Approved Professional Information for Medicines for Human Use:

PARATIV 1 g

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PARATIV 1 g Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARATIV 1 g

Each 100 mL bottle contains 1 000 mg of paracetamol.

Contains sugar (mannitol: 38,5 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Infusion

Clear solution

The pH of the solution is 5,0 – 6,0 and osmolality is 285 – 315 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARATIV 1 g is indicated for:

- the short-term treatment of mild to moderate pain e.g. after dental procedures and minor orthopaedic procedures.
- the short-term treatment of fever, when the oral route is unsuitable.

4.2 Posology and method of administration

Posology

Intravenous route.

DO NOT EXCEED THE RECOMMENDED DOSE

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

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

Healthcare providers are reminded that it is essential to follow both the weight-related dose recommendations and to consider individual patient risk factors for hepatotoxicity, including hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration. (See section 4.2, Special population, Hepatic impairment)

Recommended dosage in adult patients

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

PARATIV 1 g 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:

PARATIV 1 g: 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.

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.

Dosing is based on patient weight.

Dosing recommendations are presented in the table below:

Patient weight ***(non-oedematous weight)****	**Paracetamol dose per administration**	**Volume per administration**	**Maximum volume of PARATIV 1 g per administration based on upper weight limits of group (mL)**	**Maximum Daily Dose *****
> 33 kg to ≤50 kg	15 mg/kg	1,5 mL/kg	75 mL	60 mg/kg not exceeding 3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	4 g

* The dosage should be calculated on non-oedematous weight.

*** **Maximum daily dose:** The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted

accordingly taking such products into account.

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 5.2).

Hepatic impairment:

Paracetamol should be used with caution in patients with mild to moderate liver impairment and is contra-indicated when there is active disease, particularly alcoholic hepatitis because of CYP 2E1 induction. (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.

Paediatric population

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

Method of administration

General

For all patients, PARATIV 1 g is to be administered as a 15-minute intravenous infusion. Before administration, the product should be visually inspected for any particulate matter and

discolouration. It is intended for single-use only. Once opened, the vial should be used immediately.

As PARATIV 1 g 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.

PARATIV 1 g should not be mixed with other medicine.

4.3 Contraindications

PARATIV 1 g is contra-indicated in:

- patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients (listed in section 6.1.)
- cases of severe hepatocellular insufficiency or decompensating active liver disease including alcoholic hepatitis.

4.4 Special warnings and precautions for use

PARATIV 1 g 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.

Dosages of PARATIV 1 g in excess of those recommended may cause severe liver damage.

RISK OF MEDICATION ERRORS

Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death (see section 4.2 and 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 PARATIV 1 g must immediately be discontinued and appropriate treatment instituted.

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

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

Doses higher than the recommended entails risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of administration with a peak seen usually after 4 - 6 days. Treatment with antidote should be given as soon as possible (See section 4.9).

Text for 100 mL vials:

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see section 4.2).

Precautions for use

Paracetamol should be used with caution in cases of:

- Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia), (see Section 4.2, Recommended dosage in patients with hepatic impairment and Section 5.2, Special populations, Hepatic impairment),
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min) (see sections 4.2 and 5.2),
- Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia),
- Chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day),
- Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione),
- Dehydration, hypovolaemia.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease should not use excessive quantities of PARATIV 1 g.

Excipients: mannitol

Parativ 1 g contains mannitol.

Mannitol may cause mild laxative effects.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on PARATIV 1 g:

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose, as contained in PARATIV 1 g, should be considered when administered concomitantly with probenecid.
- Salicylamide may prolong the elimination half-life ($t_{1/2}$) of paracetamol, as contained in PARATIV 1 g.
- Caution should be paid to the concomitant use of PARATIV 1 g and enzyme-inducing substances as these substances increase the risk of paracetamol induced liver injury. These

substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, and ethanol (see section 4.9).

- Phenytoin administered concomitantly with PARATIV 1 g 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 PARATIV 1 g on other medicines:

- PARATIV 1 g may increase the chance of unwanted effects when administered with other medicines.
- Concomitant use of paracetamol, as contained in PARATIV 1 g, (4 g per day for at least 4 days) with oral anticoagulants (coumarins including warfarin) may lead to variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol, as contained in PARATIV 1 g, treatment has been discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus/newborn infant.

Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects.

