1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

STILPANE SYRUP 6,5 mg/ 5 mg/ 120 mg per 5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of STILPANE SYRUP contains 6,5 mg promethazine hydrochloride, 5 mg codeine phosphate and 120 mg of paracetamol.

Preservatives:

Methyl hydroxybenzoate 0,09 % *m/v*

Propyl hydroxybenzoate 0,01 % *m/v*

Contains sugar: Sorbitol 1,01 g

Contains sweeteners: Sodium cyclamate 50,46 mg, sodium saccharin 5,22 mg, acesulfame potassium 2,32 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

STILPANE SYRUP is a clear, dark reddish-purple syrupy liquid with a blackcurrant odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

STILPANE SYRUP is indicated for the symptomatic treatment of mild to moderate pain and fever.

4.2. Posology and method of administration

Special populations

Elderly

The dosage should be reduced in elderly and debilitated patients.

Paediatric Population

Age 2 to 5 years: Take one medicine measure (5 ml) three times daily.

Age 6 to 12 years: Take one to two medicine measures (5 ml to 10 ml) three times daily.

DO NOT EXCEED THE RECOMMENDED DOSE.

STILPANE SYRUP is contraindicated in children under the age of two years (see section 4.3).

If symptoms persist consult your doctor.

Method of administration

For oral administration.

4.3. Contraindications

STILPANE SYRUP is contraindicated in:

- Patients with hypersensitivity to promethazine hydrochloride, codeine phosphate, paracetamol, or to any excipients in STILPANE SYRUP (see section 6.1).
- Patients who are sensitive to other opioid analgesics.
- Patients who are sensitive to one antihistamine may be sensitive to others.
- Patients with severe liver or kidney complications.

- Patients with obstructive airway disease, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, and after operations on the biliary tract.
- Acute alcoholism.
- Convulsive disorders.
- Head injuries and conditions in which intracranial pressure is raised.
- Children under the age of two years.
- Pregnancy and lactation.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- Codeine, as contained in STILPANE SYRUP, is also contraindicated in conditions where inhibition of peristalsis is to be avoided, where there is a risk of paralytic ileus, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis) or diarrhoea caused by poisoning.
- In all paediatric patients (0 to 18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

STILPANE SYRUP should not be given during an attack of bronchial asthma or in heart disease secondary to chronic lung disease.

Promethazine hydrochloride and codeine phosphate, as contained in STILPANE SYRUP, should not be given to comatose patients.

The use of promethazine hydrochloride, as contained in STILPANE SYRUP, may be associated with sudden infant death syndrome.

4.4. Special warnings and precautions for use

Consult a doctor if no relief is obtained from the recommended dosage or if pain or fever persists or gets worse, if new symptoms occur or if redness and swelling is present, as these could be signs of a

serious condition.

Do not take STILPANE SYRUP continuously without consulting a doctor:

- For pain:

  - for more than 10 days (adults).

  - for more than 5 days (children).

- For fever:

  - for more than 3 days.

Pigments should be examined periodically for abnormal skin pigmentation (discolourisation) or eye changes.

Promethazine hydrochloride

STILPANE SYRUP may lead to drowsiness and impaired concentration, that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against performing potentially hazardous activities/duties where loss of concentration may lead to accidents.

Caution should be used when the following medical conditions exist: prostatic hypertrophy, urinary retention, narrow angle glaucoma, emphysema or chronic bronchitis and porphyria.

Paradoxical hyperexcitability, nervousness and insomnia may occur in children and the elderly taking antihistamines. Elderly patients are especially susceptible to dizziness, sedation, confusion, hypotension and to anticholinergic effects such as dry mouth and urinary retention.

Promethazine hydrochloride should not be used in patients with pre-existing central nervous system depression, bone marrow depression, phaeochromocytoma or Reye's syndrome.

Use with care in patients with jaundice, Parkinsonism, diabetes mellitus, hypothyroidism and

myasthenia gravis.

Risk of severe constipation if used with antidiarrhoeal medicines such as diphenoxylate. Increased risk of constipation and urinary retention if used with other anticholinergic medicines. Use with caution in patients with obstructive bowel disorders, liver impairment (see section 4.3), and impaired renal function (see section 4.3).

Promethazine hydrochloride should be used cautiously in patients with cardiovascular or hepatic diseases (see section 4.3), closed angle glaucoma or asthma (see section 4.3).
The positive results of a skin allergy test may be suppressed.

Paracetamol

STILPANE SYRUP contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison centre must be contacted immediately.

