1.3.1.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

STILPANE 150 mg/8 mg/320 mg/32 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of STILPANE contains:

Meprobamate	150 mg
Codeine phosphate	8 mg
Paracetamol	320 mg
Caffeine anhydrous	32 mg

Preservatives:

Nipastat	0,02 % *m/m*

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

STILPANE is a green, mottled, biconvex tablet, debossed “C26” on the one side and bisected on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology

For short term use only. Do not use STILPANE for longer than 10 days.

Should not be used in children under 12 years of age.

Adults and children over 12 years:

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

DO NOT EXCEED THE RECOMMENDED DOSE.

Paediatric population

STILPANE should not be used in children under 12 years of age (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

STILPANE is contraindicated in:

- Patients with hypersensitivity to meprobamate, codeine phosphate, paracetamol, caffeine anhydrous or to any of the excipients in STILPANE (see section 6.1).
- Patients with hypersensitivity to other opioid analgesics.
- Porphyria (including acute forms of porphyria, especially variegate porphyria, acute intermittent porphyria and hereditary coproporphyria).
- Pregnancy and lactation (see section 4.6).
- Patients with severe liver or kidney complications (see section 4.4).
- Pulmonary insufficiency.
- STILPANE may induce convulsions in patients with a history of epilepsy.
- Obstructive airways disease, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- After operations on the biliary tract.
- Acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raised.
- Comatose patients.
- During an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment (see section 4.5).
- Patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.
- Children under 12 years of age.
- Codeine, as contained in STILPANE, 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.

- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems (see section 4.4).

4.4. Special warnings and precautions for use

STILPANE 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 the prolonged continuous use of STILPANE may lead to dependency and addiction (see section 4.2).

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

Meprobamate

STILPANE should not be used for periods longer than 10 days (see section 4.2).

Concomitant alcohol and CNS depressant use

Patients receiving meprobamate, as contained in STILPANE, 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 (see section 4.3 and 4.5).

Elderly, debilitated and patients with mental depression

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

Impaired hepatic, renal or respiratory function

STILPANE should be used with caution in patients with impaired hepatic or renal function, and as with all sedatives, in patients with impaired respiratory functions (see section 4.3).

Porphyria

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

Dependence and withdrawal

Prolonged use of meprobamate may lead to the development of dependence of the barbiturate alcohol type. There is a serious dependence risk with a typical withdrawal syndrome.

Hepatic metabolism

Meprobamate may induce the hepatic microsomal enzymes involved in medicine metabolism: the metabolism of medicine such as oral contraceptives, corticosteroids, phenytoin, phenothiazines, and tricyclic antidepressants may be enhanced if given concurrently (see section 4.5).

Codeine phosphate

Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, asthma (see section 4.3), impaired liver function (see section 4.3), urethral

stricture, prostatic hypertrophy, hypotension or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders (see section 4.3), and myasthenia gravis.

The dosage should be reduced in elderly and debilitated patients.

Pregnancy and labour

Administration of STILPANE during labour may cause respiratory depression in the newborn infant. If women take this medicine during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome (see sections 4.3 and 4.6).

Concomitant alcohol and CNS depressant use

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines (see section 4.3 and 4.5).

Dependence, tolerance, and potential for abuse

The prolonged use of high doses of codeine has produced dependence of the morphine type. Codeine, as contained in STILPANE, causes an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.

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. Patients may also further express the need to 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.

Opioid-Induced Hyperalgesia or Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid moiety).

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.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain.

Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

CYP2D6 metabolism

Depending on the genetic variability of CYP2D6, the individual metabolizing capacity for codeine may vary. Even therapeutic doses can lead to increased formation of the active metabolite morphine resulting in clinical signs of morphine intoxication (see section 4.3, section 4.8 and section 4.9).

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in paediatric patients 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 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.

