1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

STILPANE CAPSULES 150 mg/8 mg/320 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of STILPANE CAPSULES contains 150 mg meprobamate, 8 mg codeine phosphate and 320 mg paracetamol.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

STILPANE CAPSULES is a white powder encapsulated with a no. 0 elongated capsule, with an opaque green cap and body printed with a Lennon logo and “Lennon” and “Stilpane”

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

STILPANE CAPSULES are indicated for short term use (no longer than 10 days) in mild to moderate pain and fever, and pain associated with anxiety or tension.

4.2. Posology and method of administration

Adults and children over 12 years

Take two capsules three or four times a day as required.

DO NOT EXCEED THE RECOMMENDED DOSE.

For short term use only. Do not use STILPANE CAPSULES continuously for longer than 10 days without consulting your doctor.

Paediatric population

Not recommended for children under 12 years of age (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

STILPANE CAPSULES is contraindicated in:

- Patients with hypersensitivity to meprobamate, codeine phosphate, paracetamol or any of the excipients of STILPANE CAPSULES (see section 6.1).
- Patients with hypersensitivity to other opioid analgesics.
- Patients with severe liver or kidney complications.
- Patients with pulmonary insufficiency.
- Patients with acute intermittent porphyria or porphyria variegate.
- Patients with a history of epilepsy as STILPANE CAPSULES may induce convulsions.
- Patients with obstructive airways disease, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- After operations on the biliary tract.
- Acute alcoholism.

- Convulsions, head injuries and conditions in which intracranial pressure is raised.
- Comatose patients.
- During an attack of bronchial asthma or in heart failure secondary to lung disease.
- Patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.
- Children under 12 years of age (see section 4.2).
- Codeine phosphate, as contained in STILPANE CAPSULES, 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.
- All paediatric patients 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).

4.4. Special warnings and precautions for use

STILPANE CAPSULES 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.

Codeine phosphate:

Exceeding the prescribed dose together with continuous use of STILPANE CAPSULES may lead to dependency and addiction (see section 4.2).

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

The lowest effective dose should be used, and the duration of treatment should be as short as possible.

Meprobamate

STILPANE CAPSULES should not be used for more than 10 days (see section 4.2).

Elderly, debilitated and patients with mental depression

STILPANE CAPSULES should be avoided in elderly and debilitated patients and in those with mental depression.

History of epilepsy

STILPANE CAPSULES may induce convulsions in patients with a history of epilepsy (see section 4.3).

Impaired hepatic, renal or respiratory function

STILPANE CAPSULES should be used with caution in patients with impaired hepatic or renal function. STILPANE CAPSULES should not be used in patients with impaired respiratory function (see section 4.3).

Concomitant use with alcohol and CNS depressants

Patients receiving STILPANE CAPSULES should be warned that their tolerance to ingested

alcohol and other depressants of the central nervous system may be lowered with consequent impairment of judgment and co-ordination.

Dependence and withdrawal

There is a high risk of dependency with a typical withdrawal syndrome. STILPANE CAPSULES should not be used for the stress of daily living.

Porphyria

Symptoms of porphyria may be exacerbated (see section 4.3).

Paracetamol

Liver and kidney disease

Paracetamol, as contained in STILPANE CAPSULES, dosages in excess of those recommended may cause severe liver damage. Prolonged excessive use can cause irreversible kidney damage (see section 4.3).

Patients suffering from liver or kidney disease should take STILPANE CAPSULES under medical supervision (see section 4.3).

Myasthenia gravis

Use with caution in patients with myasthenia gravis.

Glutathione depleted states

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol, as contained in STILPANE CAPSULES, may increase the risk of metabolic acidosis. Use with caution in patients with glutathione depletion due to metabolic deficiencies.

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), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines, as contained in STILPANE. If a patient develops SCAR, treatment with STILPANE must immediately be discontinued and appropriate treatment instituted.

Flucloxacillin

Caution is advised if paracetamol, as contained in STILPANE CAPSULES, 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.

Codeine phosphate

CYP2D6 metabolism

Depending on the genetic variability of CYP2D6, the individual metabolising capacity for codeine phosphate, as contained in STILPANE CAPSULES, may vary. Even therapeutic doses can lead to increased formation of the active compound morphine resulting in clinical signs of morphine intoxication (see sections 4.8 and 4.9).

STILPANE CAPSULES should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function, prostatic hypertrophy, hypotension or shock.

STILPANE CAPSULES should be used with caution in patients with inflammatory or obstructive bowel disorders.

