1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

LENADOL 10 mg/5 mg/400 mg/50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of LENADOL contains 10 mg codeine phosphate, 5 mg diphenhydramine hydrochloride, 400 mg paracetamol and 50 mg caffeine anhydrous.

Preservatives:

Methyl parahydroxybenzoate 0,019 % *m/m*

Propyl parahydroxybenzoate 0,003 % *m/m*

Contains sugar: Lactose monohydrate 32,87 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Yellow, round, flat, bevelled edge tablet, bisected on one side, and debossed with “A79” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LENADOL relieves fever and pain-tension states.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

Take one to two tablets every 3 to 4 hours, to a maximum of 8 tablets daily.

Method of administration

For oral administration.

4.3 Contraindications

LENADOL is contraindicated in:

- Patients with hypersensitivity to codeine phosphate, diphenhydramine hydrochloride, paracetamol, caffeine anhydrous or to any excipients in LENADOL (see section 6.1).
- Patients hypersensitive to other opioid analgesics.
- Patients with severe liver or kidney complications.
- Pregnancy and breastfeeding (see section 4.6).
- Asthma, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- Head injuries and conditions in which intracranial pressure is raised.
- Heart failure secondary to chronic lung disease.
- A history of cardiac disease.
- Epilepsy and all convulsive states.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.5).
- Acute alcoholism.

- Comatose patients.
- Children under 12 years of age.
- In 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)
- 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.
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- Porphyria.

4.4 Special warnings and precautions for use

LENADOL 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.

LENADOL contains codeine and exceeding the prescribed dose, together with prolonged and continuous use, may lead to dependence and addiction.
The lowest effective dose should be used, and the duration of treatment should be as short as possible.

Consult your doctor if no relief is obtained with the recommended dosage. Do not use continuously for longer than 5 days without consulting your doctor.

Codeine phosphate

Codeine, as contained in LENADOL, should be given with caution or in reduced doses in patients with adrenocortical insufficiency. The dosage should be reduced in the debilitated and in the elderly. It should be used with caution or in reduced doses in patients with hypothyroidism, impaired kidney or liver function (see section 4.3), prostatic hypertrophy, urethral stricture, hypotension, shock, or myasthenia gravis.

CYP2D6 metabolism

Codeine, as contained in LENADOL, is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme, an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser, there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher-than-expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation, and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal (see section 4.3).

Post-operative use in children

There have been reports in the published literature that codeine as contained in LENADOL, 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, as contained in LENADOL, 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.

Drug dependence, tolerance, and potential for abuse

For all patients, prolonged use of LENADOL may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Should be used with caution in patients with 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 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.

Drug withdrawal syndrome

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

Drug 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 medicine 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, as contained in LENADOL, presents with increased pain.

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

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 (safety switching the patient to a different opioid moiety).

Monoamine Oxidase Inhibitors (MAOIs)

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 4.3).

Alcohol

Alcohol should be avoided whilst under treatment with codeine as contained in LENADOL.

Sedatives

Concomitant use of LENADOL and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant

prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible.
These 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 caregivers to be aware of these symptoms (see section 4.5).

Paracetamol

As LENADOL contains paracetamol, doses in excess of those recommended may cause severe liver damage to occur. Not more than 4 000 mg should be taken in 24 hours. There may be an added risk of liver damage when patients with certain pre-existing liver diseases are given paracetamol, as contained in LENADOL. It is recommended that patients suffering from hepatitis or who are recovering from any form of liver disease should not take paracetamol, as contained in LENADOL.

Sensitivity reactions resulting in reversible skin rash or blood dyscrasia may occur following paracetamol intake, as contained in LENADOL (see section 4.8).

Prolonged excessive use may cause irreversible kidney damage.

Patients suffering from kidney or liver disease should take paracetamol, as contained in LENADOL, under strict medical supervision.

