SCHEDULING STATUS: S2

PROPRIETARY NAME AND DOSAGE FORM:

STOPAYNE SYRUP BLACKCURRANT

COMPOSITION:

Each 5 ml contains:

Codeine phosphate	5 mg
Promethazine hydrochloride	6, 5 mg
Paracetamol	120 mg
Preservative: Methyl hydroxybenzoate	0, 12% m/v
Contains sugar: Liquid glucose	1 g

Antioxidant: Sodium metabisulphite

List of excipients: blackcurrant flavour, citric acid anhydrous, colour blackcurrant, colour raspberry red, disodium edetate, glycerol, polyvinylpyrrolidone, propylene glycol, saccharin sodium, sorbitol 70 % solution (Non-crystalising), xanthan gum.

PHARMACOLOGICAL CLASSIFICATION:

A 2.8 Analgesic combinations

PHARMACOLOGICAL ACTION:

Paracetamol has analgesic and antipyretic effects.

Codeine is metabolized to morphine, which in turn, exerts an analgesic effect.

Promethazine has antihistaminic and anticholinergic properties.

Pharmacokinetics:

Codeine:

Readily absorbed from the gastrointestinal tract. Half-life is 2, 5 to 4 hours. Codeine is metabolised in the liver. The cytochrome P450 enzyme 2D6 converts codeine to morphine, one of its metabolites. About 10 % of the dose is demethylated to morphine. Onset of action is 30 to 45 minutes. The time to peak effect is 1 to 2 hours. Duration of action is 4 hours. Codeine is eliminated via the kidneys.

Promethazine HCl:

Well absorbed after oral administration. Half-life is 7 to 14 hours. Onset of action is 15 to 60 minutes, duration of action is 4 to 6 hours; may persist for up to 12 hours. Promethazine is excreted as metabolites within 24 hours and is eliminated via the kidneys. Protein binding is high (65 to 90 %).

Paracetamol:

Absorption following oral administration is rapid and almost complete. Paracetamol is metabolised in the liver primarily by conjugation. Paracetamol has half-life of 1 to 4 hours, time to peak concentration of 0, 5 to 2 hours. Paracetamol is renally excreted primarily as metabolites and 3 % of a dose may be excreted unchanged.

INDICATIONS:

STOPAYNE SYRUP BLACKCURRANT is indicated for the relief of mild to moderate pain associated with fever in children 2 years and older.

CONTRAINDICATIONS:

Hypersensitivity to any of the ingredients.

Contraindicated in patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment.

STOPAYNE SYRUP BLACKCURRANT should not be given to children under 2 years of age.

Safety in pregnancy and lactation has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Dosages in excess of those recommended may cause severe liver damage. This medication may lead to

drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.

This medicine contains paracetamol.

In the event of overdosage or suspected overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison control centre must be contacted immediately.

Patients suffering from liver or kidney disease should take paracetamol under medical supervision.

Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function, prostatic hypertrophy or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders. Exceeding the prescribed dose, together with the prolonged and continuous use of this medication may lead to dependence of the morphine type and addiction.

Promethazine hydrochloride may mask the warning symptoms of damage caused by ototoxic drugs and may affect the metabolism of drugs in the liver. Promethazine must be used with caution in conditions such as narrow angle glaucoma and urinary retention. Large doses may precipitate fits in epileptics. Serious life-threatening cases of respiratory depression, including fatalities have been reported with promethazine use in paediatric patients less than 2 years of age.

Contains Liquid glucose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary condition of sorbitol intolerance should not take **STOPAYNE SYRUP BLACKCURRANT**.

INTERACTIONS:

The anticholinergic effects of agents with anticholinergic properties may be enhanced.

The depressant effects are aggravated by alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

Monoamine oxidase inhibitors may enhance the anticholinergic effects.

The warning signs of damage caused by ototoxic agents may be masked.

May affect the activity of the other medicines by delaying their absorption.

Antidiarrhoeals may increase risk of severe constipation and central nervous system depression. Hypotension-producing medication effects may be potentiated.

Hepatotoxic medicines may increase the risk of hepatotoxicity.

Enzyme inducing medicines may increase the risk of hepatoxicity and possible decrease in therapeutic effects of paracetamol.

Metoclopramide may accelerate the absorption of paracetamol.

Probenecid may affect the excretion of paracetamol and alter the plasma concentrations.

Cholestyramine reduces the absorption of paracetamol if given within 1 hour.

Anticoagulants, the effects may be enhanced and possible gastrointestinal ulceration or bleeding may occur.

Corticosteroids, clopidogrel, ticlopidine, bisphosphonates, oxpentifylline may increase the risk of gastrointestinal bleeding and ulceration.

The hypoglycaemic effect of antidiabetic agents may be increased.

Digoxin serum concentrations may be increased.

Lithium concentration may be increased in a steady state.

Methotrexate plasma concentration may be increased and prolonged and there may be an increased risk of methotrexate toxicity.

Increased risk of nephrotoxicity may occur with nephrotoxic medicines e.g. ciclosporin.

Reduction or reversal of the antihypertensive effect may occur with antihypertensives or diuretics.

