1.3.1.1 PACKAGE INSERT

SCHEDULING STATUS: S2

PROPRIETARY NAME AND DOSAGE FORM:

TENSOPYN PAEDIATRIC SYRUP

COMPOSITION:

Each 5 ml syrup contains:

Paracetamol	150,0 mg
Codeine phosphate	4,0 mg
Preservatives*:*	
Sodium Benzoate	0,1 % m/v
Potassium Sorbate	0,2 % m/v

The other ingredients are:

Propylene glycol, glycerine, macrogol, sodium cyclamate, acesulfame-K, butylated hydroxytoluene, sodium chloride, blackcurrent flavour, cherry flavour, purified water.

Sugar free.
Contains sweetener:
Acesulfame-K 7,5 mg
Sodium cyclamate 10 mg

PHARMACOLOGICAL CLASSIFICATION:

A.2.8 Analgesic combinations

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Paracetamol has analgesic and antipyretic properties.

Codeine Phosphate has analgesic properties.

Pharmacokinetics:

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is presented in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours. Paracetamol is metabolised predominantly in the liver and excreted in the urine mainly as the glucoronide and sulphate conjugates. Less than 5 % is excreted as unchanged paracetamol.

A minor hydroxylated metabolite (*N*-acetyl-p-benzoquinoneimine) is usually produced in very small amounts by cytochrome P450 iso-enzymes in the liver and kidneys. It is usually detoxified by conjugation with glutathione but may accumulate following paracetamol overdosage and cause tissue damage.

Codeine phosphate is absorbed from the gastrointestinal tract. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. Codeine is metabolized by *0* - and *N* - demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidneys, mainly as conjugates with glucuronic acids. The plasma half-life has been reported to be between 3 and 4 hours after an oral dose.

INDICATIONS:

TENSOPYN PAEDIATRIC SYRUP is indicated for the symptomatic relief of mild to moderate pain and fever in children.

CONTRA-INDICATIONS:

Hypersensitivity to paracetamol, opiates or any of the other ingredients in **TENSOPYN PAEDIATRIC SYRUP.**

During an attack of bronchial asthma, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, heart failure secondary to chronic lung disease, liver or kidney damage, head injuries and where intracranial pressure is raised.

Premature infants or neonates.

TENSOPYN PAEDIATRIC SYRUP is contra-indicated in patients receiving monoamine oxidase inhibitors or within 10 days of stopping such treatment.

WARNINGS:

Contains codeine. Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction. This product 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.

If the patient does not respond, a doctor should be consulted.

Do not take continuously for more than 10 days without consulting a doctor.

Patients should be examined periodically for abnormal skin pigmentation or eye changes.

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

Overdosage is very dangerous in young children.

INTERACTIONS:

Refer to section "**CONTRA-INDICATIONS**" and "**SIDE EFFECTS AND SPECIAL PRECAUTIONS**".

Paracetamol: The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by medicines such as metoclopramide. Excretion may be affected and plasma concentrations altered when administered with probenecid. Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration. Paracetamol must be given with caution if concomitantly used with antibacterials, anticoagulants, antiepileptics, antivirals and probenecid.

Codeine Phosphate:

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives and phenothiazines.

PREGNANCY AND LACTATION:

TENSOPYN PAEDIATRIC SYRUP is not recommended for use in pregnancy and lactation.

Paracetamol crosses the placenta and is presented in breast milk.

DOSAGE AND DIRECTIONS FOR USE:

DO NOT EXCEED THE RECOMMENDED DOSE.

Infants: 6 months to 1 year:	2,5 ml (half a medicine measure) every four hours.
Children I - 5 years:	5,0 ml (one medicine measure) every four hours.
Children 6 - 12 years:	5 to 10 ml (one to two medicine measures) every four hours.

Should not be administered more than four times daily.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The following side-effects may occur with **TENSOPYN PAEDIATRIC SYRUP:**

Skin and appendages disorders:

Less frequent: Yellow eyes or skin, pinpoint red spots on skin, allergic reactions, hives or itching, sores, ulcers, or white spots on lips or in the mouth, skin eruptions, skin rash. This rash is usually erythromatous or urticarial, but sometimes more serious and may be accompanied by drug fever and mucosal lesions. Redness or flushing of face.

Musculoskeletal system disorders:

Less frequent: Trembling or uncontrolled muscle movements or muscle rigidity.

Central and peripheral nervous system disorders

Frequent: Dizziness, drowsiness, confusion, dry mouth, sweating, facial flushing, faintness, sedation, vertigo.