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol, as contained in LENADOL, may increase the risk of metabolic acidosis.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic syndrome (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines, as contained in LENADOL. If a patient develops SCAR, treatment with LENADOL must immediately be discontinued and appropriate treatment instituted.

High Anion gap metabolic acidosis (HAGMA)

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

Diphenhydramine hydrochloride

Diphenhydramine, as contained in LENADOL, should be used with care in conditions such as closed-angle glaucoma, urinary retention, prostatic hyperplasia, myasthenia gravis, hepatic impairment and mild to moderate renal impairment (see section 4.3).

Antihistamines

Avoid use of other antihistamine-containing preparations, including topical antihistamine and cough and cold medicines.

Alcohol

Avoid concurrent use with alcohol, as diphenhydramine, as contained in LENADOL, may increase the sedative effects of alcohol (see section 4.5).

Caffeine anhydrous

Caffeine, as contained in LENADOL, should be taken with care by patients with a history of peptic ulceration or hyperacidity. With prolonged use, some degree of tolerance and psychic dependence may occur.

Excessive intake of caffeine (e.g., coffee, tea, and some canned drinks) should be avoided while taking LENADOL.

Paediatric population

LENADOL 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).

Excipients

LENADOL contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take LENADOL.

Preservatives:

LENADOL contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction

LENADOL SHOULD NOT BE TAKEN WITH SEDATIVES AND TRANQUILISERS.

Monoamine oxidase inhibitors (MAOIs) (e.g. moclobemide, selegiline, linezolid) due to the possible risk of excitiation or depression, avoid concomitant use for 14 days after discontinuation of MOAIs (see section 4.3).

Codeine as contained in LENADOL, may affect the activity of other medicines by delaying their absorption.

Alcohol

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

Anaesthetics

Concomitant administration of codeine, as contained in LENADOL and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.

Antidepressants

The depressant effects of opioid analgesics, as contained in LENADOL, may be enhanced by tricyclic antidepressants.

Anti-dysrhythmics

Codeine, as contained in LENADOL, delays the absorption of mexiletine. The analgesic activity of codeine is likely to be significantly impaired by quinidine which impairs codeine metabolism.

Sedative medicines

The concomitant use of opioids such as codeine, as contained in LENADOL, 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 dose and duration of concomitant use should be limited (see section 4.4).

Anxiolytics and hypnotics

Enhanced sedative effect.

Antipsychotics

Enhanced sedative and hypotensive effect.

Antihistamines

Concomitant administration of codeine, as contained in LENADOL, and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Cisapride, domperidone and metoclopramide

Codeine as contained in LENADOL, antagonises the effect of cisapride, metoclopramide and domperidone on gastrointestinal activity.

Sodium oxybate

Concomitant administration of codeine, as contained in LENADOL and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Cimetidine

Cimetidine may inhibit the metabolism of codeine as contained in LENADOL resulting in increased plasma concentrations.

Laboratory tests

Opioids such as codeine as contained in LENADOL 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.

Paracetamol

Barbiturates

The risk of liver-cell toxicity of paracetamol as contained in LENADOL, may be somewhat greater in patients who receive concurrent medicines which induce hepatic enzymes, such as the barbiturates.

Metoclopramide, domperidone and colestyramine

The absorption of paracetamol, as contained in LENADOL, may be accelerated by metoclopramide or domperidone and absorption reduced by colestyramine.

Warfarin and other coumarins

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.

Salicylates

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

Isoniazid

Chronic use of isoniazid may increase the risk of liver damage when combined with paracetamol, even at recommended doses.

Probenecid

Excretion may be affected, and plasma concentrations altered when administered with probenecid.

Flucloxacillin

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

Diphenhydramine hydrochloride

Alcohol and other central nervous system depressants

Diphenhydramine, as contained in LENADOL, may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and neuroleptics. Patients should avoid alcoholic drinks.

