SCHEDULING STATUS
S0

1. NAME OF THE MEDICINE
PANADO PAEDIATRIC SYRUP - STRAWBERRY, 120 mg/ 5 mL, Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 mL syrup contains:
Paracetamol 120 mg

Preservative:	Sodium benzoate	0,3 % *m/v*
Sweeteners:	Sodium cyclamate	7,50 mg
	Sorbitol	280 mg

PANADO PAEDIATRIC SYRUP – STRAWBERRY also contains:
Propylene glycol 80 mg per 5 mL.
Sugar free.
Tartrazine free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup
A clear, dark pink syrup with an odour and taste of strawberry.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
PANADO PAEDIATRIC SYRUP - STRAWBERRY 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.

Paediatric population
Infants*:*

3 months to 1 year:	2,5 to 5 mL (60 to 120 mg)

Children*:*

1 to 5 years:	5 to 10 mL (120 to 240 mg)
6 to 12 years:	10 to 20 mL (240 to 480 mg)

PANADO PAEDIATRIC SYRUP - STRAWBERRY – 5 mL Sachet
Always administer using a medicine measure or a syringe.
For single use only.
Discard remaining contents of sachet after administration of the correct dosage.

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.

Method of administration
For oral administration.
Shake the bottle before use.

4.3 Contraindications
- Hypersensitivity to paracetamol or to any of the excipients of PANADO PAEDIATRIC SYRUP - STRAWBERRY listed in section 6.1
- Severe liver function impairment.

4.4 Special warnings and precautions for use

PANADO PAEDIATRIC SYRUP – STRAWBERRY 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 PANADO PAEDIATRIC SYRUP - STRAWBERRY in excess of those recommended may cause severe liver damage.

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 this product continuously for more than 10 days without consulting your doctor.

Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not be given excessive quantities of PANADO PAEDIATRIC SYRUP – STRAWBERRY. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Paracetamol should be given with care to patients with impaired kidney or liver function.
Use with caution in renal disease, alcohol dependence, chronic malnutrition or dehydration.

High anion gap metabolic acidosis (HAGMA):
Caution is advised if paracetamol, as contained in PANADO PAEDIATRIC SYRUP – STRAWBERRY, 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's, treatment with PANADO PAEDIATRIC SYRUP - STRAWBERRY must immediately be discontinued and appropriate treatment instituted (see section 4.8).

Excipients:
PANADO PAEDIATRIC SYRUP - STRAWBERRY contains:

- Sorbitol.
  PANADO PAEDIATRIC SYRUP - STRAWBERRY contains 280 mg sorbitol in each 5 mL dose which is equivalent to 56 mg/mL.
  The additive effect of concomitantly administered medicines 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 the rare hereditary fructose intolerance (HFI) should not be given PANADO PAEDIATRIC SYRUP – STRAWBERRY.

- Propylene glycol.
  PANADO PAEDIATRIC SYRUP – STRAWBERRY contains 80 mg propylene glycol in each 5 mL dose which is equivalent to 16 mg/mL.
  Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
  While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk (see section 5.2, Distribution').
  Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

- Sodium benzoate as preservative.
  PANADO PAEDIATRIC SYRUP – STRAWBERRY contains 16,50 mg sodium benzoate in each 5 mL dose which is equivalent to 3,3 mg/mL.
  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 PAEDIATRIC SYRUP - STRAWBERRY contains less than 1 mmol sodium (23 mg) per 5 mL that is to say it is essentially `sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

- *Hepatotoxic medicines:* Increased risk of hepatotoxicity of paracetamol, as contained in PANADO PAEDIATRIC SYRUP - STRAWBERRY.

- *Enzyme inducing medicines:* Increased risk of hepatotoxicity of paracetamol, as contained in PANADO PAEDIATRIC SYRUP - STRAWBERRY. Possible decrease in therapeutic effects of PANADO PAEDIATRIC SYRUP - STRAWBERRY.
  The hepatotoxicity of paracetamol, as contained in PANADO PAEDIATRIC SYRUP - STRAWBERRY, particularly after overdosage, may be increased by medicines which induce liver microsomal enzymes such as carbamazepine, barbiturates (e.g. phenobarbital), fosphenytoin, phenytoin, primidone, rifampicin, tricyclic antidepressants, St. John's wort (*Hypericum perforatum*) and alcohol due to increased and more rapid formation of toxic metabolites. 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 (e.g., PANADO PAEDIATRIC SYRUP – STRAWBERRY), the plasma half-life of which can be prolonged.

- *Metoclopramide or domperidone:* Absorption of PANADO PAEDIATRIC SYRUP - STRAWBERRY may be accelerated.

- *Cholestyramine:* Absorption of PANADO PAEDIATRIC SYRUP - STRAWBERRY is reduced if given within one hour of cholestyramine.

- *Salicylates:* Prolonged concurrent use of PANADO PAEDIATRIC SYRUP - STRAWBERRY 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 regular daily use of paracetamol (e.g., PANADO PAEDIATRIC SYRUP - STRAWBERRY) with increased risk of bleeding; occasional doses have no significant effect.
  Concurrent, chronic, high-dose administration of PANADO PAEDIATRIC SYRUP - STRAWBERRY may increase the anticoagulant effect.
  Paracetamol, as contained in PANADO PAEDIATRIC SYRUP - STRAWBERRY, 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 PAEDIATRIC SYRUP - STRAWBERRY regularly.

