PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

SEDAPAIN

Each tablet contains 10 mg codeine phosphate, 5 mg doxylamine succinate, 450 mg paracetamol, and 30 mg caffeine anhydrous

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Codeine Phosphate	10 mg
Doxylamine Succinate	5 mg
Paracetamol	450 mg
Caffeine Anhydrous	30 mg

"Sugar-Free"

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

A round yellow, flat bevelled edged tablet with a breakline on one side and imprinted "D59" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For mild to moderate pain associated with tension.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children 12 years and older: 2 tablets every 4 hours as needed. Do not exceed 8 tablets per day.

Do not use continuously for longer than 10 days without consulting your doctor.

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

Method of administration

For oral use.

Special populations

The dosage in renal functional impairment must be reduced.

Use with caution in renal disease.

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

Paediatric population

SEDAPAIN is not recommended for children under 12 years of age (refer to section 4.4)

4.3 Contraindications

- Hypersensitivity to any of the active ingredients, i.e. paracetamol, codeine or other opioid analgesics, doxylamine succinate, caffeine or to any of the other ingredients in SEDAPAIN (see section 6.1).
- Severe liver function impairment.
- Acute intermittent porphyria.
- Acute asthma (during an attack)
- Respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- After operation on the biliary tract.
- Acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raised.
- It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.

- In patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment, as there is a risk of serotonin syndrome (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Risk of paralytic ileus.
- In all paediatric patients (0 –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).
- In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

SEDAPAIN 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.

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

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

Do not take concurrently with any other paracetamol or codeine containing medicines.

Care is advised in the administration of SEDAPAIN to patients with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urinary retention, susceptibility to angle-closure glaucoma, shock, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of cardiac arrhythmias or convulsions, and in patients with a history of medicine abuse or emotional instability.

~~The dosage in renal functional impairment must be reduced.~~

Should be taken with caution by asthmatics.

~~Do not use continuously for longer than 10 days without consulting your doctor~~.

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

~~Use with caution in renal disease~~.

~~Dosage in excess of those recommended may cause severe liver damage.~~

Paracetamol

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

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 (FOE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with SEDAPAIN must immediately be discontinued and appropriate treatment instituted.

Codeine phosphate

Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function, myasthenia gravis, prostatic hypertrophy or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders.

Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and colonic obstruction.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. The dosage should be reduced in elderly and debilitated patients.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions (see section 4.2 and 4.3).

Prolonged use of high doses of codeine has produced dependence.

Caffeine anhydrous

Caffeine anhydrous should be given with care to patients with a history of peptic ulceration. With prolonged use some degree of tolerance and psychic dependence may occur.

Give with caution to patients with hyperthyroidism, cardiac arrhythmias or other cardiovascular

disease, or epilepsy as these conditions may be exacerbated.

Doxylamine succinate

Doxylamine succinate has anticholinergic properties and should be used with care in conditions such as glaucoma and prostatic hypertrophy.

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of opioids, including codeine, and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of sedative medicines, such as benzodiazepines or related medicines, with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe codeine as contained in SEDAPAIN concomitantly with sedative medicines such as benzodiazepines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Risks from concomitant use of opioids and alcohol

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see section 4.5). The hazards of overdose are greater in those with non-cirrhotic alcoholic liver diseases.

CY2D6 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 analgesic effect will not be obtained. 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 (see section 4.3 and 4.6).

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.

Paediatric population

SEDAPAIN is not recommended for children under 12 years of age.

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 also 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. These factors may worsen symptoms of morphine toxicity.

4.5 Interaction with other medicines and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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.

SEDAPAIN may enhance the sedative effects of central nervous system (CNS) depressants such as alcohol, barbiturates, anaesthetics, hypnotics, other opioid analgesics, anxiolytic sedatives, antipsychotics, tricyclic antidepressants and phenothiazines, resulting in increased CNS depression. It may also have an additive antimuscarinic action with other medicines, such as atropine and some antidepressants.

Benzodiazepines

The concomitant use of opioids 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. The dosage and duration of concomitant use should be limited (see section 4.4).

Alcohol and opioids

The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect.

Concomitant use with alcohol is not recommended (see section 4.4).

