Final Approved Professional Information for Medicines for Human Use:

PYPATARAN IV

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PYPATARAN IV solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL vial contains 1 g paracetamol. One mL contains 10 mg paracetamol.

Contains sugar (mannitol): 3,447 g/100 mL.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear solution, colourless to faint yellow or pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PYPATARAN IV is indicated for:

- the short-term treatment 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.

Use the lowest effective dose for the shortest possible duration of treatment.

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 risk factors for hepatotoxicity, including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration.

Recommended dosage in adult patients

The recommended dose in adult patients weighing more than 50 kg is:

PYPATARAN IV per administration (i.e. one 100 mL vial) up to 4 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.

The recommended dose in adult patients weighing less than 50 kg and more than 33 kg (approximately 11 years old) is:

PYPATARAN IV: 15 mg/kg per administration (i.e. 1,5 mL solution per kg) up to 4 times per day. The minimum interval between each administration must be 4 hours. For these adult underweight patients, the maximum daily dose must not exceed 60 mg/kg and must not exceed 3 g in 24 hours.

Recommended dosage in paediatric and adolescent patients

The 100 mL vial is restricted to adults, adolescents, and children weighing more than 33 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***
> 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

Recommended dosage in 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).

Recommended dosage in 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 reserves of hepatic glutathione)
- dehydration.

Method of administration

For all patients, PYPATARAN IV is to be administered as a 15-minute intravenous infusion. Before administration, PYPATARAN IV 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 PYPATARAN IV is presented in glass vials, close 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.

PYPATARAN IV should not be mixed with other medicines.

4.3 Contraindications

- Hypersensitivity to paracetamol or to paracetamol hydrochloride (pro-drug of paracetamol) or to any of the excipients (see section 6.1).
- Severe hepatocellular insufficiency or decompensated active liver disease including alcoholic hepatitis. Active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatoxicity.

4.4 Special warnings and precautions for use

PYPATARAN IV solution for infusion 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.

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

In order to avoid the risk of overdose, check that other medicines administered (including prescription and non-prescription medicines) do not contain paracetamol.

Doses of PYPATARAN IV in excess of those recommended may cause very severe liver damage. Clinical symptoms and signs of liver damage are usually seen first after two days of paracetamol overdose. Maximum liver damage symptoms are usually observed after 4 to 6 days. Treatment with antidote should be given as soon as possible (see section 4.9).

Severe cutaneous adverse reactions (SCARs)

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

Salicylates in prolonged treatments together with PYPATARAN 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 PYPATARAN IV (see section 4.5).

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

The risk of PYPATARAN 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 hepatitis or alcoholism or recovering from any form of liver disease should not use excessive quantities of PYPATARAN IV.

PYPATARAN 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).

PYPATARAN IV should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert’s syndrome (familial hyperbilirubinaemia), (see section 4.2 and 5.2).
- Meulengracht Gilbert Syndrome (familial non-haemolytic jaundice)
- Severe renal insufficiency (creatinine clearance ≤ 30mL/min) (see section 4.2 and 5.2).
- Genetically caused Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency

(may lead to haemolytic anaemia due to the reduced allocation of glutathione following the administration of paracetamol).

- 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.

4.5 Interaction with other medicines and other forms of interaction

Paracetamol: Do not use PYPATARAN IV with products containing paracetamol. The combination can result in an overdose of paracetamol, causing severe liver damage (see section 4.4).

Effect of other medicines on PYPATARAN IV

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the PYPATARAN IV dose should be considered when administered concomitantly with probenecid.
- The absorption of paracetamol may be accelerated when used together with metoclopramide.
- Salicylamide may prolong the elimination half-life of paracetamol as contained in PYPATARAN 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 PYPATARAN IV and the salicylates should not be exceeded.

- Caution should be paid to the concomitant use of PYPATARAN IV and enzyme-inducing medicines as these medicines increase the risk of paracetamol induced liver injury. These medicines include but are not limited to barbiturates, isoniazid, rifampicin, carbamazepine, anticoagulants, zidovudine, amoxicillin + clavulanic acid, and ethanol (see section 4.9).
- Phenytoin administered concomitantly with PYPATARAN 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.

Effect of* PYPATARAN IV *on other medicines

- PYPATARAN IV may increase the chance of unwanted effects when administered with other medicines.
- Anticoagulants: Concomitant use of PYPATARAN IV (4 g per day for at least 4 days) with coumarins 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 PYPATARAN IV treatment has been discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical experience of intravenous administration of PYPATARAN IV is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus/newborn infant. Prospective data on pregnancies exposed to 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 foetotoxic effects. Nevertheless, PYPATARAN IV should only be used during pregnancy if clearly necessary. In this case, the recommended dosage and duration must be strictly observed.