Vision disorders:

Less frequent: Miosis,

Hearing and vestibular disorders:

Less frequent: Ringing or buzzing in the ears.

Psychiatric disorders:

Less frequent: Feelings of unreality, hallucinations, mental depression or other mood or mental changes, restlessness, deepening coma, euphoria.

Gastro-intestinal disorders:

Frequent: Nausea, vomiting, constipation.

Less frequent: Bloody or black, tarry stools, sore throat, biliary spasms.

Endocrine disorders:

Frequency not known: Pancreatitis.

Heart rate and rhythm disorders:

Less frequent: Fast, slow, or pounding heartbeat, bradycardia, palpitations.

Vascular (extracardiac) disorders:

Less frequent: Swelling of face, hypotension, orthostatic hypotension, circulatory failure, hyperthermia.

Respiratory system disorders:

Less frequent: Increased sweating, irregular breathing, shortness of breath, wheezing or troubled breathing, respiratory depression.

Platelet, bleeding and clotting disorders:

Less frequent: Unusual bleeding or bruising.

Frequency not known: Haematological reactions, thrombocytopenia, neutropenia, pancytopenia, leucopenia and agranulocytosis.

Urinary system disorders:

Less frequent: Bloody or cloudy urine, sudden decrease in amount of urine, difficult micturition, ureteric spasms, antidiuretic effect.

Body as a whole – general disorders:

Less frequent: Unusual tiredness or weakness, raised intracranial pressure.

Special precautions:

Patients suffering from kidney or liver disease should take **TENSOPYN PAEDIATRIC SYRUP** under medical supervision.

TENSOPYN PAEDIATRIC SYRUP should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, myasthenia gravis, prostatic hypertrophy or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders, prostatic hypertrophy, elderly patients and after operations on the biliary tract. The dosage should be reduced in elderly and debilitated patients.

TENSOPYN PAEDIATRIC SYRUP should be taken with caution by patients with impaired liver function. Due to the histamine-releasing effect allergic reactions such as urticaria, pruritus and itching of the nose occur in some individuals and idiosyncrasy to codeine and other narcotic analgesics are fairly common.

Breathing problems may be especially likely to occur in children younger than 2 years of age.

Unusual excitement or restlessness may be more likely to occur in children receiving **TENSOPYN PAEDIATRIC SYRUP.**

The depressant effects of codeine are enhanced by depressants of the central nervous system such as anaesthetics, hypnotics and sedatives, and phenothiazines.

The prolonged use of high doses of codeine has produced dependence.

Consult a doctor if no relief is obtained with the recommended dosage.

Do not use continuously for longer than ten days without consulting a doctor.

Store in a safe place, out of reach of children.

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 to a hospital directly. 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.

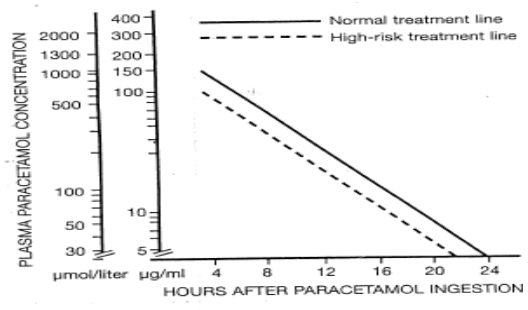
Treatment for paracetamol overdosage:

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 be treated symptomatically. 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. 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 1000 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, unless high, may be misleading. Patients at risk of liver damage and hence requiring continued treatment with N- acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the normogram below.



Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed.

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.

Codeine:

Larger doses of codeine produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur in infants and children. Death may occur from respiratory failure.

Get emergency help immediately if any of the following symptoms occur:

Cold, clammy skin, confusion, convulsions, severe dizziness, low blood pressure, severe nervousness or restlessness, pinpoint pupils of eyes, slow heartbeat, slow or troubled breathing, severe weakness.

Intensive supportive therapy may be necessary to correct respiratory failure and shock. The specific antagonist naloxone may be used to counteract severe respiratory depression.

IDENTIFICATION

A clear, colourless to pale yellow/brown syrup, with an odour and taste of fresh cherries.

PRESENTATION:

Amber glass bottle of 100 ml, fitted with a white plastic cap with a tamper-evident break ring, packed into an outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC. Protect from light. Keep the bottle well closed until ready for use. Store the bottle in the original container until ready for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

W/2.8/0023

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Cipla Medpro (Pty) Ltd

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