Paracetamol

Effects on the liver and kidneys

Paracetamol 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 under medical supervision (see section 4.3). Consult your doctor if no relief is obtained from the recommended dosage. STILPANE should be given with care to patients taking other medicines that affect the liver, e.g. barbiturates (see section 4.9).

Glutathione depleted states

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol, as contained in STILPANE, 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 generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines, as contained in STILPANE. If a patient develops SCARs, treatment with STILPANE must immediately be discontinued and appropriate treatment instituted.

Flucloxacillin

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

Caffeine

Caffeine should be given with caution to patients with peptic ulceration, hyperthyroidism, hypertension, epilepsy (see section 4.3), cardiac dysrhythmias, or other cardiovascular disease as these conditions may be exacerbated. Caffeine should also be given with caution to patients with heart failure (see section 4.3), hepatic dysfunction, chronic alcoholism, acute febrile illness, neonates (see section 4.3 and 4.6) and elderly, since in all of these circumstances the clearance may be decreased resulting in increases in serum concentrations of caffeine and serum half-life.

Paediatric population

STILPANE 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).

Children with conditions associated with respiratory problems should not use codeine, as contained in STILPANE.

4.5. Interaction with other medicines and other forms of interaction

Caffeine

Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2 and is subject to interactions with other medicines which enhance or reduce its metabolic clearance.

Alcohol: Caffeine and alcohol cause a synergistic interaction which further increases reaction time (see section 4.3).

Anti-dysrhythmics: Mexiletine reduces the elimination of caffeine. Lidocaine, flecainide and tocainide have no effect on caffeine elimination.

Antibacterials: Caffeine elimination half-life increases, and the clearance decreases when given with ciprofloxacin, enoxacin and pipemidic acid, whereas lomefloxacin, norfloxacin and ofloxacin have little or no effect on these parameters.

Antidepressants: Fluvoxamine reduces the clearance and prolongs the elimination half-life of caffeine.

Antiepileptics: The mean clearance of caffeine increases, and its half-life decreases in epileptic patients taking phenytoin. Treatment with carbamazepine or valproic acid have no effect.

Gastrointestinal medicines: Cimetidine reduces the systemic clearance of caffeine and prolongs its elimination half-life.

Lithium: Lithium concentrations increase when caffeine is eliminated from the diet. Toxicity may occur in patients maintained at higher concentrations.

Methoxsalen: Methoxsalen reduces the clearance of caffeine in patients with psoriasis.

Sex hormones: Oral contraceptives reduce the clearance and increases the elimination half-life of caffeine.

Sympathomimetics: The use of caffeine with phenylpropanolamine produces greater plasma-caffeine concentrations, greater increases in blood pressure and more reports of physical

adverse effects than either medicine alone. Giving caffeine with ephedrine produces cardiovascular, metabolic and hormonal responses, increased systolic blood pressure and heart rate, as well as raised fasting glucose and insulin.

Meprobamate

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

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 and domperidone. Excretion may be affected and plasma concentrations altered when given with probenecid. Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol. Concomitant use of medicines which slow gastric emptying, may delay absorption and onset of action 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 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 and antibiotics: Paracetamol enhances the antiviral effect of Interferon Alfa. Severe hepatotoxicity has occurred after the use of paracetamol in patients 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 contained in STILPANE.

Probenecid: Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Codeine phosphate

Phenothiazines: Codeine 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 and antihypertensives: 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 and antihypertensives 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. Alcohol should be avoided during treatment with STILPANE as psychomotor performance can be significantly reduced (see section 4.3).

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

The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Concurrent use of codeine with antidiarrhoeal and antiperistaltic medicines such as loperamide and kaolin may increase the risk of severe constipation.

Concomitant use of antimuscarinics or medicines with muscarinic action, e.g. atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Anti-dysrhythmics: Codeine delays the absorption of mexiletine and thus reduces its anti-dysrhythmic effect. The analgesic activity of codeine is likely to be significantly impaired by quinidine which impairs codeine metabolism.