Monoamine oxidase inhibitors, atropine and tricyclic antidepressants

Monoamine oxidase inhibitors may enhance the antimuscarinic effects of diphenhydramine and have an additive antimuscarinic action with medicine such as atropine and tricyclic antidepressants (see section 4.3).

Aminoglycoside antibiotics

Diphenhydramine could mask the warning signs of damage caused by ototoxic medicine such as aminoglycoside antibiotics.

Metoprolol and venlafaxine

Diphenhydramine is an inhibitor of the cytochrome p450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with medicines that are primarily metabolized by CYP2D6, such as metoprolol and venlafaxine.

Caffeine anhydrous

Lithium

Caffeine may increase clearance of lithium. Concomitant use is therefore not recommended.

4.6 Fertility, pregnancy and lactation

LENADOL is contraindicated in pregnancy and lactation as LENADOL crosses the placenta and passes into breastmilk (see section 4.3). The administration of codeine, as contained in LENADOL, during labour may cause respiratory depression in the newborn infant.

Pregnancy

Caffeine and paracetamol

Paracetamol-caffeine, as contained in LENADOL, is not recommended for use during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

Diphenhydramine hydrochloride

There are no adequate data from the use of diphenhydramine in pregnant women. Animal studies are insufficient with respect to pregnancy. The potential risk for humans is unknown. Use of sedating antihistamines such as diphenhydramine, as contained in LENADOL, during the third trimester may result in reactions in the newborn or premature neonates.

Codeine phosphate

A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine as contained in LENADOL.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

Administration during labour may depress respiration in the neonate. Opioid analgesics such as codeine, as contained in LENADOL, may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.
(see section 4.3)

Breastfeeding

Caffeine anhydrous
Caffeine as contained in LENADOL, in breast milk may potentially have a stimulating effect on breast fed infants.

Diphenhydramine hydrochloride
Diphenhydramine as contained in LENADOL has been detected in breast milk, but the effects of this on breast-fed infants are unknown.

Codeine phosphate
Administration to nursing women is not recommended as codeine phosphate may be secreted in breast milk and may cause respiratory depression in the infant (see section 4.3).

Fertility
No data available.

4.7 Effects on ability to drive and use machines

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

LENADOL may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants medicines. Patients should be warned not to drive a motor vehicle or operate dangerous machinery.

4.8 Undesirable effects

a) 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		Haematological reactions e.g. thrombocytopenia, neutropenia, pancytopenia, leucopenia, anaemia	
Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria), high-anion gap metabolic acidosis
Gastrointestinal disorders		Pancreatitis	
Hepatobiliary disorders		Hepatitis	
Skin and subcutaneous tissue disorders		Skin eruptions, rash, erythematous or urticarial*	
Renal and urinary disorders		Renal colic, nephropathy, renal failure, and sterile pyuria	

* Skin eruptions have occurred. Sensitivity reactions including skin rash may occur. This is usually erythematous or urticarial but sometimes may be more serious and may be accompanied by drug fever and mucosal lesions.

Post marketing data

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Agranulocytosis, thrombocytopenia	
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		Hepatic dysfunction	
Skin and subcutaneous tissue disorders			Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic syndrome (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)

** 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			Dose-related histamine-releasing effect, allergic reactions such as urticarial and pruritus as well as hypotension and flushing hypersensitivity syndrome as part of a maculopapular rash, fever, splenomegaly, and lymphadenopathy
Endocrine disorders			Hyperglycaemia
Metabolism and nutrition disorders			Anorexia