Labour

STILPANE CAPSULES administration during labour may cause respiratory depression in the newborn infant (see section 4.6).

Concomitant alcohol and CNS depressant use

The depressant effects of codeine phosphate as contained in STILPANE CAPSULES, are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines (see section 4.5).

Dependence, tolerance, and potential for abuse

The prolonged use of high doses of codeine phosphate as in STILPANE CAPSULES has produced dependence of the morphine type. STILPANE CAPSULES should be used with caution in patients with a history of substance abuse.

The risks are increased in individuals with current or history or family history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced or supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Discontinuation should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms.

Withdrawal syndrome

Withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. The opioid withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily nonpainful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing

OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

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

Paediatric population

STILPANE CAPSULES should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Meprobamate

Central nervous system (CNS) depressants and alcohol

The sedative effects of meprobamate are enhanced by CNS depressants including alcohol.

Meprobamate is capable of inducing hepatic microsomal enzyme systems involved in medicine metabolism: the metabolism of other medicines may be enhanced if given concurrently (see section 4.4).

Paracetamol

Hepatotoxic medicines

Paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes.

Metoclopramide and domperidone

The absorption of paracetamol may be accelerated by medicines such as metoclopramide and domperidone.

Probenecid

Excretion may be affected and plasma concentrations altered when given with probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.

Colestyramine

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

Antibacterials

Severe hepatotoxicity at therapeutic doses or moderate overdose of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see section 4.4)

Anticoagulants

STILPANE CAPSULES has no effect on the gastric mucosa or on platelet function, caution should be observed, since an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant have been observed. An increase in INR has also been reported, therefore increased monitoring may be appropriate.

Antiepileptics

Enzyme inducing medicines such as carbamazepine, phenobarbital, phenytoin or primidone increases paracetamol metabolism (glucuronidation and oxidation) and clearance from the body. This could result in an increased production of the hepatotoxic metabolite of paracetamol. If this toxic metabolite then exceeds the normal glutathione binding capacity, liver damage may occur. Therefore, the plasma-paracetamol concentrations should be halved in patients receiving enzyme-inducing medicines. Paracetamol reduces the area under the plasma concentration-time curve for lamotrigine, and its half-life, and increased the percentage of lamotrigine recovered in the urine.

Antivirals

Paracetamol enhances the antiviral effect of Interferon Alfa. Severe hepatotoxicity has occurred after the use of STILPANE CAPSULES in patients taking zidovudine and co-trimoxazole.

Coumarins (e.g. warfarin)

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding.

Codeine phosphate

Phenothiazines

Codeine phosphate, as contained in STILPANE CAPSULES, also increases the degree of sedation and the hypotensive effects of phenothiazines. Phenothiazines seem to be anti-analgesic and increases the amount of opioid required to produce satisfactory relief from pain.

Antihistamines

A number of antihistamines e.g.hydroxyzine, enhance the analgesic effects of low doses of opioids. Concomitant administration of codeine and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Alcohol

The hypotensive, sedative and respiratory depressive effects of alcohol may be enhanced.

Anaesthetics

Concomitant administration of codeine phosphate and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.

Anti-dysrhythmics

Codeine phosphate delays the absorption of mexiletine. The analgesic activity of codeine phosphate is likely to be significantly impaired by quinidine which impairs codeine phosphate

metabolism.

Antidepressants

The depressant effects of opioid analgesics such as STILPANE CAPSULES may be enhanced by tricyclic antidepressants.

Monoamine oxidase (MAO) inhibitors

The depressant effects may be exaggerated and prolonged. The use of STILPANE CAPSULES and MAOs is contraindicated (see section 4.3).

Antipsychotics

Enhanced sedative and hypotensive effect.

Anxiolytics and hypnotics

Enhanced sedative effect.

Domperidone, metoclopramide and cisapride

Codeine phosphate antagonises the effect of cisapride, metoclopramide and domperidone on gastrointestinal activity.

Sodium oxybate

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

Ulcer-healing medicines

Cimetidine may inhibit the metabolism of codeine phosphate resulting in increased plasma concentrations.

Interference with laboratory tests

Opioids such as codeine phosphate 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.

Sedative medicines such as benzodiazepines or related medicines

The concomitant use of opioids such as codeine phosphate with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.

4.6. Fertility, pregnancy and lactation

STILPANE CAPSULES should not be used in pregnancy and lactation as safety has not been established (see section 4.3).

Pregnancy

Codeine phosphate

A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine, as contained in STILPANE CAPSULES. Regular use during pregnancy may cause dependence in the foetus, leading to withdrawal symptoms in the neonate.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available (see section 4.4). Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.