Antidepressants: The depressant effects of opioid analgesics may be enhanced by tricyclic antidepressants.

Monoamine oxidase (MAO) inhibitors**:** The depressant effects may be exaggerated and prolonged. The use of STILPANE and MAOs are contraindicated (see section 4.3).

Antipsychotics: Enhanced sedative and hypotensive effect.

Anxiolytics and hypnotics: Enhanced sedative effect.

Domperidone, metoclopramide and cisapride: Codeine 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 resulting in increased plasma concentrations.

Interference with laboratory tests: Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. 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.

Sedative medicines such as benzodiazepines or related medicines: The concomitant use of opioids with sedative medicines such as benzodiazepines or CNS depressants, including alcohol, anaesthetics, hydroxyzine (anxiolytics), hypnotics, sedatives or antipsychotics and phenothiazines increases the risk of sedation, respiratory depression, hypotension, coma and death because of additive CNS depressant effect.

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids, as contained in STILPANE.

4.6. Fertility, pregnancy and lactation

Pregnancy and Breastfeeding

STILPANE should not be used during pregnancy and lactation (see section 4.3).

Codeine phosphate

STILPANE is contraindicated in women who are breastfeeding their infants and women in the third trimester of pregnancy.

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

In case of imminent birth or preterm birth, the use of codeine is contraindicated since codeine, as contained in STILPANE, crosses the placental barrier and can cause neonatal respiratory depression. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available. Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother (see section 4.3).

Administration to nursing women is contraindicated as codeine phosphate, as contained in STILPANE, may be secreted in breast milk and may cause respiratory depression in the infant. If the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal (see section 4.3).

Paracetamol

A large amount of data on pregnant women indicate neither malformative, nor foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol *in utero* show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency (see section 4.3).

Fertility

No fertility information available.

4.7. Effects on ability to drive and use machines

STILPANE has major influence on the ability to drive or operate machinery.

The use of STILPANE 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) Tabulated list of adverse reactions

Paracetamol

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from available data)
Blood and the lymphatic system disorders			Neutropenia, pancytopenia, leukopenia, thrombocytopenia, agranulocytosis and anaemia
Immune system disorders			Anaphylaxis, cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Very rare cases of serious skin reactions have been reported
Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Ear and labyrinth disorders			Hearing loss

Cardiac disorders			Possible increase in the risk of hypertension
Respiratory, thoracic and mediastinal disorders		Bronchospasm*	
Gastrointestinal disorders		Pancreatitis	Nausea and vomiting
Hepatobiliary disorders		Hepatic enzyme increase, hepatic dysfunction	
Skin and subcutaneous tissue disorders		Sensitivity reactions resulting in reversible skin rash, usually erythematous or urticarial, pruritis	Sensitivity reactions accompanied by medicine fever and mucosal lesions, 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)
Renal and urinary disorders		Renal colic, renal failure, sterile pyuria	Nephropathy
Investigations			Increased transaminases

*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 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	Addiction, dependence, sleep disturbances	Hallucinations, dysphoria, euphoria, changes of mood, restlessness, confusion	Mental depression, nightmares
Nervous system disorders	Drowsiness, dizziness, seizures, tolerance, headache, vertigo	Confusion, euphoria, mood changes, restlessness, miosis, hallucinations, sedation, faintness. Large doses of codeine can cause excitement and convulsions	Deepening coma, raised intracranial pressure, dyskinesia
Eye disorders		Miosis, visual disturbances	Blurred or double vision (diplopia) or other changes in vision
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension, tachycardia	
Vascular disorders		Postural hypotension, facial flushing	Large doses produce hypotension
Respiratory, thoracic and		Respiratory depression	Dyspnoea, cough suppression