Psychiatric disorders	Confusion	Restlessness±, mood changes±,	Excitement, euphoria, mental depression, hallucinations and nightmares, and dysphoria
Nervous system disorders	Dizziness, drowsiness,	Faintness±, sedation±, vertigo±	Headache, raised intracranial pressure, convulsions
Eye disorders		Miosis±	Blurred or double vision or other changes in vision
Cardiac disorders		Bradycardia, palpitations±	Tachycardia
Vascular disorders			Postural hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Constipation, nausea, vomiting,	Dry mouth±	Stomach cramps, pancreatitis
Hepatobiliary disorders			Biliary spasm
Skin and subcutaneous tissue disorders	Facial flushing±,	Sweating	Allergic reactions such as skin rashes, urticaria, pruritus
Musculoskeletal and connective tissue disorders			Muscle rigidity, uncontrolled muscle movements
Renal and urinary disorders			Urinary retention, ureteric spasm, antidiuretic effect difficulty with micturation, dysuria
Reproductive system and breast disorders			Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido
General disorders and administrative site conditions		Drug withdrawal syndrome	Hypothermia malaise, tiredness, and facial oedema

± These effects occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain.

These are less common than with morphine.

Codeine may cause respiratory depression, circulatory failure, hypotension, orthostatic hypotension, deepening coma with larger doses.

Diphenhydramine hydrochloride

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, aplastic anaemia
Immune system disorders			Skin rashes, urticaria, purpura, angioedema, bronchospasm
Metabolism and nutrition disorders			Symptoms of porphyria may be exacerbated
Psychiatric disorders			Elation or depression, irritability, nightmares confusion*, paradoxical excitation* (eg increased energy, restlessness, nervousness) *the elderly are more prone to confusion and paradoxical excitation
Nervous system disorders	Sedation varying from slight drowsiness to deep sleep including inability to concentrate, dizziness, unsteadiness		Headache, tingling, paraesthesia, convulsions, dyskinesias
Eye disorders			Blurred vision
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Tachycardia, cardiac dysrhythmias, palpitations
Vascular disorders			Hypotension
Respiratory, thoracic and mediastinal disorders			Thickened respiratory-tract secretions, tightness of the chest
Gastrointestinal disorders	Dry mouth		Nausea, vomiting, diarrhoea, constipation, colic, epigastric pain, anorexia
Skin and subcutaneous tissue disorders			Erythema multiforme, exfoliative or bullous dermatitis
Musculoskeletal and connective tissue disorders			Muscular weakness, incoordination, muscle twitching
Renal and urinary disorders			Difficulty in micturition, urinary retention, anuria
General disorders and administrative site conditions	Fatigue		Lassitude

Post marketing Data

Caffeine anhydrous

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Psychiatric disorders			Restlessness, excitement anxiety and irritability

Nervous system disorders			Headache, insomnia, dizziness
Eye disorders			Scintillating scotoma
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Tachycardia, extrasystoles, palpitations
Gastrointestinal disorders			Nausea, increased gastric secretion which may cause gastric ulceration
Musculoskeletal and connective tissue disorders			Muscle tremor

b) Description of selected adverse reactions

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic syndrome (DRESS), Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with LENADOL must immediately be discontinued and appropriate treatment instituted.

There is a risk of serious heart problems, seizures, coma and death associated with the use of high doses of diphenhydramine containing medicines.

c) Other special populations

Elderly

Dosage should be reduced in elderly patients.

Sedating antihistamines such as diphenhydramine as contained in LENADOL, may cause confusion and paradoxical excitation in the elderly.

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 SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9 Overdose

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

Codeine phosphate

Symptoms

Symptoms of overdosage are constipation, nausea, vomiting, anorexia, dizziness, drowsiness, abdominal pain, gastrointestinal haemorrhage, potentially fatal liver damage, cerebral oedema and renal tubular necrosis, hyperglycaemia and hypoglycaemia.

Central stimulation and exhilaration, followed by cardiovascular collapse, respiratory depression, and coma.

Treatment

Naloxone hydrochloride 400 µg is given subcutaneously, intramuscularly, or intravenously, repeated at intervals of 2 to 3 minutes if necessary. Respiration may be assisted.