Breastfeeding

Codeine phosphate

Administration to nursing women is not recommended as codeine phosphate, as contained in STILPANE CAPSULES, may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

No data available

4.7. Effects on ability to drive and use machines

STILPANE CAPSULES has major influence on the ability to drive or operate machinery. The use of STILPANE CAPSULES may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or central nervous system depressants. Affected patients should not drive or operate machinery (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

Adverse effects of paracetamol as contained in STILPANE CAPSULES are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Other side effects may include constipation, nausea, dizziness and drowsiness.

Regular prolonged use of codeine phosphate as contained in STILPANE CAPSULES is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.

b) Tabulated list of adverse reactions

Paracetamol

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Neutropenia, pancytopenia, leucopenia, thrombocytopenia, anaemia, agranulocytosis
Immune system disorders		Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Very rare cases of serious skin reactions have been reported.	
Respiratory, thoracic and mediastinal disorders		Bronchospasm*	
Hepatobiliary disorders		Hepatitis	Pancreatitis Hepatic dysfunction
Skin and subcutaneous tissue disorders		Skin rashes, usually erythematous or urticarial, dermatitis	Other allergic reactions accompanied by medicine fever and mucosal lesions, risk of fixed drug eruptions (FDE) and Drug-induced hypersensitivity syndrome (DIHS)
Renal and urinary disorders			Renal colic, renal failure and sterile pyuria

***** There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Codeine phosphate

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Immune system disorders			Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate; fever, splenomegaly and lymphadenopathy also occurred.
Endocrine disorders			Hyperglycaemia
Metabolism and nutrition disorders			Anorexia
Psychiatric disorders		mood changes, hallucinations	Euphoria, dysphoria , nightmares, mental depression, drug dependence (see section 4.4), mood changes, hallucinations
Nervous system disorders	Drowsiness	Confusion, restlessness, sedation, dizziness, faintness. Large doses of codeine can cause excitement and convulsions	Vertigo, hypothermia, raised intracranial pressure, headache.
Eye disorders			Miosis, blurred or double vision or other changes in vision
Cardiac disorders		Bradycardia, palpitations	Tachycardia,
Vascular disorders		Orthostatic hypotension, facial flushing	
Respiratory, thoracic and mediastinal disorders			Dyspnoea. Large doses produce respiratory depression
Gastrointestinal disorders	Constipation	Dry mouth, nausea, vomiting	Stomach cramps, risk of acute pancreatitis

Hepatobiliary disorders			Biliary spasm (may be associated with altered liver enzyme values).
Skin and subcutaneous tissue disorders		Pruritus, urticaria, sweating,	Contact dermatitis, itching of the nose and idiosyncrasy, allergic reactions such as skin rashes and facial oedema
Musculoskeletal and connective tissue disorders		Muscle rigidity following high doses	Uncontrolled muscle movements.
Renal and urinary disorders		Difficulty in micturition	Urinary retention, ureteric spasm, dysuria. An antidiuretic effect may also occur with codeine.
Reproductive system and breast disorders			Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido.
General disorders and administrative site conditions		Drug withdrawal syndrome	Malaise, tiredness

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

Meprobamate

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia
Nervous system disorders	Drowsiness, ataxia	Weakness, headache, disturbances of vision, excitement, dizziness	Paraesthesia
Eye disorders			Disturbances of vision
Cardiac disorders		Tachycardia and cardiac dysrhythmias	

Vascular disorders			Hypotension
Respiratory, thoracic and mediastinal disorders			Bronchospasm
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	
Hepatobiliary disorders			
Skin and subcutaneous tissue disorders		Skin rashes, urticaria	Purpura, angioedema, erythema multiforme
Renal and urinary disorders			Anuria

c) Description of selected adverse reactions

Sensitivity reactions resulting in reversible skin rash or blood disorders may occur. Treatment should be discontinued as soon as these hypersensitivity reactions occur.

Post marketing data for paracetamol, as contained in STILPANE CAPSULES, has reported Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) as an undesirable effect with unknown frequency (see section 4.4). Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis have also been reported as undesirable effects with unknown frequency (see section 4.4).

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

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.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9. Overdose

Symptoms

In the event of an overdosage, consult a doctor immediately, or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible. The latest information regarding the treatment of overdosage can be obtained from the nearest poison centre. The consequences can be extremely serious because of the narrow margin between therapeutic and toxic doses. Liver damage, which may be fatal, may only appear after a few days. Kidney failure has been described following acute intoxication.