Contains paracetamol. Do not use with any other paracetamol-containing products.
Dosages in excess of those recommended, may cause severe liver function damage.

Patients suffering from hepatitis or alcoholism or recovering from any form of liver disease (see section 4.3), should not take paracetamol.

Use with caution in renal disease (see section 4.3).

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-

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 SCAR, treatment with STILPANE SYRUP must immediately be discontinued and appropriate treatment instituted.

Metabolic acidosis

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

Use with caution in patients with glutathione depletion due to metabolic deficiencies.

High Anion gap metabolic acidosis (HAGMA)

Caution is advised if STILPANE SYRUP 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 STILPANE SYRUP. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Codeine phosphate

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

Potentiates the effect of alcohol and other sedatives. Should be used with caution in patients with personal or family history of substance abuse or mental health disorders (see section 4.3).

There is a risk of severe constipation if used with antidiarrhoeal medicines such as diphenoxylate.

There is also an increased risk of constipation and urinary retention if used with other anticholinergic medicines.

Codeine phosphate, as contained in STILPANE SYRUP, should be given with caution or in reduced doses to patients with hypotension, hypothyroidism, compromised respiratory function, adrenocortical insufficiency, impaired kidney or liver function (see section 4.3), prostatic hypertrophy, urethral stricture, shock or head injury. It should be used with caution in patients with inflammatory or obstructive bowel syndrome (see section 4.3). It should be given with caution to patients with myasthenia gravis. The administration during labour may cause respiratory depression in the new-born infant.
Dosage should be reduced in debilitated (tired/weakened/run down) patients.

Acute asthma
Not recommended for use in patients with acute asthma. Use with caution or in reduced doses in asthma and decreased respiratory reserve; avoid use during an acute asthma attack (see section 4.3).

CYP2D6 metabolism
Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7 % of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of

circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see section 4.3). All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised (see section 4.3) including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Excipients

STILPANE SYRUP contains sorbitol:

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 medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Patients with the rare hereditary condition of sorbitol intolerance and/or hereditary fructose intolerance (HFI) should not take or be given. STILPANE SYRUP.

STILPANE SYRUP contains propylene glycol:

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates and in children less than 5 years old.
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.

4.5. Interaction with other medicines and other forms of interaction

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation (see section 4.3).

Alcohol and anaesthetics: the hypotensive effects may be enhanced if taken with codeine.

All sedatives, including alcohol, will potentiate depressant effects on the central nervous system if taken with antihistamines.

Promethazine hydrochloride may potentiate the hypotensive effect of some antihypertensives.

The antiparkinsonian effects of levodopa may be inhibited.

Medications tending to cause extrapyramidal reactions and those with anticholinergic effects may be potentiated. These include tricyclic antidepressants, maprotiline and monoamine oxidase inhibitors (MOAIs).

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

Codeine may affect the activity of other medicines by delaying their absorption.

Domperidone and metoclopramide: codeine antagonises the effect of cisapride, metoclopramide and domperidone on gastrointestinal activity.

The speed of absorption of paracetamol, as contained in STILPANE SYRUP, may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

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.

Pre-treatment with probenecid can decrease paracetamol, as in STILPANE SYRUP, 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.

Anti-arrhythmics: codeine delays the absorption of mexiletine. The analgesic activity of codeine is likely to be significantly impaired by quinidine which impairs codeine metabolism.

The warning signs of damage caused by ototoxic agents (agents having toxic effects on the nerve of the ear) may be masked.

Hepatotoxic and enzyme-inducing medicines: Increased risk of hepatotoxicity.

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.

Severe hepatotoxicity has occurred after use of paracetamol, as in STILPANE SYRUP, 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, as in STILPANE SYRUP.

Paracetamol, as in STILPANE SYRUP, has also been found to enhance the antiviral effect of interferon alfa.

Caution should be taken when STILPANE SYRUP 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).

Prolonged concurrent use of STILPANE SYRUP with salicylates increases the risk of adverse renal effects.

Sodium oxybate: concomitant administration of codeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Ulcer-healing medicine: Cimetidine may inhibit the metabolism of codeine resulting in increased plasma concentrations.

Interference with laboratory tests:
Opioids may interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

Antihistamines may suppress positive skin test results and should be stopped several days before the test.

False negative and positive results have been reported with some pregnancy tests.

4.6. Fertility, pregnancy and lactation

STILPANE SYRUP is contraindicated in pregnancy and lactation (see section 4.3).