Breastfeeding

After oral administration, paracetamol is excreted into breast milk in small quantities. Rash in nursing infants has been reported. Caution should be used when administering PYPATARAN IV to women who are breastfeeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions to PYPATARAN IV occur less frequently as described below. Post-marketing adverse reactions are indicated as frequency unknown.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, pancytopenia, anaemia, thrombocytopenia, leucopenia neutropenia
Immune system disorders	Less frequent	Hypersensitivity
	Frequency unknown	Anaphylaxis, angioedema, anaphylactic shock, hypersensitivity reaction
Cardiac disorders	Less frequent	Hypotension
	Frequency unknown	Tachycardia
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting
Hepato-biliary disorders	Less frequent	Hepatitis, pancreatitis, increased levels of hepatic transaminases
	Frequency unknown	Fulminant hepatitis, hepatic necrosis, hepatic failure, increased hepatic enzymes
Skin and subcutaneous tissue disorders	Frequency unknown	Acute generalised exanthematous pustulosis, toxic epidermal necrolysis, Stevens-Johnson syndrome erythema, flushing, pruritus, rash, urticaria
Renal and urinary disorders	Less frequent	Renal colic, renal failure and sterile pyuria

MedDRA system organ class	**Frequency**	**Adverse reactions**
General disorders and administration site conditions	Less frequent	Malaise
	Frequency unknown	Administration site reaction

The following side effects have been reported with the post-marketing use of paracetamol:

System Organ Class	**Undesirable effects**
Skin and subcutaneous tissue disorders	Risk of Fixed drug eruptions (FDE) Risk of Drug-induced hypersensitivity syndrome (DIHS)

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: http://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 to a hospital directly. 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.

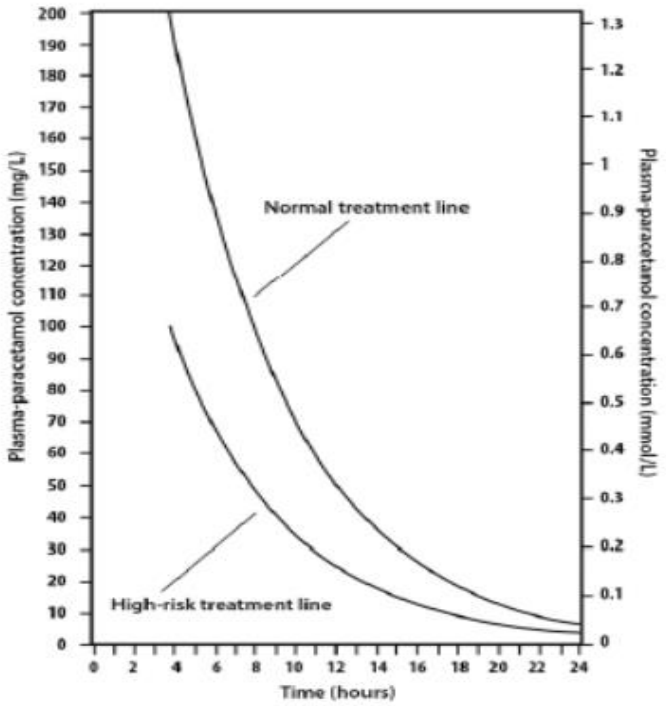
Susceptibility to PYPATARAN IV toxicity is increased in patients who have taken repeated high doses (greater than 5 - 10 g/day) of paracetamol for several days. There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition, AIDS and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Overdosing may be fatal in these cases.
Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and 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, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time /INR. Liver damage may lead to encephalopathy, coma and death.
Overdose with a single administration of 7,5 g or more of paracetamol in adults or 140 mg/kg of body weight in children, causes cytolytic hepatitis likely to induce complete and irreversible hepatic necrosis, resulting in acute or fulminant hepatic failure, hepatocellular insufficiency, metabolic acidosis and encephalopathy, which may lead to coma and death.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days and reach a maximum after 4 to 6 days.

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 PYPATARAN IV overdosage:

- Immediate hospitalisation.
- Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.
- 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 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. 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

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”. (Refer to paracetamol nomogram above).

Prothrombin index correlates best with survival.

Monitor all patients with significant ingestion for at least 96 hours.

- Symptomatic treatment.
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of the liver function. In very severe cases, however, liver transplantation may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 for 24 hours. The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15 minutes intravenous infusion of 1 g of paracetamol in adults is about 30 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.

Metabolism

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 benzoquinoneimine) 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.

Paediatric population

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

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) (see section 4.2).

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 (see section 4.3).

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

Disodium hydrogen phosphate dihydrate

Hydrochloric acid 12 (E507)

Mannitol (E421)

Nitrogen

Water for injection

6.2 Incompatibilities

PYPATARAN IV should not be mixed with other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C and protect from light.

Do not refrigerate or freeze.

6.5 Nature and contents of container

PYPATARAN is packed in a 100 mL clear type I glass bottle with a grey bromobutyl rubber stopper and a blue flip-off seal packed in an outer carton.

Pack size: one vial per carton.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused solution should be discarded.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

55/2.7/0837

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023

10 DATE OF REVISION OF THE TEXT