Paracetamol:

Prompt treatment is essential. 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 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 carbamazapine.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and possibly abdominal pain. Abnormalities of glucose metabolism and metabolic acidosis may occur. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of overdosage. Liver damage may become apparent 12 to 48 hours after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. The liver damage may progress to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of liver damage. Cardiac dysrhythmias have been reported.

Central oedema and non-specific myocardial depression have also occurred.

Treatment for paracetamol overdosage:

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.

IV: An initial dose of 150 mg/kg N-acetylcysteine in 200 ml glucose injection, given **intravenously** over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml glucose injection over the next 4 hours, and then 100 mg/kg in 1 000 ml over the next 16 hours.

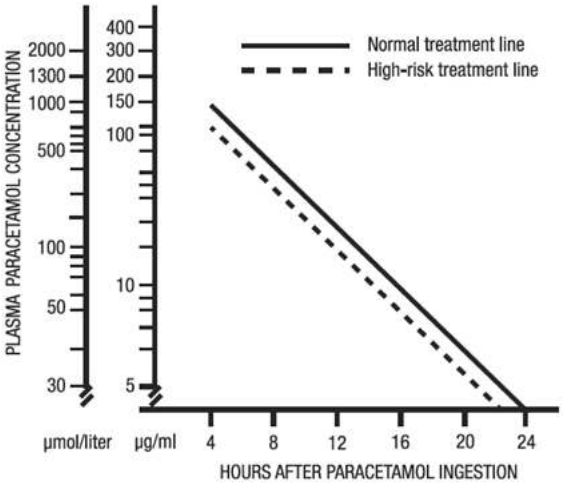
The volume of intravenous fluid should be modified for children.

Orally: Although oral treatment is not the treatment of choice, 140 mg/kg as a 5 % solution initially, followed by 70 mg/kg every 4 hours for 17 doses may be administered. N-acetylcysteine is effective if administered preferably within 8 hours of overdosage.

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 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against the 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 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”. INR correlates best with survival.

Codeine phosphate:

Respiratory depression is the most important feature of overdosage with codeine and it occurs with circulatory failure and deepening coma. Pinpoint pupils, hypotension and hypothermia, excitement and convulsions and non-cardiogenic pulmonary oedema occur.

Treatment

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.

Meprobamate

Symptoms of overdosage with meprobamate are those of central nervous system depression. Included are severe or even fatal hypotension, respiratory depression, shock, heart failure and ultimately death.

Acute meprobamate overdosage can produce stupor, coma, convulsions, circulatory and respiratory collapse.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: Codeine and other non-opioid analgesics

ATC code: N02AJ09

Mechanism of action

STILPANE CAPSULES have analgesic, antipyretic and tranquilizing properties.

5.2. Pharmacokinetic properties

Absorption

Meprobamate

Meprobamate is well absorbed when administered orally. The therapeutic half-life may be prolonged during its chronic administration.

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.

Peak plasma concentrations occur after about one hour.

The plasma half-life has been reported to be between 3 and 4 hours.

Distribution

Paracetamol

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

Biotransformation

Meprobamate

Most of the drug is metabolised in the liver by side-chain hydroxylation and glucuronidation.

Paracetamol

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10 % as glutathione conjugates. Practically no paracetamol is excreted unchanged, and the bulk is excreted after hepatic conjugation.

Codeine phosphate

It is metabolised in the liver to morphine and norcodeine, which are both excreted in the urine partly as conjugates with glucuronic acid.

Elimination

Meprobamate

The kinetics of elimination may depend on the dose.

About 10% of a dose is excreted unchanged. Meprobamate has a half-life reported to range from about 6 to 17 hours, although this may be prolonged after chronic use.

Paracetamol

Following therapeutic doses 90 to 100 % of the drug may be recovered in the urine within the first day.

Codeine phosphate

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal silicone dioxide, brilliant blue (CI no. 42090), magnesium stearate, quinolone yellow (CI no. 47005) and titanium dioxide (CI no. 77891).

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep in original container until required for use.

6.5. Nature and contents of container

100 capsules are packed into a white polypropylene securitainer sealed with a white low density polyethylene cap.

500 capsules are packed into a 1 000 ml amber-pigmented PVC container together with a silica gel sachet and sealed with a white pilfer proof HDPE screw cap.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

N/A

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Tel: 0800 118 088

8. REGISTRATION NUMBER

B0624 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Date of registration: Old medicine

10. DATE OF REVISION OF TEXT

31 March 2025

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