SCHEDULING STATUS

S0 Pack sizes smaller than 25 tablets

1 NAME OF THE MEDICINE

ZYPOL 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg.

Preservatives:

Nipastat	0,1 % m/m
Benzoic acid	0,06 % m/m

Contains sugar: Each tablet contains 20 mg sucrose per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A flat, round, green tablet with a break line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of moderate pain and fever such as headaches, toothache and pain associated with colds and flu.

4.2 Posology and method of administration

Posology

Children under 6 years: Not recommended.

Children 6 to 12 years: Half to one tablet every 6 hours. Not more than 4 tablets to be taken in any 24-hour period.

Children over 12 years: One tablet every four to six hours. Not more than 4 tablets to be taken in any 24-hour period.

Adults: One to two tablets every four to six hours. Not more than 8 tablets to be taken in any 24-hour period.

DO NOT EXCEED THE RECOMMENDED DOSE

Method of administration

ZYPOL is for oral administration.

4.3 Contraindications

- Hypersensitivity to paracetamol, or any of the excipients listed in section 6.1.
- Sever liver function impairment.

4.4 Special warnings and precautions for use

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

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 continuously for more than 7 days for pain in adults (5 days for children) and more than 3 days for fever without consulting a doctor.

Patients suffering from hepatitis or alcoholism or recovering from any form of liver disease should not take excessive quantities of ZYPOL Tablets.

Caution is recommended in patients with moderate renal failure and patients on dialysis, as plasma concentrations of ZYPOL Tablets and its conjugates are increased.

Use with caution in renal impairment, chronic malnutrition, or dehydration.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruption (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with ZYPOL Tablets must immediately be discontinued and appropriate treatment instituted (see Section 4.8).

ZYPOL contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

4.5 Interaction with other medicines and other forms of interaction

Hepatotoxic medicines: Increased risk of hepatotoxicity.

Enzyme-inducing medicines: Increased risk of hepatotoxicity and possible decrease in therapeutic effects of ZYPOL.

Metoclopramide: Absorption of ZYPOL may be accelerated.

Domperidone: Absorption of ZYPOL may be accelerated.

Probenecid: Pre-treatment with probenecid can decrease ZYPOL clearance and increase its half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Cholestyramine: Absorption of ZYPOL Tablets is reduced if given within one hour of cholestyramine.

Salicylates: Prolonged concurrent use of ZYPOL Tablets with salicylates increases the risk of adverse renal effects.

Antibiotics: Chronic use of isoniazid, an antibiotic medicine often prescribed for tuberculosis, may increase the risk of liver damage when combined with ZYPOL Tablets, even at recommended doses.

Warfarin and anticoagulants: Concurrent, chronic, high-dose administration of ZYPOL Tablets may increase the anticoagulant effect.
Paracetamol is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon) and isolated reports have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.
Antiepileptics: The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing medicines such as carbamazepine, phenobarbital, phenytoin, or primidone.
Antibacterials: The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing drugs such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.
Antivirals: Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole. However, neither short-term nor long-term studies (the latter also in an individual
patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.
Paracetamol has also been found to enhance the antiviral effect of interferon alfa.

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breastfeeding

Following oral administration, small amounts of paracetamol are excreted into breast milk, however not in a clinical significant amount. Paracetamol can be administered during lactation at therapeutic doses.

Fertility

No detrimental effects on fertility upon normal use are known.

4.7 Effects on ability to drive and use machines

ZYPOL has no or negligible influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions
Blood and the lymphatic system disorders	Less frequent	Agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, neutropenia, anaemia
Immune system disorders	Frequency not known	Hypersensitivity reactions are characterised by urticaria, dyspnoea and hypotension. Angioedema can also occur.
Metabolism and nutrition disorders	Less frequent	Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Ear and labyrinth disorders	Frequency not known	Hearing loss
Cardiac disorders	Frequency not known	Possible increase in the risk of hypertension
Gastrointestinal disorders	Less frequent	Pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis
Renal and urinary disorders	Less frequent Frequency not known	Renal colic, renal failure and sterile pyuria Nephropathy
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis, skin rashes, severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruption (FDE)

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. 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

In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Control Centre must be contacted immediately.