mediastinal disorders			
Gastrointestinal disorders	Constipation, nausea, vomiting, pancreatitis	Dry mouth	Stomach cramps
Hepatobiliary disorders		Biliary spasm (may be associated with altered liver enzyme values), liver disorder	Biliary colic
Skin and subcutaneous tissue disorders		Pruritus, urticaria, sweating, rashes	Contact dermatitis, itching of the nose, allergic reactions such as skin rashes, facial oedema
Musculoskeletal and connective tissue disorders		Muscle rigidity following high doses	Uncontrolled muscle movements
Renal and urinary disorders		Difficulty in micturition, ureteric spasm, urinary retention, dysuria (increased frequency, decrease in amount)	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	Malaise		Hypothermia, tiredness, idiosyncrasy
Investigations		Haemoglobin decreased	

Caffeine anhydrous

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from available data)
Nervous system disorders	Insomnia, headache, anxiety, restlessness		Vertigo, palpitations, tremor, hypotension, excitement
Eye disorders			Scintillating scotoma
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Tachycardia and extrasystoles
Gastrointestinal disorders	Nausea, vomiting, abdominal pain	Gastrointestinal bleeding	Caffeine increases gastric secretions and may cause gastric ulceration

Meprobamate

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from available data)
Blood and the lymphatic System disorders			Agranulocytosis, eosinophilia, leukopenia, 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	Hypotension
Respiratory, thoracic and mediastinal disorders			Bronchospasm
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	
Skin and Subcutaneous tissue disorders		Skin rashes, urticaria	Purpura, angioedema, anuria, erythema multiforme

b) 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, has reported Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) as an undesirable effect with unknown frequency (see section 4.4).

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

c) Paediatric population

STILPANE is not recommended for use in children under twelve years of age (see section 4.3)

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9. Overdose

Symptoms

Prompt treatment is essential. In the event of overdosage, consult a doctor immediately, or take the patient to the nearest hospital immediately. 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. Kidney failure has been described following acute intoxication.

Meprobamate

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

Codeine phosphate

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.

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative medicines have been co-ingested, including alcohol, or the overdose is very large. The triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid over dosage with dilation of the pupils occurring as hypoxia develops. Nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely. Dry mouth, sweating, hypothermia, confusion, convulsions, severe dizziness, severe drowsiness and facial flushing are other symptoms of overdose. Nervousness or restlessness, excitement, hallucinations, bradycardia, circulatory failure, 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.

Paracetamol

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 carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and possibly abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis may develop even in the absence of liver damage.

Cardiac dysrhythmias have been reported.

Symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage. Liver damage may manifest initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may progress to encephalopathy, coma and death. Central oedema and non-specific myocardial depression have also occurred.

Caffeine

Severe overdosage or idiosyncrasy due to caffeine may lead to agitation, diuresis, repeated vomiting with extreme thirst, abdominal or stomach pains, facial flushing, confusion, delirium, hyperthermia, cardiac dysrhythmias including tachycardia, electrolyte disturbances, convulsions, anxiety, nervousness, insomnia, excitement, muscle twitching and death.

The symptoms of caffeine overdose may be masked by the depression of consciousness associated with possible codeine overdose when associated with this combination.

Treatment

Treatment of 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.

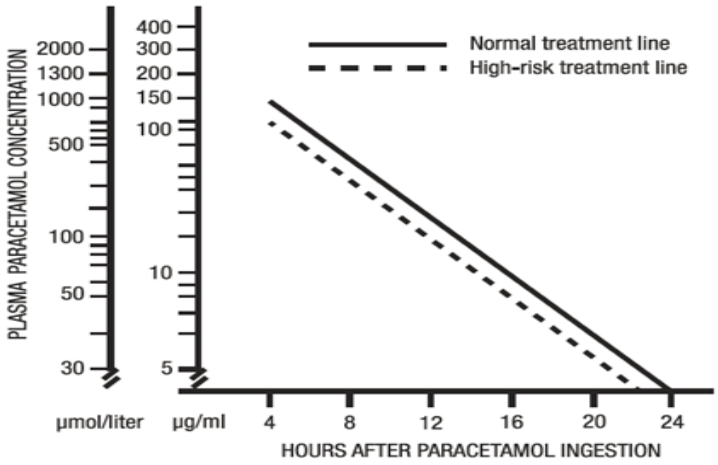
IV: An initial dose of 150 mg/kg in 200 ml glucose injection, given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml glucose injection over the next 4 hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next 16 hours.