Nevertheless, PARATIV 1 g should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Breastfeeding

After oral administration, paracetamol, as contained in PARATIV 1 g, is excreted into breast milk in small quantities. Rash in nursing infants has been reported. Caution should be used when administering PARATIV 1 g to women who are breastfeeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are less frequent, they are described below:

Organ system	**Frequency**	
	Frequent	**Less Frequent**
General		Malaise Hypersensitivity reaction
Cardiovascular		Hypotension
Liver		Increased levels of hepatic transaminases, hepatitis, pancreatitis
Platelet/blood		Thrombocytopenia, agranulocytosis, leukopenia, pancytopenia, neutropenia, anaemia.
Renal and urinary disorders		Renal colic, renal failure and sterile pyuria

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

Cases of erythema, flushing, pruritus and tachycardia have been reported.

Postmarketing experience:

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

Organ System	Adverse event
Blood and lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Nausea Vomiting
General disorders and administration site condition	Administration site reaction
Hepatobiliary disorders	Fulminant hepatitis Hepatic necrosis

	Hepatic failure Increased hepatic enzymes
Immune system disorders	Anaphylactic shock Anaphylaxis Hypersensitivity reaction Angio-oedema
Skin and subcutaneous tissue disorders	Erythema Flushing Pruritus Rash Urticaria Acute generalised exanthematous Pustulosis Toxic epidermal necrolysis Stevens-Johnson syndrome 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 PARATIV 1 g is important. It allows continued monitoring of the benefit/risk balance of PARATIV 1 g. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

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 ingestion. Clinical symptoms of liver damage are usually evident initially after two days and reach a maximum after 4 to 6 days.

Overdose, 7,5 g or more of paracetamol in a single administration in adults and 140 mg/kg of body weight in a single administration in children, causes hepatic cytolysis likely to induce

complete and irreversible necrosis, resulting in 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.

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

Emergency measures

Immediate hospitalisation.

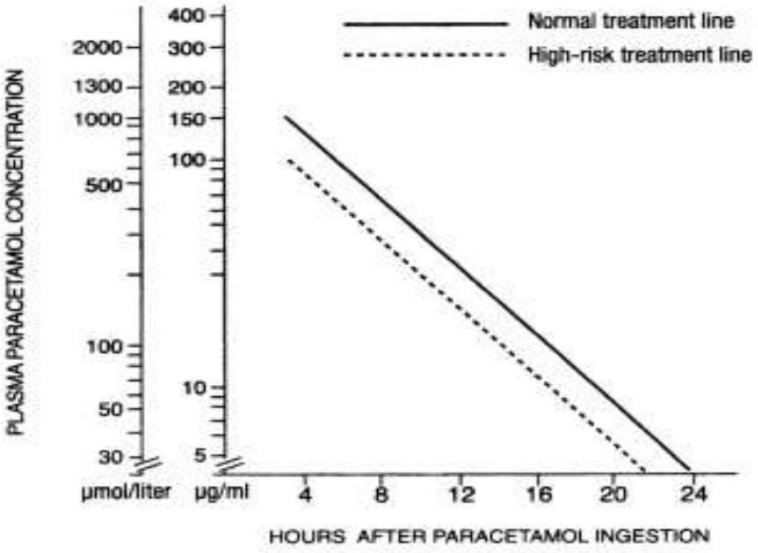
Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.

The treatment includes administration of the antidote, N-acetylcysteine (NAC), by the i.v. or oral route, if possible before the 10th hour. NAC can, however, give some degree protection even after 10 hours, but in these cases prolonged treatment is given.

An initial dose of 150 mg/kg N-acetylcysteine in 200 mL dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children. Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified

according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



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

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.

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 liver function. In very severe cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class:

A 3.2 Analgesic and antipyretic

Pharmacotherapeutic group:

Other Analgesics and Antipyretics

ATC Code: N02BE01

Mechanism of action

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

5.2 Pharmacokinetic properties

Absorption

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

The maximal plasma concentration (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.

Biotransformation

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4 %) is metabolised by

cytochrome P450 to a reaction intermediate (N-acetyl 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 population

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. (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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the Professional Information.

Studies on local tolerance of PARATIV 1 g in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous

Hydrochloric acid 5N (pH-adjustment)

Mannitol

Sodium hydroxide 5N (pH-adjustment)

Water for injection

6.2 Incompatibilities

PARATIV 1 g should not be mixed with other medicine.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in original package.

6.5 Nature and contents of container

PARATIV 1 g is available in 100 mL polypropylene blow-fill-sealed bottles. The blow-fill-sealed bottles are over sealed with a molded plastic cap with a rubber gasket and a pull ring, or with plastic caps with embedded elastomers (twin ports), enclosed with a pouch.

Pack size of 10 bottles.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

50/3.2/1034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 December 2021

10. DATE OF REVISION OF THE TEXT

24 October 2023