4.7. Effects on ability to drive and use machines

Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

Paracetamol:

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Blood and lymphatic disorders		Neutropenia, pancytopenia, leukopenia, thrombocytopenia, agranulocytosis, anaemia	
Immune system disorders		Anaphylaxis, cutaneous hypersensitivity reactions including, among others, angioedema. Very rare cases of serious skin reactions have been reported	Sensitivity reactions, resulting in skin rashes or blood disorders
Psychiatric disorders	Confusion, hallucinations, central effect includes euphoria		
Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Nervous system disorders	Sedation (varying from slight drowsiness to deep sleep), dizziness, incoordination		
Ear and labyrinth disorders		Tinnitus	Hearing loss
Cardiac disorders			Possible increase in the risk of hypertension
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Bronchospasm (There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs)	

Gastrointestinal disorders	Gastro-intestinal disturbances such as, nausea, vomiting, diarrhoea, constipation, anorexia or increased appetite, epigastric pain, pancreatitis may occur		
Hepatobiliary disorders		Hepatic dysfunction, this medicine can cause liver damage which may be fatal, if taken in excess	Hepatitis
Skin and subcutaneous tissue disorders	Skin rashes and other allergic reactions may occur		Dermatitis, 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), fixed drug eruption (FDE)
Musculoskeletal, connective tissue and bone disorders			Muscular weakness
Renal and urinary disorders		Kidney damage (prolonged excessive use), renal colic, renal failure, sterile pyuria	Nephropathy
General disorders and administrative site conditions	Lassitude		
Investigations			Increased transaminases. Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol, as contained in STILPANE SYRUP. These elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol

Promethazine hydrochloride:

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Blood and lymphatic disorders			Agranulocytosis, leukopenia, haemolytic anaemia, thrombocytopenic purpura, eosinophilia
Immune system disorders			Idiosyncrasy, angioedema, lupus erythematous-like syndrome, allergic reactions, including anaphylactic reaction, urticaria, angioedema.
Metabolism and nutrition disorders		Anorexia or increased appetite	Decreased appetite
Psychiatric disorders		Irritability and restlessness	Depression, hallucinations, insomnia, agitation, confusional state, anxiety
Nervous system disorders	Sedation, lassitude, dizziness, hypertension, muscular weakness and in-coordination, somnolence, headache	Elation or depression, irritability, hallucination, dryness of the mouth, tightness of the chest and tingling, weakness of the hands may occur, in infants and children it may act as a cerebral stimulant, tachycardia	Epileptiform seizures (in patients with focal lesions of the cerebral cortex), extrapyramidal symptoms with muscle spasms and dystonia
Eye disorders			Blurred vision, deposition of pigment in the eyes, corneal and lens opacities
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Increase in heart rate	Bradycardia followed by tachycardia with palpitations and dysrhythmias (in high doses), hypotension
Vascular disorders			May also produce antimuscarinic effects including flushing
Respiratory, thoracic and mediastinal disorders			Antimuscarinic effects including thickened respiratory tract secretions, dryness of the nose, tightness of the chest
Gastrointestinal disorders		Nausea, vomiting, diarrhoea, colic, epigastric pain	Antimuscarinic effects including dryness of the mouth, reduction in tone and motility of the gastrointestinal tract resulting in constipation and increased gastric reflux
Hepatobiliary disorders			Jaundice of the obstructive type
Skin and subcutaneous tissue disorders		Photosensitivity, skin rashes, cases of allergic reactions, including urticaria, rash, pruritus and anaphylaxis have been reported	Allergic dermatitis, thrombocytopenic purpura

Musculoskeletal and connective tissue disorders			Weakness of hands, restless legs syndrome
Renal and urinary disorders		Difficulty in micturition, dysuria	Polyuria, urinary retention
General disorders and administrative site conditions			Medicine fever, lowering of blood temperature (occasionally pyrexia), tiredness

Codeine phosphate:

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Immune system disorders			Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate, fever
Endocrine disorders			Hyperglycaemia
Metabolism and nutrition disorders			Anorexia
Psychiatric disorders	Confusion		Restlessness, changes of mood, abuse, mental depression, hallucinations and nightmares, mood changes, euphoria and dysphoria
Nervous system disorders	Drowsiness	Hypothermia, deepening coma, euphoria, muscle rigidity, dry mouth, sweating, facial flushing, restlessness, changes of mood	Raised intracranial pressure, convulsions (especially in infants and children), dizziness, headache, raised intracranial pressure may occur in some patients
Eye disorders		Miosis	Blurred or double vision or other changes in vision.
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Hypotension, Orthostatic hypotension, circulatory failure	Bradycardia, palpitations, tachycardia
Vascular disorders			Facial flushing, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders			Dyspnoea. Large doses produce respiratory depression
Gastrointestinal disorders	Nausea, vomiting, constipation	Acute pancreatitis, increase risk of abdominal pain	Dry mouth, stomach cramps
Hepatobiliary disorders			Biliary spasm, antidiuretic effect
Skin and subcutaneous tissue disorders		Urticaria, pruritus	Contact dermatitis, allergic reactions such as skin rashes, sweating and facial oedema
Musculoskeletal, connective tissue and bone disorders			Muscle rigidity (high doses), uncontrolled muscle movements
Renal and urinary disorders			Difficulty in micturition, ureteric spasm, antidiuretic effect, urinary retention, dysuria
Reproductive system and breast disorders			Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido
General disorders and administrative site conditions	Sweating		Hypothermia, malaise, tiredness, drug withdrawal syndrome

b) Description of selected adverse reactions

Paracetamol

Sensitivity reactions resulting in reversible skin rashes or blood disorders may occur. The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions. Other allergic reactions may occur.

Paradoxical central nervous system stimulation may occur especially in children, with insomnia, nervousness, tachycardia, tremors, ataxia, irritability and convulsions.

Post marketing data for paracetamol, as contained in STILPANE SYRUP, has reported Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-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) as an undesirable effect with unknown frequency (see section 4.4).

Codeine

The euphoric activity of codeine and similar compounds has led to its abuse.

There may be biliary spasm, micturition may be difficult, ureteric spasm and also an antidiuretic effect.

These effects occur more commonly in ambulant patients than in those at rest in bed.

Post marketing data for codeine, as contained in STILPANE SYRUP, has reported increased risk of abdominal pain, including pancreatitis as an undesirable effect with unknown frequency.

Promethazine hydrochloride

Infants, newborns and prematures are susceptible to the anticholinergic effects, while other children may display paradoxical hyperexcitability, disorientation.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reactions Reporting form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

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 patients who have taken repeated high doses (greater than 5 g/day 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

In the first 24 hours symptoms 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 hours to 48 hours, or later after ingestion of paracetamol, initially by 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 dysrhythmias have been reported.

Treatment

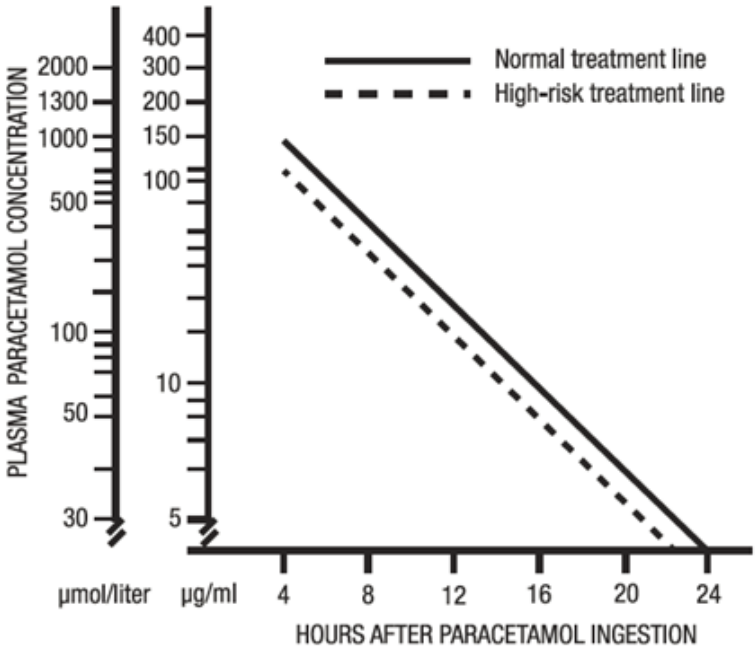
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible

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.

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 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.

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

Overdosage with promethazine hydrochloride causes a central excitatory effect which constitutes its greatest danger. Symptoms include drowsiness or paradoxical excitement, hallucinations, ataxia, incoordination, athetosis and convulsions.

Fixed dilated pupils with a flushed face, sinus tachycardia, dyspnoea, urinary retention, dry mouth and fever can occur. Other symptoms include a terminally, deepening coma with cardiorespiratory

collapse. Children and the elderly are more likely to exhibit anticholinergic and central nervous system stimulant effects. The elderly is prone to hypotension.

