SCHEDULING STATUS

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1. NAME OF THE MEDICINE

PANADO TABLETS, 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 500 mg paracetamol.

Sugar free.

Potassium Sorbate (0,12 % *m/m*)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to slightly off-white, round, biconvex tablets embossed with “PANADO” on one side and with break line and two indentations on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANADO TABLETS is indicated for the symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE

Adults: One tablet every 3 hours or one to two tablets every 4 to 6 hours while symptoms persist. Do not

exceed 4 gram in 24 hours.

Children 6 to 12 years: Half to one tablet while symptoms persist, to be repeated every 4 hours if needed to a maximum of 4 doses per 24 hours for not longer than 5 days.

Children under 6 years: Not recommended. Paracetamol syrup should rather be considered for use if such a medicine is necessary.

Method of administration

For oral use only.

The tablet should be swallowed with a glass of water.

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the excipients of PANADO TABLETS listed in section 6.1.
- Severe liver function impairment.

4.4 Special warnings and precautions for use

PANADO TABLETS contain 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 in excess of those recommended may cause severe liver damage.

Prolonged or frequent use is discouraged. Do not use this product continuously for more than 10 days without consulting your doctor.

Patients should be advised not to take other paracetamol containing products concurrently.

Consult a medical practitioner in cases of high fever, signs of secondary infection, if pain and symptoms persist for more than three days 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.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities of PANADO TABLETS.

Caution is advised in the administration of PANADO TABLETS to patients with severe renal impairment, acute hepatitis, concomitant administration of medicines that affect the liver function, glucose-6-phosphatedehyrogenase deficiency, haemolytic anaemia, alcohol abuse, chronic dehydration and malnutrition.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. Alcohol must not be used during treatment period. The daily dose should not exceed 2 000 mg in such case.

After prolonged use (> 3 months) of analgesics intake every day or more often, headaches may occur or worsen. Headaches caused by overuse of analgesics should not be handled by increasing the dose. In those cases, the use of analgesics should be taken after consulting a doctor. Caution is advised in asthmatic patient sensitive to acetylsalicylic acid (aspirin), because bronchospasm with paracetamol (cross-reaction) has been reported.

Self-medication with paracetamol (i.e., PANADO TABLETS) should be limited when taking anticonvulsants because with the concomitant use of both, liver toxicity is potentiated and the bioavailability of paracetamol is reduced, especially when using high doses of paracetamol (see section 4.5).

Caution is advised if PANADO TABLETS is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5 oxoproline,

is recommended.

Severe cutaneous adverse reactions (SCARs):

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 eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with PANADO TABLETS must immediately be discontinued and appropriate treatment instituted (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Hepatotoxic medicines: Increased risk of hepatotoxicity of paracetamol, as contained in PANADO TABLETS.

Metoclopramide and domperidone: Absorption of PANADO TABLETS may be accelerated.

Cholestyramine: Absorption of PANADO TABLETS is reduced if given within one hour of cholestyramine.

Salicylates: Salicylamide may prolong the elimination $t_{½}$ of paracetamol.

Prolonged concurrent use of PANADO TABLETS with salicylates increases the risk of adverse renal effects.

Warfarin and anticoagulants: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of PANADO TABLETS with increased risk of bleeding. Occasional doses have no significant effect.

Concurrent, chronic, high-dose administration of PANADO TABLETS may increase the anticoagulant effect. Paracetamol, as contained in PANADO TABLETS, 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, as contained in PANADO TABLETS, regularly.

Enzyme inducing medicines: Increased risk of hepatotoxicity of paracetamol, as contained in PANADO TABLETS. Possible decrease in therapeutic effects of PANADO TABLETS.
Paracetamol (i.e., PANADO TABLETS) is extensively metabolised in the liver and can therefore interact with medicines with the same metabolic pathway or induce/inhibit the same metabolic pathway. Chronic use of alcohol or medicines which induce liver enzymes, such as rifampicin, barbiturates, some anti-epileptic medicines (e.g. carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone) tricyclic antidepressants and St. John's wort can increase the hepatotoxicity of PANADO TABLETS as a result of an increased and fast formation of toxic metabolites. Caution is therefore necessary with concomitant use of enzyme-inducing medicines.

