SCHEDULING STATUS: S1

PROPRIETARY NAME AND DOSAGE FORM:

VON PARACETAMOL 500 mg (Tablets)

COMPOSITION:
Each tablet contains 500 mg paracetamol.
Preservatives: Nipastat 0,1 % *m/m*
Benzoic acid 0,06 % *m/m*
Other ingredients: Gelatin, maize starch, magnesium stearate, quinolene yellow (CI 47005), sodium metabisulphite, sodium starch glycolate and talc.
Sugar free

CATEGORY AND CLASS:
A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
Paracetamol has analgesic and antipyretic activity.

Pharmacokinetic properties
Paracetamol is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring approximately 10 – 60 minutes after oral doses.
Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. The elimination half-life of paracetamol varies from about 1 – 3 hours.
Paracetamol is mainly metabolised in the liver, following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The metabolites of paracetamol are mainly excreted in the urine. Less than 5 % is excreted as unchanged paracetamol.

INDICATIONS:
The relief of mild to moderate pain and fever such as headaches, toothache and pain associated with colds and flu.

CONTRAINDICATIONS:
VON PARACETAMOL 500 mg is contraindicated in the following:
- Hypersensitivity to paracetamol, or any of the other ingredients in VON PARACETAMOL 500 mg tablets.
- Severe liver function impairment.

WARNINGS AND SPECIAL PRECAUTIONS:
- Consult a doctor or pharmacist if pain or fever persists or gets worse at the recommended dosage, or if new symptoms occur.
- Do not use this product continuously without consulting a medical practitioner:
  Pain – for more than 7 days in adults (5 days for children); and
  Fever – for more than 3 days.
- Dosages in excess of those recommended may cause severe liver damage.
- Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease should not take excessive quantities of VON PARACETAMOL 500 mg.
- Caution is recommended in patients with moderate renal failure and patients on dialysis, as plasma concentrations of VON PARACETAMOL 500 mg and its conjugates are increased.
- Use with caution in renal impairment, chronic malnutrition or dehydration.

VON PARACETAMOL 500 mg 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.

INTERACTIONS:
Hepatotoxic medicines: Increased risk of hepatotoxicity.

Enzyme-inducing medicines: Increased risk of hepatotoxicity and possible decrease in therapeutic effects of VON PARACETAMOL 500 mg.
Metoclopramide: Absorption of VON PARACETAMOL 500 mg may be accelerated.
Probenecid: Pre-treatment with probenecid can decrease VON PARACETAMOL 500 mg clearance, and increase its half-life.
Cholestyramine: Absorption of VON PARACETAMOL 500 mg is reduced if given within one hour of cholestyramine.
Salicylates: Prolonged concurrent use of VON PARACETAMOL 500 mg with salicylates increases the risk of adverse renal effects.
Antibiotics: Chronic use of isoniazid, an antibiotic drug often prescribed for tuberculosis, may increase the risk of liver damage when combined with VON PARACETAMOL 500 mg, even at recommended doses.

HUMAN REPRODUCTION:
VON PARACETAMOL 500 mg is generally considered safe for use in pregnant patients, if used infrequently (not daily or on most days).
VON PARACETAMOL 500 mg is distributed into breastmilk, in amounts too small to be considered harmful to a breast-fed infant. No significant adverse effects have been seen in breast-fed infants whose mothers received paracetamol.

DOSAGE AND DIRECTIONS FOR USE:

Children under 6 years:	Not recommended.
Children 6 – 12 years:	½ - 1 tablet every 6 hours. Not more than 4 doses to be taken in any 24-hour period.
Children over 12 years:	1 tablet every 4 – 6 hours. Not more than 4 tablets to be taken in any 24-hour period.
Adults:	1 – 2 tablets every 4 – 6 hours. Not more than 8 tablets to be taken in any 24-hour period.

DO NOT EXCEED THE RECOMMENDED DOSE

SIDE EFFECTS:
Side effects of VON PARACETAMOL 500 mg are rare and usually mild.
Skin rashes and hypersensitivity reactions may occur.
Skin rashes are usually erythematous or urticarial, but sometimes more serious and may be accompanied by fever and mucosal lesions.
Hypersensitivity reactions are characterised by urticaria, dyspnoea and hypotension. Angioedema can also occur.
The use of paracetamol has been associated with the occurrence of neutropenia, pancytopenia and leucopenia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
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 drugs 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 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 arrhythmias have been reported.
After maternal overdosage during pregnancy, foetal metabolism of paracetamol that crosses the placenta can produce hepatotoxic metabolites, causing foetal hepatotoxicity.

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.

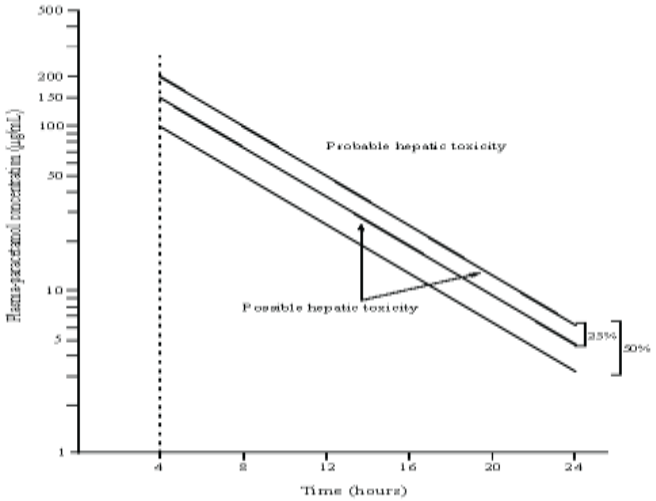
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: 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.**

Oral: 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.



Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55**: 871–6.

Figure 1 - Sweetman, Sean C, ed, 2009, *Martindale – The Complete Drug Reference (*36th Edition), London: The Pharmaceutical Press, pg. 109

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” (*refer to paracetamol nomogram above)*. Prothrombin index correlates best with survival.
Monitor all patients with significant ingestions for at least ninety-six hours.
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.

IDENTIFICATION:
A round, flat, yellow tablet with a central score line on one side.

PRESENTATION:
Plastic buckets or containers (HDPE) of 1000 or 5000 tablets.

STORAGE INSTRUCTIONS:
Store at or below 25 ˚C in a cool, dry place. Protect from light and moisture.
Keep containers and buckets tightly closed. Do not remove tablets from buckets or containers until required for use.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:
B/2.7/1480

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Gulf Drug Company (Pty) Ltd
22 Burnside Drive
Old Mill Industrial Park
Mount Edgecombe, 4300

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:
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Date of registration: 04/01/1984