PROFESSIONAL INFORMATION FOR PYRACET 125 & 250

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PYRACET 125 suppositories

PYRACET 250 suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PYRACET 125: Each suppository contains 125 mg paracetamol.

PYRACET 250: Each suppository contains 250 mg paracetamol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PYRACET 125: white or almost white suppository, homogeneous appearance, odourless or low odour characteristic of the mass.

PYRACET 250: white or almost white suppository, homogeneous appearance, odourless or low odour characteristic of the mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PYRACET 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 PYRACET 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 years 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 necessary 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 PYRACET125 suppositories in children under six months or weighing less than 7 kg, or PYRACET 250 in children under two years or weighing less than 13 kg, is not recommended.

Method of administration:

The suppository should be inserted per rectum (see section 6.6).

Only whole suppositories should be administered – do not break the suppository before administration.

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

- Hypersensitivity to paracetamol or any of the other ingredients (see section 6.1).

4.4 Special warnings and precautions for use

This product 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 PYRACET in excess of those recommended may cause severe liver damage.

Liver damage is also associated with certain risk factors (see sections 4.5 and 4.9).

If liver damage is suspected, then liver function tests should be performed.

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In the presence of the following disorders, PYRACET 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

Consult a medical practitioner if pain or fever persists or gets worse at the recommended dosage, if new symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition.

Do not use PYRACET continuously without consulting a medical practitioner:
For pain – for more than 5 days.
For fever – for more than 3 days.

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 PYRACET.

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.

Store in a safe place out of the reach of children.

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

Use with caution in renal disease.

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

Use with caution in patients with impaired kidney or liver function.

PYRACET should not be combined with other analgesic medications that contains paracetamol.

4.5 Interaction with other medicines and other forms of interaction

Hepatotoxic medicines – increased risk of hepatotoxicity.

Enzyme induced medicines – increased risk of hepatotoxicity.

Medicines which induce hepatic microsomal enzymes such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

Enzyme-inducing medicines, such as some antiepileptic medicines (phenytoin,

phenobarbital, carbamazepine, primidone) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approx. 60 %. Other medicines with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of causing lowered concentrations of paracetamol.
In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing medicines.

Patients receiving PYRACET 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).

The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. The effect appears to increase as the dose of paracetamol is increased, but can occur with doses as low as 1.5–2 g paracetamol per day for at least 5–7 days. 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. Occasional doses have no significant effect.

Probenecid inhibits the glucuronidation of paracetamol which can affect the clearance of paracetamol. This should be considered when these medicines are administered concomitantly.

Paracetamol may affect the pharmacokinetics of chloramphenicol. This interaction should be considered when these medications are administered concomitantly, especially in malnourished patients.

Possible decrease in therapeutic effects of PYRACET:
Metoclopramide – absorption of PYRACET may be accelerated.
Cholestyramine – absorption of PYRACET is reduced if given within one hour of

cholestyramine.

Prolonged concurrent use of PYRACET 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 indicates neither malformative, nor feto/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:

Paracetamol is excreted in breast milk but not in clinically significant amounts.
Available published data do not contraindicate breastfeeding.

4.7 Effects on ability to drive and use machines

PYRACET may cause fatigue (see section 4.8). Caution is advised when driving a vehicle or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions:

System Organ Class	**Frequency**	**Side effects**

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Blood and the lymphatic system disorders	Less frequent	Thrombocytopenia, leucopenia, agranulocytosis, pancytopenia, neutropenia, anaemia
Immune system disorders	Less frequent	Hypersensitivity reactions such as Quincke's oedema, dyspnoea, sweating, nausea, sharp fall in blood pressure including shock*
Nervous system disorders	Frequent Less frequent	Fatigue, mild headache Respiratory depression (after large doses and in patients with increase intracranial pressure or head trauma), sleep disturbances, euphoria (large doses). The prolonged administration of large amounts may lead to dependence
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm (analgesic asthma)
Gastrointestinal disorders	Frequent	Redness of the rectal mucous membranes
Hepato-biliary disorders	Less frequent Frequency unknown	Hepatitis, liver damage Hepatic necrosis (may occur after overdosage)
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis, reversible skin rashes and other allergic reactions^, exanthema, urticaria, angioedema

	Frequency unknown	Serious skin reactions
Renal and urinary disorders	Less frequent	Renal colic, renal failure, sterile pyuria
Endocrine disorders	Less frequent	Pancreatitis
Investigations	Less frequent	Increase in creatinine (mostly secondary to hepatorenal syndrome)

* Patients should be instructed to discontinue treatment and to contact a doctor at the first signs of hypersensitive reactions.

