SCHEDULING STATUS

S0

1 NAME OF THE MEDICINE

PANADO EFFERVESCENT, 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 500 mg paracetamol.

Excipients with known effects:

Each PANADO EFFERVESCENT tablet contains:

Sweeteners:	Aspartame	15,00 mg
	Sodium saccharin	6,50 mg
	Sorbitol	50,00 mg
Sodium:		409,70 mg
Sodium benzoate:		60,00 mg

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets.

Flat, white, bevelled-edge, round tablet.

After effervescence: clear solution with slight sediment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

DO NOT EXCEED THE RECOMMENDED DOSE.

Posology

Adults:

Two tablets dissolved in at least half a glass of water up to 4 times daily as required.

Children 6 to 12 years:

Half to one tablet dissolved in at least half a glass of water.

Children should not be given doses of PANADO EFFERVESCENT tablets more frequently than every 4 hours and not more than 4 doses should be given in any 24-hour period.
Children should not be given PANADO EFFERVESCENT tablets for more than 3 days without consulting a doctor.
Not suitable for children under 6 years of age. Do not exceed the stated dose.

Method of administration
Oral use.
Place the tablets in at least half a glass of water and allow to dissolve completely before swallowing.
After dissolving the tablets, a clear solution with slight sediment will be produced.

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the ingredients of PANADO EFFERVESCENT tablets listed in section 6.1.
- Severe liver function impairment.

4.4 Special warnings and precautions for use

PANADO EFFERVESCENT 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 in excess of those recommended may cause severe liver damage.
Prolonged or frequent use of PANADO EFFERVESCENT may be dangerous. Do not use continuously for more than 10 days without consulting a doctor. Do not exceed the stated dose.

Consult a doctor if no relief is obtained from the recommended dosage.
Patients should be advised not to take other paracetamol containing products concurrently.

Patients suffering from liver or kidney disease should take PANADO EFFERVESCENT under medical supervision. Caution is advised in the administration of PANADO EFFERVESCENT to patients with acute hepatitis, concomitant treatment with medicines affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic

anaemia, alcohol abuse dehydration and chronic malnutrition.

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

Caution is advised in asthmatic patients sensitive to aspirin (acetylsalicylic acid), because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5 % of the patients tested.

Abrupt discontinuation of long-term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

Caution is advised if PANADO EFFERVESCENT 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 generalised 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 SCAR, treatment with PANADO EFFERVESCENT tablets must immediately be discontinued and appropriate treatment instituted (see section 4.8).

PANADO EFFERVESCENT tablets contain sodium benzoate, sorbitol and aspartame:

- PANADO EFFERVESCENT contains sodium benzoate 60,00 mg in each effervescent tablet. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

- PANADO EFFERVESCENT contains 50 mg sorbitol in each effervescent tablet. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
  The content of sorbitol in medicines for oral use may affect the bioavailability of other medicines for oral use administered concomitantly.
  Patients with hereditary fructose intolerance (HFI) should not take
  PANADO EFFERVESCENT tablets.

- PANADO EFFERVESCENT contains 15 mg aspartame in each effervescent tablet. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. May be harmful for people with phenylketonuria.

Sodium content:
PANADO EFFERVESCENT contains 409,70 mg sodium per effervescent tablet equivalent to 21 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction
Hepatotoxic medicines: Increased risk of Hepatotoxicity of paracetamol, as contained in PANADO EFFERVESCENT.

Warfarin and anticoagulants: The anticoagulant effect of warfarin and other coumarins may be enhanced by regular use of PANADO EFFERVESCENT with increased risk of bleeding. The effect may occur already at daily doses of 2 000 mg after 3 days. Occasional doses have no significant effect on bleeding tendency.
Concurrent, chronic, high-dose administration of PANADO EFFERVESCENT may increase the anticoagulant effect.
Paracetamol, as contained in PANADO EFFERVESCENT, 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 INR values should be done during the duration of the combination and after its discontinuation.

Enzyme inducing medicines: Use of medicines that induce liver enzymes, such as carbamazepine, fosphenytoin, phenytoin, primidone, phenobarbital, rifampicin, tricyclic antidepressants and St John's wort (*Hypericum perforatum*) can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites and possible decrease in therapeutic effects of PANADO EFFERVESCENT. Therefore, caution should be taken in case of 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 EFFERVESCENT, 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.

Probenecid: Probenecid nearly halves the clearance of paracetamol and increase its plasma half-life by inhibiting its conjugation with glucuronic acid. This probably means that the dose of PANADO EFFERVESCENT can be halved when being given at the same time as probenecid.

Metoclopramide and domperidone: Concurrent intake of medicines that accelerate gastric emptying, such as metoclopramide or domperidone, accelerates the absorption and onset of effect of paracetamol.