The leucopenic and/or thrombocytopenic effects may be increased with bone marrow depressants.

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation have not been established. (See '**CONTRAINDICATIONS**').

DOSAGE AND DIRECTIONS FOR USE:

Three times a day or as prescribed:

2 to 5 years: 5 ml (One medicine measure)

Over 5 years: 5 to10 ml (One to two medicine measures)

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

SIDE EFFECTS:

Codeine

Immune system disorders:

Less frequent: urticaria.

Psychiatric disorders:

Less frequent: restlessness and confusion.

Frequency unknown: change of mood.

Nervous system disorders:

More frequent: drowsiness.

Less frequent: miosis.

Frequency unknown: muscle rigidity and convulsions.

Frequency unknown: raised intracranial pressure and deepening coma.

Ear and labyrinth disorders:

Frequency unknown: vertigo.

Cardiac disorders:

Less frequent: bradycardia and palpitations.

Vascular disorders:

Less frequent: orthostatic hypotension.

Frequency unknown: circulatory failure.

Respiratory, thoracic and mediastinal disorders:

Less frequent: respiratory depression.

Gastrointestinal disorders:

More frequent: constipation.

Less frequent: nausea, vomiting and dry mouth.

Skin and subcutaneous tissue disorders:

Less frequent: pruritus, sweating and facial flushing.

Renal and urinary disorders:

Less frequent: micturition may be difficult.

General disorders and administration site conditions:

Frequency unknown: hypothermia.

Promethazine

Blood and lymphatic system disorders:

Frequency unknown: jaundice, thrombocytopenia, purpura, leucopenia and agranulocytosis.

Immune system disorders:

Frequency unknown: allergic reaction and angioedema.

Metabolism and nutrition disorders:

Less frequent: anorexia.

Frequency unknown: increased appetite.

Psychiatric disorders:

Less frequent: excitation in children, irritability and nightmares.

Nervous system disorders:

More frequent: sedation.

Less frequent: blurred vision.

Frequency unknown: muscular weakness, headache, tinnitus, extrapyramidal reaction and inco-ordination.

Vascular disorders:

Less frequent: hypotension.

Gastrointestinal disorders:

Frequency unknown: nausea, vomiting, epigastric pain and diarrhoea or constipation.

Skin and subcutaneous tissue disorders:

Less frequent: photosensitivity.

Renal and urinary disorders:

Less frequent: difficulty in micturition.

Paracetamol

Blood and lymphatic system disorders:

Frequency unknown: blood disorders.

Skin and subcutaneous tissue disorders:

Frequency unknown: skin rash.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible.

Codeine:

This produces central stimulation with exhilaration and convulsions, followed by vomiting, drowsiness, respiratory depression and cyanosis, and coma. Treatment is supportive and symptomatic.

Paracetamol:

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 adults who have taken repeated high doses (greater than 5 to 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 of paracetamol overdose: 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 of paracetamol, initially be elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations 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. Cerebral oedema and non-specific myocardial depression have occurred.

Treatment of overdose:

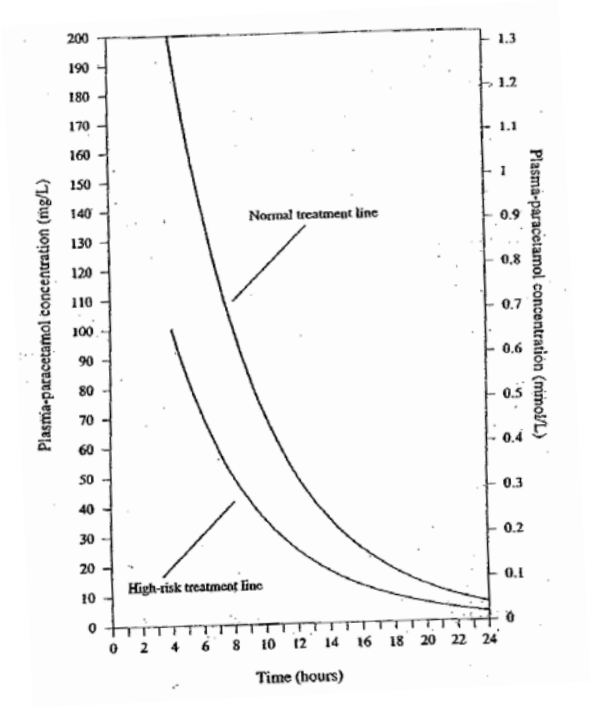
Although evidence is limited it is recommended that an adult who has ingested 5 to 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. 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, endotrachael 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 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 as a 5 % solution may be administered initially, followed by 70 mg/kg every four hours for seventeen doses. If activated charcoal is used then it should be removed by gastric lavage as it may interfere with absorption of orally administered acetylcysteine and decrease its efficacy.

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 treatment nomogram.

Figure 1. A linear plot of plasma-paracetamol concentration against hours after ingestion.



Patients 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.

IDENTIFICATION:

Mauve syrup, with a blackcurrant flavour.

PRESENTATION:

Amber glass bottles of 100 ml.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

B/2.8/867

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