Alcohol: Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

Antiepileptics and oral contraceptives: The use of medicines that induce hepatic microsomal enzymes such as anticonvulsants and oral contraceptives may increase the extent of metabolism of paracetamol, as contained in PANADO TABLETS, resulting in reduced plasma concentrations of paracetamol and a faster elimination rate. 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.

Paracetamol, as contained in PANADO TABLETS, may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

Probenecid: Probenecid blocks the binding of paracetamol to glucuronic acid reducing paracetamol clearance by a factor of about 2 and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged. If probenecid is taken concurrently, the PANADO TABLETS dose should be reduced.

Antibacterials: The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing medicines such as rifampicin.

Isoniazid reduces the paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

PANADO TABLETS can increase the plasma concentration of chloramphenicol.

Caution should be taken when paracetamol, as contained in PANADO TABLETS is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4).

Antivirals: With chronic concomitant use of PANADO TABLETS and zidovudine, neutropenia often occurs and is probably due to the reduced metabolism of zidovudine.

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, as contained in PANADO TABLETS, has also been found to enhance the antiviral effect of interferon alfa.

Interference with laboratory tests

Paracetamol, as contained in PANADO TABLETS, may affect uric acid tests by wolframato phosphoric acid and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in breastfeeding has not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

PANADO TABLETS has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System Organ Class (SOC)	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	*Less frequent*	Agranulocytosis (long-term use), thrombocytopenia, thrombocytopenic purpura, leukopenia, haemolytic anaemia, platelet disorders, stem cell disorders, pancytopenia, neutropenia, anaemia.
Immune system	*Less frequent*	Hypersensitivity (excluding angioedema), hypersensitivity

disorders		reaction, requiring discontinuation of treatment (angioedema, ventilation difficulty, hyperhidrosis, nausea, hypotension, shock, anaphylactic reaction).
	Frequency unknown	Drug-induced hypersensitivity syndrome (DIHS), hypersensitivity reactions characterised by urticaria, dyspnoea, and hypotension * (see section 4.4).
Metabolism and nutrition disorders	*Less frequent*	Hypoglycaemia.
Psychiatric disorders	*Less frequent*	Depression NOS*, confusion, hallucinations.
Nervous system disorders	*Less frequent*	Tremor NOS, headache NOS.
Eye disorders	*Less frequent*	Abnormal vision.
Cardiac disorders	*Less frequent*	Oedema.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Bronchospasm in patients sensitive to aspirin and other Nonsteroidal anti-inflammatory drugs (NSAIDs).
Gastrointestinal disorders	*Less frequent*	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting, pancreatitis.
Hepato-biliary disorders	*Less frequent*	Abnormal hepatic function, hepatic failure, hepatic necrosis**, jaundice, hepatotoxicity, hepatitis.
Skin and subcutaneous tissue disorders	*Less frequent*	Dermatitis, skin rashes, sweating, purpura, angioedema, urticaria and other allergic reactions. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions.
	Frequency unknown	Acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), drug-induced dermatosis, Stevens-

		Johnson syndrome (SJS), fixed drug eruptions (FDE) (see section 4.4).
Renal and urinary disorders	*Less frequent*	Sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, nephrite interstitial, haematuria, enuresis), renal colic.
General disorders and administration site conditions	*Less frequent*	Dizziness (excluding vertigo), malaise, pyrexia, sedation, medicine interaction NOS.
Injury, poisoning and procedural complications	*Less frequent*	Overdose and poisoning

* NOS: Not otherwise specified

** Administration of 6 grams of paracetamol may already lead to hepatic damage (in children: more than 140 mg/kg); higher doses cause irreversible hepatic necrosis.

