PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

Empaped® 125 mg Suppositories

Empaped® 250 mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Empaped® 125 mg: Each suppository contains 125 mg paracetamol

Empaped® 250 mg: Each suppository contains 250 mg paracetamol

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suppositories

White to ivory coloured, torpedo shaped suppositories of approximately 26 mm length.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Empaped® is indicated for the relief of mild to moderate pain and fever when oral therapy is not feasible.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

The dose of **Empaped®** depends on the patient's age and body weight.

In general, the single dose is usually between 10 to 15 mg/kg body weight, and the maximum daily dose is 60 mg/kg body weight.

The dosage interval depends on the symptoms and the maximum daily dose, and should be at least 6 hours.

A medical practitioner should be consulted if symptoms persist for more than three days.

Paediatric population

Infants (6 months to ≤ 2 years)

One 125 mg suppository up to 4 times daily.

Children (2 to 8 years)

One 250 mg suppository up to 4 times daily.

The suppository should be inserted per rectum.

Special populations

Hepatic insufficiency and mild renal insufficiency:

In patients with disorders of liver and kidney function or Gilbert's syndrome, the dose should be reduced and the dosage interval should be increased. Without medical advice, a daily dose of 2 g should not be exceeded.

Patients with severe renal insufficiency:

In the presence of severe kidney failure (GFR ≤ 30 ml/min) the dosage interval should be at least eight hours.

Elderly patients:

Dose adjustment is not required in the elderly.

However, in debilitated, immobilized elderly patients with impaired liver / kidney function, a dose reduction or prolongation of the dosing interval may be required. Without medical advice, the maximum daily dose of 60 mg/kg body weight (up to a maximum of 2 g/day) should not be exceeded in the following cases:

- Body weight less than 50 kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Children and adolescents with low body weight:

The use of **Empaped® 125 mg** suppositories in children under six months or weighing less than 7 kg, or **Empaped® 250 mg** in children under two years or weighing less than 13 kg, is not recommended

Method of administration

Empaped® suppositories should be inserted deeply into the rectum after a bowel movement. They may be warmed up in the hands or dipped for a short time into warm water to improve their sliding properties.

4.3 Contraindications

Empaped® should not be used in the presence of:

- Hypersensitivity to paracetamol or any of the ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

This medicine 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 **Empaped®** in excess of those recommended may cause severe liver damage.

Patients suffering from hepatitis, or recovering from any form of liver disease, should not use excessive quantities of **Empaped®**.

To avoid the risk of overdose, it must be ensured that any concurrently used medication does not contain paracetamol.

In the presence of the following disorders, **Empaped®** should be used with great caution (longer interval between doses or in reduced doses) and under careful medical supervision:

- hepatocellular insufficiency (Child-Pugh < 9),
- chronic alcohol abuse,
- severe renal insufficiency (GFR < 30 ml/min (see section 4.2), Gilbert's syndrome (Meulengracht's disease),
- concomitant use of medicines impairing the liver function,
- disorders associated with reduced glutathione levels (dose adjustment, e.g. in patients with diabetes mellitus, HIV, Down's syndrome, tumours, if applicable),
- Glucose-6-phosphate dehydrogenase deficiency (favism)
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Body weight less than 50 kg
- Elderly patients

High fever, evidence of secondary infection, and symptoms persisting for more than three days, should receive medical attention.

As a rule, medicines containing paracetamol should be used for a few days only, and should not be given in large doses without a medical practitioner's or a dentist's advice.

If large amounts of analgesics are taken for extended periods of time, or if these medicines are not used properly, they may cause headache, which may not be treated with increased doses of EMPAPED.

In general, the habitual use of analgesics, especially of those containing more than one active ingredient, may lead to permanent kidney damage, including the risk of kidney failure (analgesic nephropathy).

Headache, fatigue, muscular pain, nervousness and vegetative symptoms may occur after abrupt discontinuation of prolonged, improper use of large amounts of analgesics. These symptoms will subside after a couple of days. No analgesics should be taken within this period. The use of analgesics should not be resumed without a medical practitioner's advice.

Use with caution in renal disease.

The risk of neutropenia is increased with the concomitant use of **Empaped®** with zidovudine (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

The administration of probenecid inhibits the binding of paracetamol to glucuronic acid, reducing paracetamol clearance by a factor of about 2. The dose of **Empaped®** should therefore be reduced if the patient concomitantly receives probenecid.