The hypotensive actions of diuretics and anti-hypertensive medicines may be potentiated when used concurrently with opioid analgesics. Concurrent use of hydroxyzine with codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

The respiratory depressant effect caused by neuromuscular blocking medicines may be additive to the central respiratory depressant effects of opioid analgesics. Quinidine can inhibit the analgesic effect of codeine.

Concurrent use of codeine with antidiarrheals and anti-peristaltic medicines such as loperamide and kaolin may increase the risk of severe constipation. Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics.

Naltrexone also blocks the therapeutic effect of opioids.

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

Doxylamine: Monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with these products as there is a risk of serotonin syndrome (see section 4.3 and 4.4).

The effects of atropine and tricyclic antidepressants may be enhanced by Doxylamine succinate.

Doxylamine succinate may mask the symptoms of damage caused by ototoxic drugs and may affect metabolism of drugs in the liver. Doxylamine succinate may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers.

Concomitant administration of pethidine and possibly other opioid analgesics to patients taking MAOIs has been associated with very severe and sometimes fatal reactions such as 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).

Incompatibilities: Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeine-phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two medicines, even at low moisture levels.
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 also 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.
The metabolism of paracetamol is possibly accelerated by carbamazepine, phenytoin, phenobarbital, primidone (also there have been isolated reports of hepatotoxicity).

4.6 Fertility, pregnancy and lactation

The safety of SEDAPAIN in pregnancy and lactation has not been established (see section 4.3).
SEDAPAIN should not be used during pregnancy or lactation.

~~*Pregnancy*~~

~~Reported epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.~~

~~A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Reported 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.~~

Codeine crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible association with respiratory and cardiac malformations has been reported. Regular use during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate. Use during pregnancy should be avoided if possible.

Use of opioid analgesia during labour may cause respiratory depression in the neonate, especially the premature neonate. These medicines should not be given during the delivery of a premature baby.

Breastfeeding

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Codeine should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites 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 and 4.4).

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

SEDAPAIN may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressant agents. Patients should be warned against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accident.

4.8 Undesirable effects

	Paracetamol	**Doxylamine succinate**	**Caffeine anhydrous**	**Codeine phosphate***
Blood and the lymphatic system disorders				
Less frequent	Thrombocytopenia Leukopenia Pancytopenia Neutropenia Agranulocytosis	Thrombocytopenia Leukopenia Agranulocytosis Haemolytic anaemia		
Frequency unknown		Eosinophilia		
Immune system disorders				
Less frequent	Hypersensitivity reactions	Hypersensitivity reactions		Allergic reactions
Frequency unknown	Anaphylactic shock Angioedema	Bronchospasm Angioedema Anuria Allergy Anaphylaxis		
Psychiatric disorders				
Frequent		Psychomotor impairment		Drowsiness Confusion
Less		Extrapyramidal effects	insomnia	Hallucinations

frequent		Sleep disturbances (including insomnia, nightmares) Confusion Nervousness Irritability Elation or depression		Nightmares Depression Anorexia
Frequency unknown				Restlessness Changes in mood Euphoria Decreased libido
Nervous system disorders				
Frequent		CNS depression Drowsiness (usually diminished within a few days) Headache Paradoxical stimulation (especially in children)		Drowsiness
Less frequent		Dizziness Tremor Muscles twitching, Convulsions Paraesthesia	Headache	Dizziness Headache Convulsions Uncontrolled muscle movements
Frequency unknown		Slight drowsiness to deep sleep Lassitude Incoordination	Restlessness Excitement Muscle Tremor	Deepening coma Dizziness