- *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 resulting in reduced plasma concentrations of the medicine 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:* Pre-treatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged. This probably means that the dose of PANADO PAEDIATRIC SYRUP - STRAWBERRY can be halved when being given at the same time as probenecid.

- *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 PAEDIATRIC SYRUP - STRAWBERRY 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 PAEDIATRIC SYRUP - STRAWBERRY 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 has also been found to enhance the antiviral effect of interferon alfa.

- *Interference with laboratory tests:* Paracetamol, as contained in PANADO PAEDIATRIC SYRUP - STRAWBERRY, may affect uric acid tests by wolframato phosphoric acid and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Fertility, pregnancy and breastfeeding
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 PAEDIATRIC SYRUP - STRAWBERRY has no or negligible influence on the ability to drive and use machines**.**

4.8 Undesirable effects
Tabulated summary of adverse reactions

System Organ Class (SOC)	Frequency	Undesirable effect
Blood and lymphatic system disorders	*Less frequent*	Blood disorder (including agranulocytosis and thrombocytopenia) [1], leukopenia, pancytopenia, neutropenia, anaemia.
Immune system disorders	*Less frequent*	Anaphylactic reaction, hypersensitivity reactions characterized by urticaria, dyspnoea, and hypotension (see section 4.4).
	Frequency unknown	Drug-induced hypersensitivity syndrome (DIHS).
Metabolism and nutrition disorders	*Frequency unknown*	Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.
Ear and labyrinth disorders	*Frequency unknown*	Hearing loss.
Cardiac disorders	*Frequency unknown*	Possible increase in the risk of hypertension.
Gastrointestinal disorders	*Less frequent*	Pancreatitis.
	Frequency unknown	Nausea and vomiting.
Hepato-biliary disorders	*Less frequent*	Hepatitis.
	Frequency unknown	Liver injury [2, 6].
Skin and subcutaneous tissue	*Less frequent*	Dermatitis, skin rashes, and other allergic reactions such as Stevens-Johnson Syndrome (SJS), Toxic

disorders [5]		Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP). The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions. More mild rashes and other hypersensitivity reactions also occur occasionally.
	Frequency unknown	Fixed drug eruptions (FDE) (see section 4.4), pruritus, urticaria.
Renal and urinary disorders	*Less frequent*	Renal colic, renal failure, sterile pyuria, nephropathy toxic.
	Frequency unknown	Renal papillary necrosis [3].
Investigations	*Frequency unknown*	Transaminases increased [4]

Description of selected adverse reactions

[1] Reported following paracetamol use, but not necessarily causally related to paracetamol.

[2] Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year.

[3] Reported after prolonged administration.

[4] Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

[5] Very rare cases of serious skin reactions have been reported.

[6] Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol, as contained in PANADO PAEDIATRIC SYRUP – STRAWBERRY, for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal.

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 asked to report any suspected adverse 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 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.

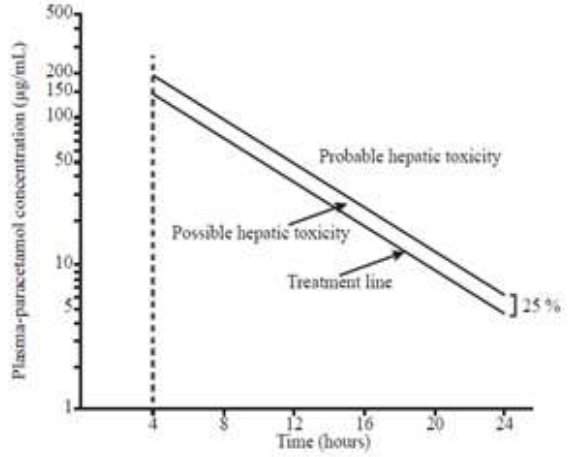
Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

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 **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 [4] 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 ingestion for at least ninety-six hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.7 Antipyretics or antipyretic and anti-inflammatory analgesics.
Pharmacotherapeutic group: Other analgesics and antipyretics (Anilides)
ATC code: N02BE01

Paracetamol has analgesic and antipyretic properties.
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.
The plasma half-life is about 2 hours.

Distribution
Plasma protein binding is variable.
Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

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

Elimination
Paracetamol is renally excreted primarily as conjugated metabolites.

Special populations
No data available.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E 422)
Polyvinylpyrrolidone K25
Propylene glycol (E 1520)
Sodium benzoate (E 211)
Xanthan gum
Flavour strawberry 216330
Colour carmoisine red H.7110
Hydrochloric acid (for pH adjustment)
Sorbitol (E 420)
Sodium cyclamate
Purified water

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.
Do not refrigerate or freeze.
Exposure to air should be kept to a minimum.

6.5 Nature and contents of container

50 mL & 100 mL round bottles (clear glass) with a screw closure (EXPE) packed in unit cartons.
50 mL & 100 mL round bottles (clear PVC) with a snap-on pilfer proof closure packed in unit cartons.
5 mL sachets packed into unit cartons. Sachets are composed of polyester/aluminium foil/metallocene co-extruded.
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)

35/2.7/0112

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

26 March 2002

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