CLEAN PROPOSED PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

B-DOL tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Codeine Phosphate	10 mg
Doxylamine succinate	5 mg
Paracetamol	450 mg
Caffeine	30 mg

Sugar Free

Contains Quinolene yellow CI 47005

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Round, yellow flat tablet scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

B-DOL tablets are indicated for mild to moderate pain associated with tension.

4.2 Posology and method of administration

Posology

Adults and children 12 years and older:

2 tablets every 4 hours as needed.

Do not exceed 8 tablets per day.

Method of administration

To be taken orally.

4.3 Contraindications

- Known hypersensitivity to paracetamol, doxylamine succinate, codeine phosphate or caffeine, or to any of the excipients listed in section 6.1.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.4 and 4.5).
- Severe liver function impairment (see section 4.4).
- Acute intermittent porphyria.
- 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.
- Pregnancy and lactation (see section 4.6).
- In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

B-DOL 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.
Patients suffering from liver or kidney disease should take paracetamol under medical supervision.
Consult your doctor if no relief is obtained with the recommended dosage. Do not use continuously for more than 10 days without consulting your doctor.

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

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

Care is advised in the administration of B-DOL 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 drug abuse or emotional instability.

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

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.

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).

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 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.

Severe cutaneous adverse reactions (SCARs)

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

Mental health disorders

B-DOL should be used with particular care in patients with a personal or family history of substance abuse or mental health disorders including, but not limited to major depression, anxiety and alcohol and drug abuse.

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.

B-DOL may enhance the sedative effects of 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 antidiarrhoeal and antiperistaltic 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.

Doxylamine: Monamine 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).

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.

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

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 indicate 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.

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).

4.7 Effects on the ability to drive and use machines

The use of this medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. Patients should be cautioned about operating vehicles or machinery or engaging in activities which require them to be fully alert.

4.8 Undesirable effects

Tabulated summary of adverse reactions

	Paracetamol	**Doxylamine succinate**	**Caffeine**	**Codeine phosphate**
Blood and the lymphatic system disorders				
Less frequent	Thrombocytopaenia Leucopaenia Pancytopaenia Neutropaenia Agranulocytosis	Thrombocytopaenia Leucopaenia Agranulocytosis Haemolytic anaemia		
Immune system disorders				
Less frequent	Sensitivity reactions			
Frequency unknown		Hypersensitivity reactions Bronchospasm Angioedema Anaphylaxis		
Metabolism and nutrition disorders				
Frequency unknown		Dry mouth		Dry mouth
Psychiatric disorders				
Frequent				Drowsiness Confusion
Frequency unknown		Psychomotor impairment Extrapyramidal effects Sleep disturbances	Insomnia	Restlessness Changes in mood Euphoria Decreased libido Hallucinations
Nervous system disorders				
Frequent		CNS depression		

	Paracetamol	Doxylamine succinate	Caffeine	Codeine phosphate
Frequency unknown		Slight drowsiness to deep sleep Lassitude Dizziness Incoordination (although paradoxical stimulation may occasionally occur, especially in children) Headache Photosensitivity Convulsions Paraesthesias Tremor Depression	CNS stimulation Headache Anxiety Restlessness Dizziness Tremor	Dizziness Headache Raised intracranial pressure
Eye disorders				
Frequency unknown		Blurred vision		Miosis
Ear and labyrinth disorders				
Frequency unknown		Tinnitus		Vertigo
Cardiac disorders				
Frequency unknown		Palpitations Arrhythmias Hypotension	Palpitations	Bradycardia Tachycardia Palpitations Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders				
Frequency unknown		Thickened respiratory-tract secretions		
Hepato-biliary disorders				
Frequency unknown		Jaundice		

	Paracetamol	Doxylamine succinate	Caffeine	Codeine phosphate
Gastrointestinal disorders				
Frequent				Nausea Vomiting Constipation
Less Frequent				Increased risk of abdominal pain, including pancreatitis
Frequency unknown		Constipation Increased gastric reflux Nausea Vomiting Diarrhoea Epigastric pain	Gastrointestinal irritation Nausea Vomiting Abdominal pain Diarrhoea Gastrointestinal disturbances	
Skin and subcutaneous tissue disorders				
Less frequent	Reversible skin rash			
Frequency unknown	Erythema Urticaria Mucosal lesions Risk of fixed drug eruptions and drug-induced hypersensitivity syndrome	Rashes		Pruritus Urticaria
Musculoskeletal, connective tissue and bone disorders				
Frequency unknown		Myalgia		
Renal and urinary disorders				
Frequency unknown		Urinary difficulty or retention		Difficulty in micturition Ureteric or biliary spasm Antidiuretic effect

	Paracetamol	Doxylamine succinate	Caffeine	Codeine phosphate
Reproductive system and breast disorders				
Frequency Unknown				Decreased potency
General disorders and administrative site conditions				
Frequency unknown	Fever	Sweating Hair loss		Sweating Facial flushing Hypothermia

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 Reaction Reporting form', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

4.9 Overdose

PARACETAMOL:

Specialised and prompt treatment is essential as soon as possible. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. The latest information regarding the treatment of overdosage can be obtained from the nearest poison centre. 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 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.

Treatment for paracetamol overdosage:

Any adult person who has had about 7.5 grams 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.
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 glucose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml glucose injection over the next four hours, and then 100 mg/kg in 1000 ml glucose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children.
Orally (not the treatment of choice): 140 mg/kg as a 5 % solution initially, followed by 70 mg/kg every four hours for seventeen doses. N-acetylcysteine is more likely to be effective if administered within 8 hours of overdosage.
If N-acetylcysteine is not available, methionine 2.5 g may be given immediately, followed by 2.5 g every four hours for three doses. Patients should however preferably be transferred to a facility where N-acetylcysteine can be given.
Monitor all patients with significant ingestions for at least ninety-six hours.

DOXYLAMINE SUCCINATE:
The most common symptom reported is impaired consciousness. Additionally, psychotic behaviour, seizures, and antimuscarinic symptoms such as tachycardia and mydriasis have been observed. Rhabdomyolysis has occurred.

CAFFEINE:
Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) 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 or lavage. 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 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 haemoperfusion or haemodialysis may be required.

CODEINE PHOSPHATE:
Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and

deepening coma. Convulsions may occur. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops.
In acute poisoning by an opioid taken by mouth the stomach should be emptied. A laxative may be given to aid peristalsis. Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses of opioid analgesics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.8 Analgesic combinations.
Pharmacotherapeutic group: Anilides, Paracetamol combinations ATC Code: NO2B E51.

Pharmacological action
B-DOL has analgesic, antipyretic and antihistaminic properties.
Paracetamol is an effective, well-documented analgesic preparation.
Codeine is a proven analgesic medicine, which has a suggested central action.
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

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 metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include Odemethylation 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 hours (84,4 ± 15,9 %).

The O-demethylation of codeine to morphine is catalyzed 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide
Magnesium stearate
Povidone
Quinolene yellow H8573 (C.I. 47005)
Starch maize
Sodium starch glycolate
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 dry place.
Protect from light. Keep containers well closed.

6.5 Nature and contents of container

Blister packs of 10 tablets per blister strip.
20, 100, 500 and 1000 tablets in PVC containers;
20 and 100 tablets in a securitainer and 1000 tablets in a white HDPE bottle.

6.6 Special precautions for disposal and other handling

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd
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8 REGISTRATION NUMBER

35/2.8/0065

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31 July 2002

10 DATE OF REVISION OF THE TEXT

30 May 2024