^ The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by drug fever and mucosal lesions.

Reporting of suspected adverse reactions:

Reporting of 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 an overdosage, consult a doctor immediately, or take the person directly to a hospital.
A delay in starting treatment may mean that the 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 or other medicines that induce liver enzymes.

Symptoms of paracetamol overdose 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 the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the 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:

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

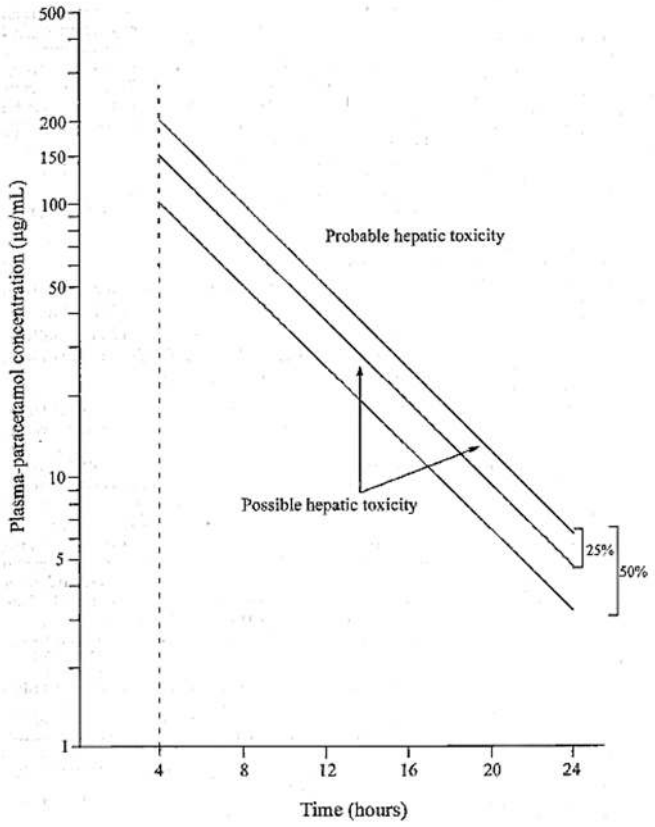

Figure 1 - Sweetman, Sean C, ed, 2009, Martindale – The Complete Drug Reference (37th Edition).

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.

For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N- acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity.
Monitor all patients with significant ingestions for at least ninety six hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

A 2.7 Antipyretic or antipyretic and anti-inflammatory analgesics

Pharmacotherapeutic group: Anilides

ATC code: N02BE01

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

5.2 Pharmacokinetic Properties

Absorption

After rectal administration paracetamol is well absorbed with peak plasma concentrations reached within 1.5 to 2.5 hours. The average elimination half-life is 2 to 3 hours. Plasma protein binding is variable.

Biotransformation

Paracetamol is metabolised in the liver primarily by conjugation with glucuronic acid (about 60 %), sulphuric acid (about 35 %) and cysteine (about 3 %).

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Elimination

Paracetamol is renally excreted primarily as conjugated metabolites.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 Months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package.

6.5 Nature and contents of container

Suppositories are packed in PVC/PE strips, each one containing 6 suppositories.

Pack sizes: 12 suppositories.

6.6 Special precautions for disposal and other handling

Peel the wrapper apart to remove the suppository, gently push into the rectum pointed end first.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

PROFESSIONAL INFORMATION FOR PYRACET 125 & 250

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Waterford Place

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South Africa

8. REGISTRATION NUMBERS

PYRACET 125: 50/2.7/0475

PYRACET 250: 50/2.7/0476

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 15 March 2022

Date of publication: 15 May 2023