Special caution is necessary for patients receiving **Empaped®** in combination with active substances causing induction of liver transaminases (phenytoin, phenobarbital, carbamazepine, rifampicin) or with potentially hepatotoxic compounds (see section 4.9).
Patients receiving **Empaped®** in combination with AZT (zidovudine), are more likely to develop a neutropenia. These substances should be used in combination with paracetamol only on medical advice (see section 4.4).

Cholestyramine reduces the uptake of paracetamol.

The concomitant use of anticoagulants, especially warfarin, may increase INR levels and may increase the risk of bleeding. Therefore, long-term administration of paracetamol (longer than 10 days) to patients treated with anticoagulants should only be done under medical supervision. Monitoring the INR values is recommended. The occasional use of paracetamol has no significant influence on the bleeding tendency.

Prolonged concurrent use of **Empaped®** with salicylates increases the risk of adverse renal effects.
Effect on laboratory tests:
Paracetamol may influence tests for uric acid with phosphotungstic acid as well as blood glucose determination with glucose oxidase peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time, at the lowest possible frequency and not in combination with other medicines.

Breastfeeding

Small amounts of paracetamol are excreted in human milk. No deleterious effects or adverse reactions during lactation have been observed. Thus, paracetamol may be given to nursing women in therapeutic doses.

Fertility

No information available

4.7 Effects on ability to drive and use machines

Empaped® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, <1/100); rare (≥ 1/10 000, < 1/1 000); very rare (≤ 1/ 10 000), including isolated reports, not known (cannot be estimated from available data).

System Organ Class	Frequency category	Adverse reaction
Blood and lymphatic system disorders	Very rare	Changes to the blood count such as thrombocytopenia, agranulocytosis.
Immune system disorders	Very rare	In predisposed persons bronchospasm (analgesic asthma), hypersensitivity reactions ranging from erythema to urticaria and anaphylactic shock.
Hepato-biliary disorders	Rare	Increase in liver transaminases
Skin and subcutaneous tissue disorders	Very rare	Cases of serious skin reactions have been reported.

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 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 overdosage, consult a doctor or take the person to the nearest hospital immediately.

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.

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, initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. 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 for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of an 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.

IV Administration:

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 of dextrose injection over the next 4 hours, and then 100 mg/kg in 1000 ml dextrose injection over the next 16 hours.

The volume of intravenous fluid should be modified for children.

Oral administration:

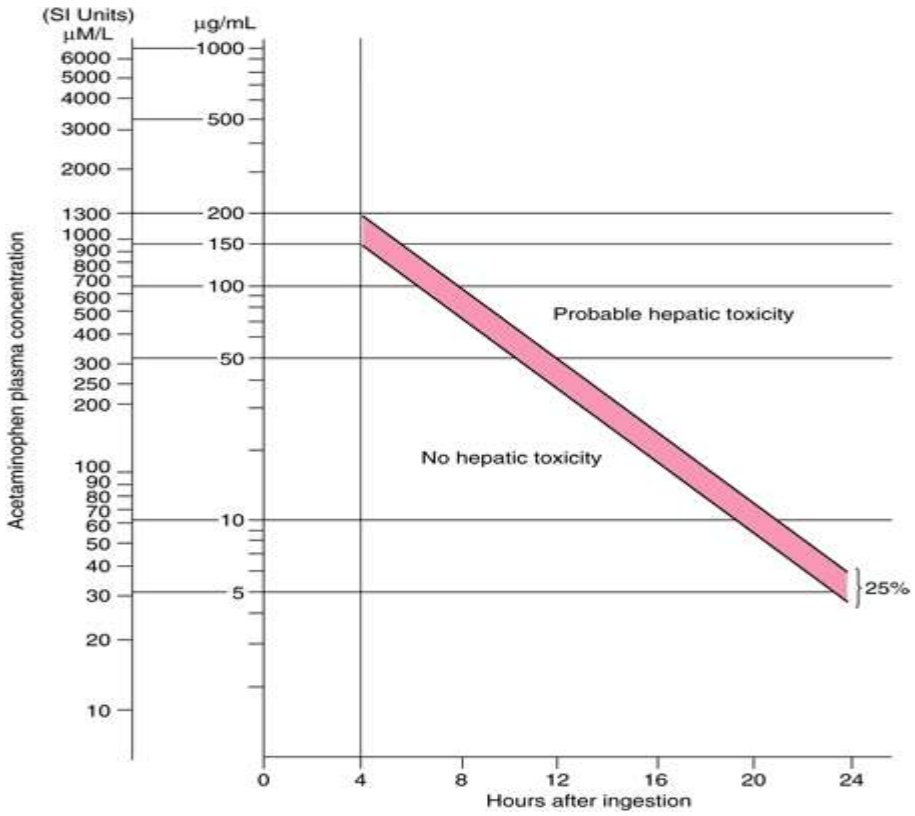
Although the oral formulation is not the treatment of choice, 140 mg/kg N-acetylcysteine dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

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.