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.

Symptoms:

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 dysrhythmias have been reported. Nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Cerebral oedema and nonspecific myocardial depression have also occurred.

After maternal overdosage during pregnancy, foetal metabolism of paracetamol that crosses the placenta can produce hepatotoxic metabolites, causing foetal hepatotoxicity.

Treatment for paracetamol overdosage:

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.

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.

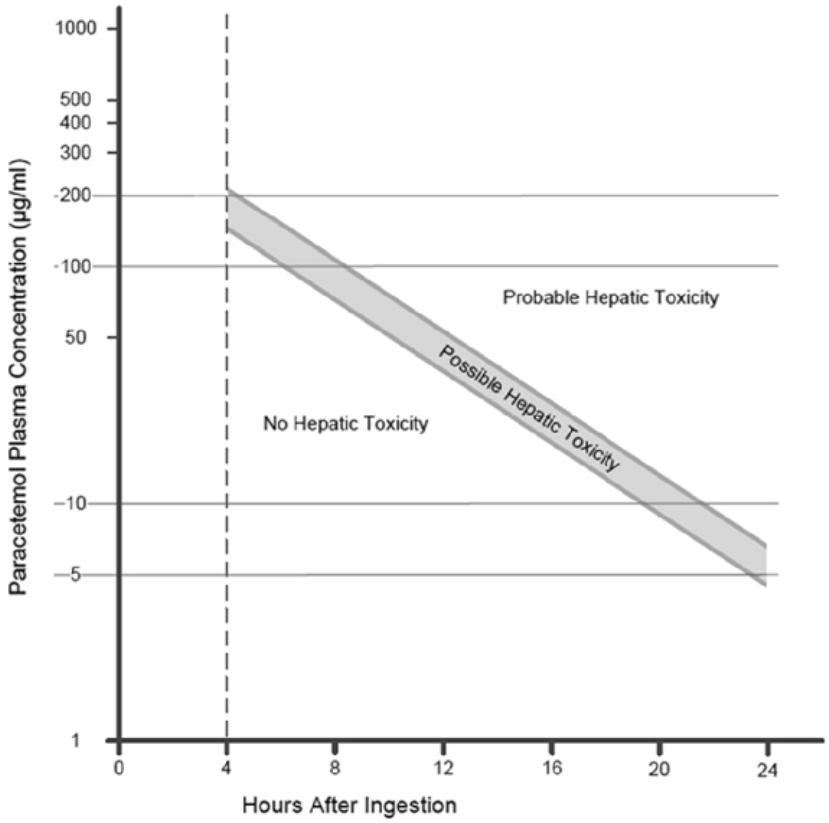

Figure 1: A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

Pharmacotherapeutic group: Other analgesics and antipyretics. ATC Code: N02BE01.

Paracetamol has analgesic and antipyretic activity.

The mechanism of action is associated with inhibition with prostaglandin synthesis.

5.2 Pharmacokinetic properties

Absorption:

Paracetamol is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring approximately 10 – 60 minutes after oral doses.

Distribution:

Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

Biotransformation:

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.

Elimination:

The elimination half-life of paracetamol varies from about 1 – 3 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch Maize, Powdered Sucrose, Nipastat, Benzoic Acid, Gelatin, Green Apple Colour, Magnesium Stearate, Modified Starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Securitainers - 36 months

Blisters – 24 months

LDPE Patient Ready Packs (PRP) – 15 months

6.4 Special precautions for storage

Store in a cool dry place, in well-closed containers, at or below 25 °C.

Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Securitainers of 24 tablets.

PVC/Aluminium foil blister packs of 20 and 24 tablets.

White LDPE patient ready packs containing 20 tablets.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road and Bluegum Avenue

Anchorville, Lenasia

1827

South Africa

8 REGISTRATION NUMBER

29/2.7/0617

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 May 1996

10 DATE OF REVISION OF TEXT

27 June 2024