sy metaboliete word hoofsaaklik in die uriene uitgeskei.
Minder as 5 % van die dosis word as onveranderde parasetamol uitgeskei. Sowat 90 % tot 100 % van die dosis kan binne die eerste 24 uur van toediening in die uriene as metaboliete herwin word. Die plasmahalfleeftyd van parasetamol is 2,7 uur vir volwassenes, 1,5 tot 2 uur vir babas en kinders en 3,5 uur vir pasgeborenes. Totale liggaamsuitskeiding is 18 L/h op alle ouderdomme.

Spesiale populasies
Nierontoereikendheid:
In gevalle van ernstige nierversaking (kreatinienopruiming < 30 mL/min), word die eliminasie van parasetamol vertraag, die eliminasie-halfleeftyd wissel van 2 tot 5,3 uur. Vir die glukuronied- en die 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 uur tussen toedienings te laat by pasiënte met ernstige nierversaking (kreatinienopruiming ≤ 30 mL/min) (sien afdeling 4.2).
Bejaarde persone:
Die farmakokinetika en die metabolisme van parasetamol word nie by bejaarde proefpersone gewysig nie.
Geen dosisaanpassing is nodig in hierdie populasie nie.

6. FARMASEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Sitroensuur monohidraat
Dinatriumwaterstoffosfaatdihidraat
Propileenglikol
Natriummetabisulfiet
Natriumkloried
Water vir inspuiting.

6.2 Onverenigbaarhede
PARACETAMOL BIOTECH IV moet nie met ander medisyne gemeng word nie.

6.3 Raklewe
Onoopgemaakte flessies:
36 maande.
Na die eerste opening:
Gebruik dadelik.

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.
Gooi oorblywende gedeelte weg.

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

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Voor toediening moet die produk visueel geïnspekteer word vir enige deeltjies en verkleuring, bv. vergeling. Dit is slegs bedoel vir eenmalige gebruik. Sodra dit oopgemaak is, moet die flessie onmiddellik gebruik word
Enige ongebruikte oplossing moet weggegooi word.

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45/2.7/0443

9. DATUM VAN EERSTE MAGTIGING/HERNUWING VAN DIE MAGTIGING
23 Maart 2015

10. DATUM VAN HERSIENING VAN DIE TEKS
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