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.

All patients with significant ingestion should be monitored for at least 96 hours.

Rumack-Matthew nomogram for single acute acetaminophen poisoning.



Semi logarithmic plot of plasma acetaminophen levels vs. time.

Notes for use of this nomogram:

- The time coordinates refer to time of ingestion.
- Serum levels drawn before 4 h may not represent peak levels.
- The graph should be used only in relation to a single acute ingestion.
- The solid line 25 % below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose. Patients whose plasma-paracetamol concentrations are on or above this line, should be treated.

- The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: A 2.7 Antipyretic or antipyretic and anti-inflammatory analgesics

Pharmacotherapeutic group: Other Analgesics and Antipyretics (Anilides)

ATC code: N02BE01

Paracetamol has analgesic and antipyretic actions. It acts predominantly by inhibiting prostaglandin synthesis.

Paracetamol is assumed to have a central and a peripheral action and has been shown to cause a pronounced inhibition of cerebral prostaglandin synthesis, while the peripheral synthesis of prostaglandin is only slightly inhibited. Furthermore, it inhibits the effect of the endogenous pyrogens on the hypothalamic regulation of the body temperature.

5.2 Pharmacokinetic properties

Absorption

After rectal administration, 68 to 88 per cent of paracetamol is absorbed. Peak plasma concentrations are attained after 3 to 4 hours.

Bioavailability

The relative bioavailability for paracetamol suppositories is 102,3 % in relation to the oral dosage form.

Distribution

Paracetamol is rapidly distributed throughout all tissues. It reaches comparable concentrations in blood, plasma and saliva. Binding to plasma proteins is of minor importance.

Biotransformation

Paracetamol is metabolised chiefly in the liver via two major routes – by conjugation to glucuronic acid and to sulphuric acid. This latter route is quickly saturated after the administration of amounts exceeding the therapeutic dose. A small part of the medicine is metabolised through the cytochrome P450 (mainly CYP2E1), a catalyst leading to the formation of N-acetyl-p-benzoquinonimine, a metabolite usually rapidly detoxicated by glutathione and bound to cysteine and mercapturic acid. A large amount of this toxic metabolite is found in the presence of massive paracetamol poisoning.

Elimination

Elimination takes place chiefly by way of the urine. Ninety per cent of the dose administered is eliminated within 24 hours through the kidneys, mainly as glucuronides (60 to 80 per cent)

and sulphate conjugates (20 to 30 per cent). Less than 5 per cent is excreted as such. The elimination half-life is about two hours. Longer half-lives were seen in patients with impaired liver and kidney function, after overdosage and in the newborn. The maximum and the average duration of the medicine's effect (4 to 6 hours), correlate more or less with its plasma concentration.

Renal insufficiency

The excretion of paracetamol and its metabolites is delayed in patients with severe renal insufficiency (GFR < 30 ml/min).

Elderly patients

The capacity for conjugation remains unchanged.

5.3 Pre-clinical data on safety

In animal studies for acute, sub-chronic and chronic toxicity of paracetamol, rat and mouse, gastrointestinal lesions, changes in blood count, degenerative changes in liver and renal parenchyma as well as necrosis were observed. The reason for these changes is to be sought on the one hand in the mechanism of action and on the other hand in the metabolism of paracetamol. Those metabolites, which are believed to be the cause of the toxic effect and the resulting changes in organs, have also been found in humans. During long-term use (i.e. 1 year) in the range of maximum therapeutic doses, very rare cases of reversible chronic aggressive hepatitis were also observed. At subtoxic doses, intoxication symptoms may occur after three weeks of ingestion. Therefore, paracetamol should not be used for long periods of time and not in higher doses.

Extensive studies have shown no evidence of a relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic dose range.

Long-term studies in rats and mice have shown no evidence of relevant tumour-like effects in non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier.

Animal studies and past human experience show no evidence of foetal damage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 25 °C

Protect from light.

6.5 Nature and contents of container

Aluminium strips of 5 suppositories each. Available in packs of 10 suppositories.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

LITHA PHARMA (PTY) LTD

106 16th Road

Midrand

1686

8 REGISTRATION NUMBERS

Empaped® 125 mg: X/2.7/193

Empaped® 250 mg: X/2.7/194

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

15 November 1995

10 DATE OF REVISION OF THE TEXT

23 August 2021