Post-marketing experience:

The following side effects have been reported and frequencies are unknown:

Fixed drug eruptions (FDE) and drug-induced hypersensitivity syndrome (DIHS) (see section 4.4).

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

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.

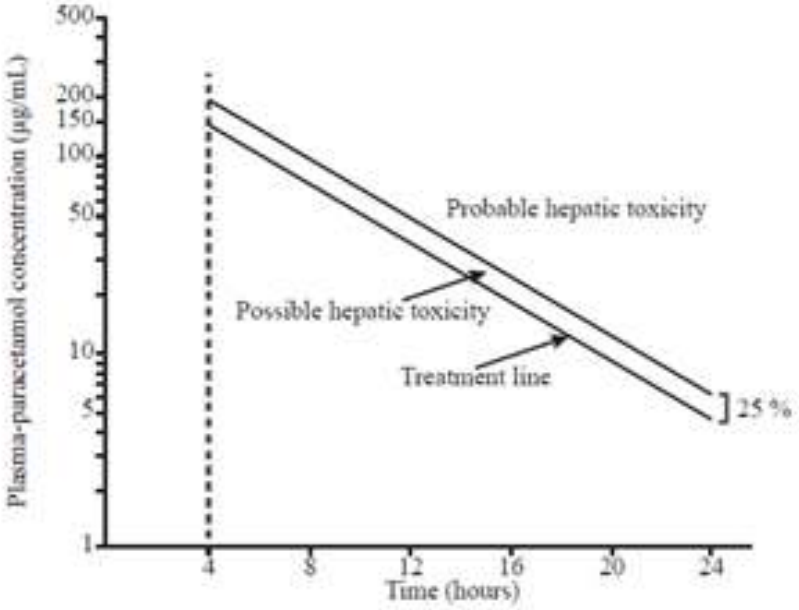
Management

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 i**ntravenously** 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. The nomogram should be used only in relation to a single acute ingestion.



Source: Martindale: The Complete Drug Reference -37th Edition.

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.

Monitor all patients with significant ingestions for at least ninety-six hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of the medicine: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.

ATC code: N02BE01.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0, 5 to 1 hour.

Once absorbed, the plasma half-life is about 2 hours.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. 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 %).

The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercaptopuric acid.

In neonates and children under 12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity

for sulphate conjugation.

Elimination

Paracetamol is renally excreted primarily as conjugated metabolites. Elimination is essentially through the urine. 90 % of the ingested dose is eliminated via the kidneys within 24 hours, predominantly as the glucuronide (60 to 80 %) and the sulphate (20 to 30 %) conjugates. Less than 5 % is eliminated in unchanged form. The elimination half-life is about 2 hours.

Special patient groups

Renal impairment

In cases of severe renal insufficiency after overdose, and in neonates the elimination half-life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations.

Elderly

The capacity for conjugation is not modified.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Potassium sorbate (0,12 % *m/m*)

Magnesium stearate

Colloidal silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/foil blister packs: 48 months

Polypropylene tracer packs: 48 months

Polypaper strip packs: 24 months

Polypropylene securitainer: 24 months

Spartan HDPE containers: 24 months

6.4 Special precautions for storage

Store at or below 25 ºC in a well-closed container protected from light.

Exposure to air should be kept to a minimum.

6.5 Nature and contents of container

Polypaper strips of 2 tablets.

2 Polypaper strips of 2 tablets each in a carton.

PVC/Aluminium foil blister packs of 12 and 24 tablets.

White polypropylene tracer packs of 24 tablets.

White polypropylene securitainers of 10 and 20 tablets.

White HDPE Spartan containers of 24 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand

1685

Customer Care: 0860 ADCOCK/232625

8. REGISTRATION NUMBER(S)

B/2.8/858

Namibia	2's, 12's & 24's	NS0	90/2.8/00159
Botswana	2's, 12's, 24's	S4	BOT0901565A/B/C

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

07 February 1983

10. DATE OF REVISION OF THE TEXT

13 August 2025