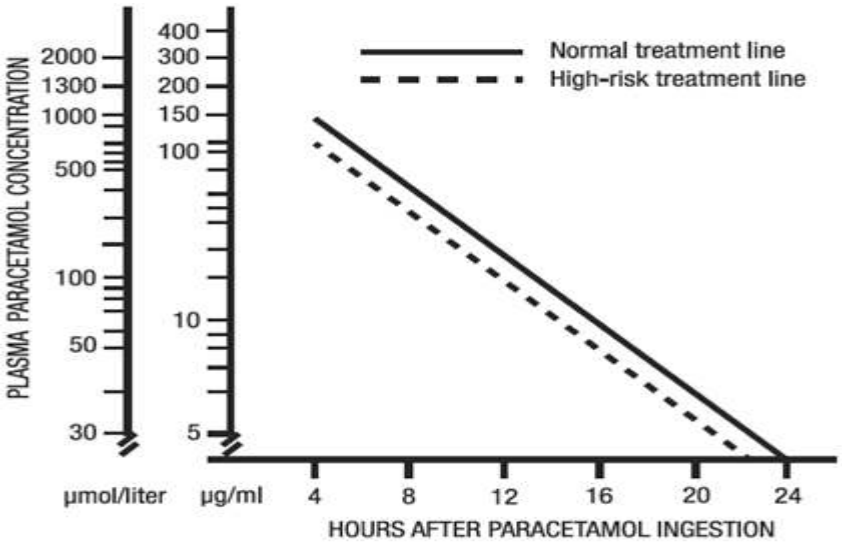
Paracetamol

Symptoms

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 to10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children. Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen

doses. A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours 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 sixteen hours repeatedly until recovery.



A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.

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. For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity. Monitor all patients with significant ingestions for at least ninety-six hours.

Diphenhydramine hydrochloride

Symptoms

Diphenhydramine overdose is likely to result in effects in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes including QT prolongation. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, dysrhythmias, coma and cardiovascular collapse.

Treatment

Treatment should be supportive and directed towards specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam. Further management should be as clinically indicated or as recommended by the national poisons centres where applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: Opioids and other non-opioid analgesics

ATC code: N02AJ06

Mechanism of action

Paracetamol

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependent on the inhibition of prostaglandin synthesis. This inhibition appears, however, to be on a selective basis.

Diphenhydramine hydrochloride

Diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of histamine at the H1 receptor sites. However, like most H1 antihistamines it has additional sedative anticholinergic (antimuscarinic) and local anaesthetic properties.

Codeine phosphate

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.

LENADOL has analgesic, antipyretic and antihistaminic properties.

5.2 Pharmacokinetic properties

Absorption

Paracetamol

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

Caffeine anhydrous

Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours.

Diphenhydramine hydrochloride

Diphenhydramine is well absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations are achieved in 2 to 3 hours and the effects usually last 4 to 6 hours.

Codeine phosphate

Codeine is well absorbed from the gastrointestinal tract following 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.

Biotransformation

Paracetamol

Practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

Diphenhydramine hydrochloride

Diphenhydramine is extensively metabolised mainly in the liver.

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

Paracetamol

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

Caffeine anhydrous

65 to 80 % of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

Diphenhydramine hydrochloride

Diphenhydramine is excreted usually as metabolites in the urine.

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

Lactose monohydrate, magnesium stearate, maize starch, methyl parahydroxybenzoate, microcrystalline cellulose, polysorbate 80, povidone, propyl parahydroxybenzoate, purified talc, quinoline yellow, sodium starch glycollate.

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 packaging until required for use.

6.5 Nature and contents of container

18 or 40 tablets are packed in a white round polypropylene container with a white linear low density polyethylene closure with tamper evident seal, together with a rayon or white foam insert and a leaflet.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

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

8 REGISTRATION NUMBER

M/2.9/4

9 DATE OF FIRST AUTHORISATION

Date of registration: 05 February 1980

10 DATE OF REVISION OF TEXT

28 May 2025

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

Botswana: BOT0400719 S3

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