SCHEDULING STATUS:

S3

1. NAME OF MEDICINE

REOPARA 10 mg/ml Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 100 mL glass bottle contains 1 g paracetamol as active ingredient.

Sugar free

Excipient with Known effect

Sodium Metabisulphite (E223)

For the full list of excipients (see section 6. 1)

3. PHARMACEUTICAL FORM

Solution for infusion. A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

REOPARA 1g 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

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 4.8)

Recommended dosage in adult patients

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

REOPARA 1g per administration (i.e. one 100 ml bottle) 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:

REOPARA 1g: 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 bottle 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 bottle) 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. 1,5ml 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.

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 ≤ 30ml/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:

General

For all patients, REOPARA 1g is to be administered as a 15-minute intravenous infusion.

4.3 Contraindications

REOPARA 1g is contraindicated in:

- Cases of hypersensitivity to paracetamol or to paracetamol hydrochloride (pro-drug of paracetamol) or to any of the excipients.
- Cases of severe hepatocellular insufficiency or decompensated active liver disease including alcoholic hepatitis.

4.4 Special warnings and precautions for use

REOPARA 1g Solution for Infusion contains paracetamol which may be fatal in overdose. In the event of over dosage 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 REOPARA 1g 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).

REOPARA 1g 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.

REOPARA 1g should be used with caution in cases of:

Hepatocellular insufficiency, including Gilbert's syndrome (familial hyperbilirubinaemia), (see section 4.2 and 5.2).

- Severe renal insufficiency (creatinine clearance ≤ 30ml/min) (see section 4.2 and section 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 REOPARA 1g.

Use with caution in renal disease.

Excipients with Known Effects:

- This product contains Sodium Metabisulphite (E223), which may rarely cause severe hypersensitivity reactions, including bronchospasm.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on REOPARA 1g:

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the REOPARA 1g dose should be considered when administered concomitantly with probenecid.
- Salicylamide may prolong the elimination half-life of paracetamol as contained in REOPARA 1g.
- Caution should be paid to the concomitant use of REOPARA 1g 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 REOPARA 1g 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 REOPARA 1g on other medicines:

- REOPARA 1g may increase the chance of unwanted effects when administered with other medicines.
- Anticoagulants: Concomitant use of REOPARA 1g (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 REOPARA 1g treatment has been discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Clinical experience of intravenous administration of Paracetamol as in REOPARA 1g 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, REOPARA 1g should only be used during pregnancy after a careful benefit-risk assessment. 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 REOPARA 1g to women who are breastfeeding.

4.7 Effects on ability to drive and use machines

REOPARA 1g has no influence on the ability to drive and use machines

4.8 Undesirable effects

The following adverse reactions have been reported during clinical use and post-marketing surveillance. The exact incidence for some events cannot be reliably estimated; these are reported as Frequency not known.

System Organ Class	Frequent	Less Frequent	Frequency not known
Blood and lymphatic system disorders	-	Thrombocytopenia, agranulocytosis, leucopenia, pancytopenia, neutropenia, anaemia	–
Cardiac disorders	-	Hypotension	Tachycardia

Gastrointestinal disorders	-	-	Nausea, vomiting
Hepatobiliary disorders	-	Increased levels of hepatic, Hepatitis, pancreatitis	Fulminant hepatitis, hepatic necrosis, hepatic failure, increased hepatic enzymes
Immune system disorders	-	-	Anaphylaxis, anaphylactic shock, Hypersensitivity angio-oedema (including potential reactions to Sodium Metabisulphite E223)
Skin and subcutaneous tissue disorders	-	-	Erythema, rash, urticaria, pruritus, flushing, Acute generalised exanthematous Pustulosis, Toxic Epidermal necrolysis,

General disorders and administration site conditions	-	Malaise, Hypersensitivity	Administration site reaction
Renal and urinary disorders	-	Renal colic, renal failure, sterile pyuria	–

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website

4.9 Overdose

(See Section 4.4 and Section 4.8)

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 REOPARA 1g 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 drugs 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.

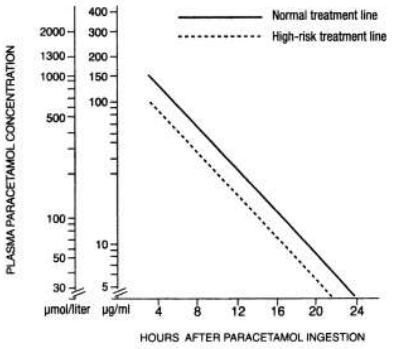
Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days and reach 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 REOPARA 1g over dosage:

- 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 1000 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.



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". (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: Analgesics; Other analgesics and antipyretics

ATC Code: N02BE01

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.

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.

Children:

The pharmacokinetic parameters of paracetamol observed in children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 h) than in adults.

Total excretion of paracetamol and its metabolites is the same at all ages.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Metabisulphite,

Disodium Edetate,

Mannitol,

Disodium hydrogen phosphate dihydrate,

Sodium hydroxide,

Citric acid Monohydrate,

Hydrochloric acid,

Water for injection.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30°C. Do not refrigerate or freeze. Protect from light.

Store in a safe place out of reach of children.

6.5 Nature and contents of container

REOPARA 1g is filled in 100 ml USP Type II colourless glass bottle with gray bromobutyl rubber stopper and blue colored flip of seal.

6.6 Special precautions for disposal and other handling

No special requirements.

Once opened, the bottle should be used immediately. Any unused portion should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Qhayisa 2014 Trading and projects Pty Ltd t/a

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8. REGISTRATION NUMBER(S)

57/2.7/0225

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/2026

10. DATE OF REVISION OF THE TEXT

Last revision: Not yet revised

REOPARA 1g is manufactured by

Aculife Healthcare Private Limited. Unit

5, IPD, Village: Sachana,

Taluka: Viramgam,

District: Ahmedabad – 382150, Gujarat,

India.