		Photosensitivity	CNS stimulation Anxiety Dizziness	Headache Raised intracranial pressure
Eye disorders				
Frequent		Blurred vision		
Less frequent				Blurred or double vision
Frequency unknown			Scintillating scotoma	Miosis
Ear and labyrinth disorders				
Less frequent		Tinnitus		Vertigo
Frequency unknown			Tinnitus	
Cardiac disorders				
Less frequent		Tachycardia Hypotension Palpitations Arrhythmias		Orthostatic hypotension
Frequency unknown			Tachycardia Extrasystole Palpitations	Hypotension Circulatory failure Tachycardia
Respiratory, thoracic and mediastinal disorders				
Less frequent		Thickened respiratory-tract secretions		Respiratory depression
Frequency		Tightness of the chest		Dyspnoea

unknown		and tingling		
Hepato-biliary disorders				
Less frequent		Jaundice		
Frequency unknown		Porphyria symptoms may be exacerbated		
Gastrointestinal disorders				
Frequent		Dry mouth Gastrointestinal disorders Nausea Vomiting Diarrhoea		Nausea Vomiting Constipation
Less frequent			Nausea	Dry mouth Increased risk of abdominal pain, including pancreatitis
Frequency unknown	Pancreatitis	Constipation Increased gastric reflux Epigastric pain	Gastric ulceration	Stomach cramps
Skin and subcutaneous tissue disorders				
Less frequent	Reversible skin rash			
Frequency unknown	Erythema Urticaria Serious skin reactions accompanied by fever	Rashes Urticaria Purpura Erythema multiforme		Pruritus Urticaria

	and mucosal lesions 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 (FOE)	Exfoliative or bullous dermatitis		
Musculoskeletal, connective tissue and bone disorders				
Frequency unknown		Myalgia		Muscle rigidity
Renal and urinary disorders				
Frequent		Urinary retention		
Frequency unknown		Difficulty in micturition		Difficulty in micturition Ureteric or biliary spasm

				Antidiuretic effect
Reproductive system and breast disorders				
Frequency unknown				Decreased potency
General disorders and administrative site conditions				
Less frequent				Malaise Tiredness
Frequency unknown		Heaviness of hands, Sweating Hair loss		Sweating Facial flushing Hyperthermia Hypothermia

* Regular prolonged use of codeine 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.

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 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

4.9 Overdose

Overdosage of the product will produce the symptoms listed under "side-effects" above in more severe form.

ANTIHISTAMINES (DOXYLAMINE SUCCINATE)

Overdosage of doxylamine succinate causes sedation. The most common symptom reported is impaired consciousness. Overdosage may be fatal especially in infants and children in whom the

main symptoms are central nervous stimulation and antimuscarinic effects, including ataxia, excitement, hallucination, muscle tremor, convulsions, dilated pupils, dry mouth, flushed face and hyperpyrexia. Deepening coma, cardiorespiratory collapse and death may occur within 18 hours.

In adults the usual symptoms are central nervous depression with drowsiness, coma and convulsions. Rhabdomyolysis has occurred. Hypotension may also occur. Treatment of antihistamine overdose is symptomatic and supportive.

PARACETAMOL

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. 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 5-10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours 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 severe liver damaged. Cardiac arrythmias have been reported.

Symptoms during the first 2 days of acute poisoning do not reflect the potential seriousness of the overdosage. Nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Liver injury may become manifest on the second day, (or later) initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. The liver damage may progress to encephalopathy, coma and death. Cerebral oedema and non-specific myocardial depression have also occurred.

Treatment for paracetamol overdosage:

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

~~Although evidence is limited it is recommended that any adult person who has ingested about 5 - 10~~

~~grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.~~

Specific therapy with an antidote such as acetylcysteine should be administered IV as soon as possible.

ACETYLCYSTEINE:

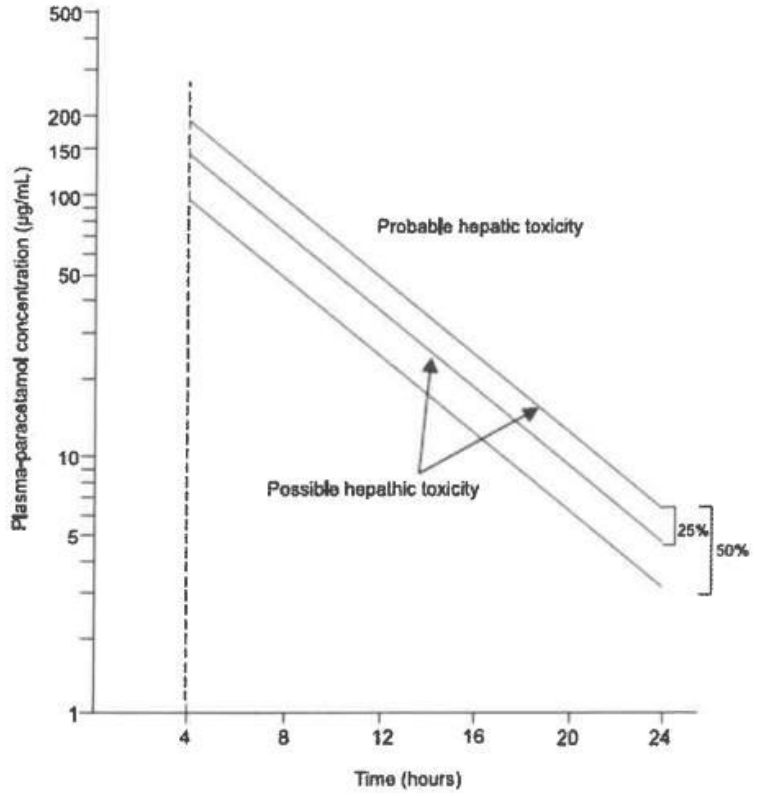
Acetylcysteine should be administered as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: An initial dose of 150 mg/kg in 200 ml glucose injection, given intravenously over 15 minutes, followed by an 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 fluids should be modified for children.

ORALLY: Although the oral formulation is not the treatment of choice,140 mg/kg as a 5 % solution initially, followed by a 70 mg/kg solution every 4 hours for 17 doses. Acetylcysteine is effective if administered within 8 hours of overdosage.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 hours 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 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”. Prothrombin index correlates best with survival. Monitor all patients with significant ingestion for at least 96 hours.

Paracetamol nomogram: A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion



CODEINE PHOSPHATE

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

CAFFEINE

Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes hematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, metabolic acidosis, convulsions and death.

Severe toxicity may not be preceded by milder symptoms. After caffeine overdosage by mouth the stomach should be emptied by emesis.

Elimination may be enhanced by repeated oral doses of activated charcoal. An osmotic laxative may also be given. Treatment is symptomatic and supportive. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium under electrocardiogram (ECG) monitoring. In the non-asthmatic patient

extreme tachycardia, hypokalaemia, and hyperglycaemia may be reversed by beta blockers. Convulsions should be controlled by the intravenous administration of diazepam. Charcoal hemoperfusion or haemodialysis may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.8 Analgesic combinations.

Pharmacotherapeutic group: Anilides, Paracetamol combinations.

ATC code: NO2B E51.

SEDAPAIN has analgesic, antipyretic and antihistaminic properties.

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

Doxylamine succinate is an ethanolamine type antihistamine with mild sedative, anti-allergic and anti-emetic properties. Because of its sedative action, it reduces the psychic tension component of tension headache and other somatic pain/tension states.

Caffeine has a mild stimulant effect on the cerebral cortex and relieves fatigue.

5.2 Pharmacokinetic properties

The pharmacokinetics of paracetamol, codeine phosphate and caffeine are widely published. Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration the effects start within 15 to 30 minutes and peak within one hour. In humans 60 – 80 % of doxylamine given has been recovered in urine at 24 hours post-dose.
The bioavailabilities of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately.

Codeine is mainly metabolised by glucuronidation to codeine-6-glucuronide.
Minor routes of metabolism include *O*-demethylation leading to morphine, *N*-demethylation to norcodeine and both *O*- and *N*-demethylation to normorphine. Morphine and norcodeine are further transformed to glucuronide conjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48 h (84,4 ± 15,9 %).

The *O*-demethylation of codeine to morphine is catalysed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine. Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide, kollidon 25, magnesium stearate, quinolone yellow, sodium starch glycollate, starch (maize) and talc.

6.2 Incompatibilities

Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeine-phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two medicines,

even at low moisture levels.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

6.5 Nature and contents of container

Blister packs of 20 or 100 tablets, securitainers of 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Litha Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

8 REGISTRATION NUMBERS

28/2.8/0523

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 February 1994

10 DATE OF REVISION OF THE TEXT

19 April 2024