Cholestyramine: The absorption of paracetamol is reduced by cholestyramine. Cholestyramine should not be given within one hour if maximum analgesic effect is to be obtained.

Salicylates: Prolonged concurrent use of paracetamol, as contained in PANADO EFFERVESCENT, with salicylates increases the risk of adverse renal effects.

Antibacterials: The plasma-paracetamol concentrations considered an indication for antidote

treatment should be halved in patients receiving enzyme inducing medicines 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.
PANADO EFFERVESCENT may affect the pharmacokinetics of chloramphenicol. Therefore, an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.
Caution should be taken when PANADO EFFERVESCENT is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

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

Interference with laboratory tests:
PANADO EFFERVESCENT may affect uric acid tests by wolframato phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy have not been established.

Breastfeeding

Safety and efficacy in breastfeeding have not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

PANADO EFFERVESCENT 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	Frequency	Undesirable effect
Blood and lymphatic system disorders	Less frequent	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia, neutropenia, methaemoglobenaemia
Immune system disorders	Less frequent	Allergies (excluding angioedema)
	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
Gastrointestinal disorders	Less frequent	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting
Hepato-biliary disorders	Less frequent	Abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice, hepatotoxicity
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, sweating, purpura, angioedema, urticaria, severe cutaneous adverse reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP)
	Frequency unknown	Fixed drug eruptions (FDE) (see section 4.4).
Renal and urinary disorders	Less frequent	Sterile pyuria (cloudy urine) and renal side

		effects
General disorders and administration site conditions	Less frequent	Dizziness (excluding vertigo), malaise, pyrexia, sedation, medicine interaction NOS, hypersensitivity reaction (requiring discontinuation of treatment)
Injury, poisoning and procedural complications	Less frequent	Overdose and poisoning

* NOS: Not otherwise specified

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). Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastrointestinal effects and vertigo 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 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 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 are pallor, nausea, vomiting, anorexia and abdominal pain (see section 4.8). 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 to all cases of suspected overdose as soon as possible, preferably within 8 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 in 200 ml dextrose injection, given **intravenously** over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml dextrose injection over the next 4 hours and then 100 mg/kg in 1 000 ml dextrose injection over the next 16 hours. **The volume of intravenous fluids should be modified for children.**

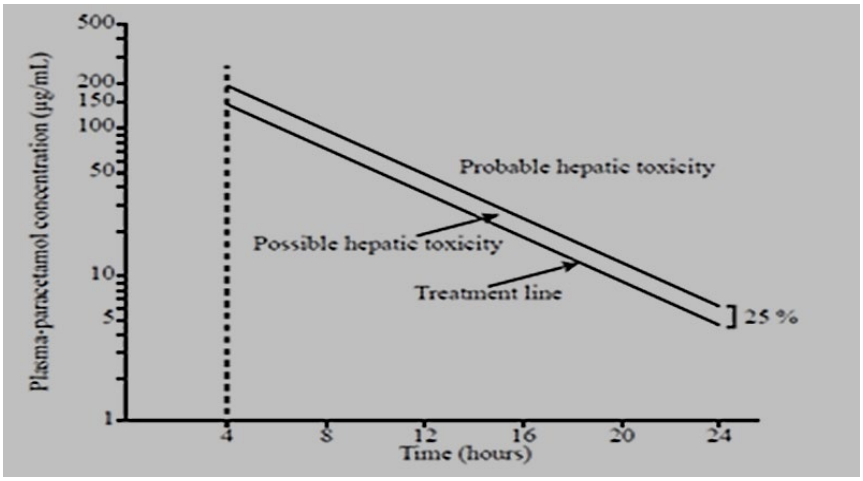
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg solution every four hours for 17 doses.

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.

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.



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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.7 Antipyretic or antipyretics and anti-inflammatory analgesics.

ATC code: N02B E01, Other analgesics and antipyretics.

Paracetamol has analgesic and antipyretic actions.

5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Biotransformation

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed 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 cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

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

Special patient groups

Renal impairment

In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly

The capacity for conjugation is not modified.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame
Citric acid anhydrous
Magnesium stearate
Povidone/ kollidon K25
Sodium bicarbonate
Sodium benzoate
Sodium carbonate anhydrous

Sodium lauryl sulphate
Sodium saccharin
Sorbitol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a well closed container protected from light. Store at or below 25 °C. Exposure to air should be kept to a minimum.

6.5 Nature and contents of container
Sixteen effervescent tablets, collectively wrapped in aluminium foil laminate, are packed in a printed polypropylene tube. The tube is sealed with a snap-on closure made of low-density polyethylene (LDPE), available either as a standard cap or a pilfer-proof closure. The tube is then enclosed in a printed carton box.

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

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V/2.7/219

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10 DATE OF REVISION OF THE TEXT

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