The volume of intravenous fluid should be modified for children.

Orally: 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 4 hours for 17 doses. Acetylcysteine is effective if administered preferably within 8 hours of overdosage.

If N-acetylcysteine is not available, methionine 2,5 mg may be given immediately, followed by 2,5 g every 4 hours for 3 doses. Patients should however, preferably be transferred to a facility where N-acetylcysteine can be given.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 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 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 16 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. All patients with significant ingestions should be monitored for at least 96 hours.

Other symptoms include central stimulation and exhilaration, followed by cardiovascular collapse and coma.

Overdosage with barbiturates can cause severe or even fatal hypotension, respiratory depression, shock, heart failure and ultimately death (see section 4.4).

Patients should be managed with intensive symptomatic and supportive therapy with particular attention being made to the maintenance of cardiovascular, respiratory, renal function and to the maintenance of electrolyte balance.

Treatment of Codeine overdosage:

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. Adequate ventilation and oxygenation should be established without delay if consciousness is impaired.

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.

Failure of a definite opioid overdose to respond to large doses of naloxone suggests that another CNS depressant medicine of brain damage is present.

Observe the patient carefully for recurrence of CNS and respiratory depression. Repeated doses of naloxone may be required. If so, intravenous infusion of naloxone may be useful. An infusion of 60% of the initial dose per hour is a useful starting point. A 200 microgram/ml

solution for infusion using an IV pump can be used and the dose adjusted to clinical response. Infusions are not a substitute for frequent review of the patient's clinical state.

Treatment of caffeine overdose

Treatment is primarily symptomatic and supportive. Acute toxicity is unlikely to occur with the low levels of caffeine in this product. For cardiac symptoms monitoring of ECG is required. Diuresis should be treated by maintaining fluid and electrolyte balance. Gastric symptoms can be treated using antacids.

Administration of activated charcoal may be useful within the first 4 hours if precautions are taken to minimise aspiration.

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

The combination of paracetamol, codeine phosphate, caffeine anhydrous and meprobamate has analgesic, antipyretic and tranquilising 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.

Caffeine anhydrous

Caffeine is absorbed readily after oral administration.

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.

Caffeine anhydrous

Caffeine is widely distributed throughout the body. Caffeine passes readily into the CNS and into saliva.

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.

Caffeine anhydrous

In adults, caffeine is metabolised almost completely via oxidation, demethylation and acetylation.

Elimination

Meprobamate

The kinetics of elimination may depend on the dose.

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.

Caffeine anhydrous

Caffeine is excreted in the urine as various metabolites with only about 1 % being excreted unchanged. Elimination half-life is approximately 3 to 6 hours in adults.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dye lake green (C.I No's: 47005, 42090, 15985), magnesium stearate, nipastat, povidone K25, sodium starch glycollate, starch, talc.

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 tablets are packed in aluminium/PVC blister strips. The strips are packed, together with a leaflet into a unit carton.

500 tablets are packed into a white polypropylene (PP) securitainer, together with a foam insert and a leaflet and sealed with a white polyethylene cap.

1 000 tablets are packed into amber PVC jars together with a foam insert and a leaflet and sealed with a screwcap.

Not all packs and pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Tel: 0800 122 912 / +27 (0)11 239 6200

8. REGISTRATION NUMBER

M/2.9/2

9. DATE OF FIRST AUTHORISATION

Date of registration: 23 November 1979

10. DATE OF REVISION OF TEXT

21 October 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Botswana: B9322890 1C

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