The stomach should be emptied by emesis or lavage. There is no specific antidote and treatment is symptomatic and supportive. It may be necessary to treat extrapyramidal reactions with barbiturates or diphenhydramine.

Respiratory depression is the most important feature of **overdosage with codeine** containing preparations and it occurs with circulatory failure and a deepening coma. Pinpoint pupils, hypotension and hypothermia, excitement and convulsions, especially in children, and non-cardiogenic pulmonary oedema occur. Immediate attention should be given to maintaining adequate respiration. Nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely. Dry mouth, sweating, confusion, severe dizziness, severe drowsiness and facial flushing are other symptoms of overdose. Nervousness or restlessness, hallucinations, bradycardia, slow or troubled breathing, severe weakness, convulsions, especially in infants and children. Rhabdomyolysis, progressing to renal failure, has been reported in over dosage with opioids.

Death may occur from respiratory failure.

Management: This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion or eight hours if sustained release preparation has been taken.

Naloxone may be given according to the following dose regimens:

Intravenous Injection:

0,8 to 2 mg repeated at intervals of 2 to 3 minutes to a maximum of 10 mg.

Child: 10 µg/kg and, if no response, subsequent doses of 100 µg/kg.

Subcutaneous or Intramuscular Injection:

As for intravenous injection but only if the i.v. route is not feasible. The onset of action is slower with s.c. or i.m. injection.

Continuous intravenous infusion:

2 mg diluted in 500 ml of intravenous infusion solution at a rate adjusted according to the patient's response.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 2.8 Analgesic combinations.

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics.

ATC code: N02AJ

Mechanism of action

STILPANE SYRUP has analgesic, antipyretic and antihistaminic properties.

5.2. Pharmacokinetic properties

Absorption

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 1 to 4 hours after therapeutic doses.

Codeine phosphate

Codeine is well absorbed from the gastrointestinal tract following oral administration.

Promethazine hydrochloride

Promethazine is well absorbed after oral administration.

Distribution

Paracetamol

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the medicine to plasma proteins is variable; 20 to 30 % may be bound at the concentrations encountered during acute intoxication.

Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

Promethazine hydrochloride

Values from 76 to 93 % have been reported for plasma protein binding.

Biotransformation

Paracetamol

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

Codeine phosphate

It is metabolised in the liver to morphine and norcodeine.

Promethazine hydrochloride

Peak plasma concentrations have been observed 2 to 3 hours after administration by this route although there is lower systemic bioavailability after oral administration due to high first pass metabolism in the liver.

Elimination

Paracetamol

Following therapeutic doses 90 to 100 % of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

Codeine phosphate

Excreted in the urine partly as conjugates with glucuronic acid. Most of the excretion products appear in the urine within 6 hours and up to 86 % of the dose is excreted in 24 hours. About 70 % of the dose is excreted as free codeine, 10 % as free and conjugated morphine and a further 10 % as free or conjugated norcodeine. Only traces are found in the faeces. The plasma half life is between approximately 3 and 4 hours.

Promethazine hydrochloride

Elimination half-lives of 5 to 14 hours have been reported. Promethazine crosses the blood-brain barrier and the placenta, and is distributed in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acesulfame potassium, colour blackcurrant (C.I. 1458), dye Lennon blackcurrant (C.I. 42090 & 14720), flavour blackcurrant, glycerol, hydroxyethylcellulose, methyl hydroxybenzoate, polyvinylpyrrolidone (Povidone), propylene glycol, propyl hydroxybenzoate, purified water, sorbitol (70 %) solution, sodium cyclamate, sodium saccharin.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C, in a well closed container.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

100 ml is packed into a natural high density polyethylene container and sealed with a round, flat topped white, high density polyethylene screw on child-lock cap with an expanded polyethylene liner and a translucent polyethylene tamper evident band. The bottle is placed in an outer cardboard carton.

100 ml is packed into a brown high density polyethylene bottle sealed with a round, flat topped white, high density polyethylene screw on child-lock cap with an expanded polyethylene liner and a translucent polyethylene tamper evident band. The bottle is placed in an outer cardboard carton.

500 ml is packed into a natural rectangular high density polyethylene bottle and sealed with a white low density polyethylene snap cap.

2,5 L is packed into a green, high-density polyethylene, tamper evident container and sealed with a high density polyethylene rachet cap.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

G0968 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Old Medicine

10. DATE OF REVISION OF TEXT

01 July 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Namibia: NS2 15/2.8/123
Botswana: B9322900 S3

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