1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

LENAZINE FORTE COUGH LINCTUS 9 mg/7,2 mg/3,6 mg per 5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of LENAZINE FORTE COUGH LINCTUS contains:

Codeine phosphate……9,0 mg

Ephedrine hydrochloride……...7,2 mg

Promethazine hydrochloride……3,6 mg

In a flavoured syrup base.

Preservative:

Methyl hydroxybenzoate 0,1 % m/v

Contains sugar: Sucrose 2 g, liquid glucose 2 g

Contains sweetener: Saccharin sodium 3,6 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LENAZINE FORTE COUGH LINCTUS is a bright orange-brown syrupy liquid with an orange odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LENAZINE FORTE COUGH LINCTUS is indicated for the alleviation of cough.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE

Adults

Take one to two medicine measuresful (5 ml to 10 ml) 2 to 3 times a day.

Children

12 years and over: Take one to one and a half medicine measuresful (5 ml to 7,5 ml) 2 to 3 times a day.

7 to 11 years: Take half to one medicine measureful (2,5 ml to 5 ml) 2 to 3 times a day.

2 to 6 years: Take quarter to half a medicine measureful (1,25 ml to 2,5 ml) 2 to 3 times a day.

Method of administration

For oral administration.

4.3 Contraindications

LENAZINE FORTE COUGH LINCTUS is contraindicated in:

- Hypersensitivity to codeine phosphate, ephedrine hydrochloride, promethazine hydrochloride or to any of the excipients in LENAZINE FORTE COUGH LINCTUS (see section 6.1).
- Respiratory depression.
- Acute alcoholism.

- Head injuries and conditions in which intracranial pressure is raised.
- Patients receiving mono-amine oxidase inhibitors or within 14 days of its termination.
- Premature infants or neonates.
- During acute attacks of asthma.
- Heart failure secondary to chronic lung disease.
- Children under 2 years of age .
- Breastfeeding mothers (see section 4.6).
- 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)
- Safety in pregnancy has not been established.
- Patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.
- 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.
- The use of promethazine as contained in LENAZINE FORTE COUGH LINCTUS may be associated with the sudden infant death syndrome.

4.4 Special warnings and precautions for use

This medicine may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol, or any other central nervous system depressant agents.

Patients should be warned not to drive a motor vehicle, operate dangerous machinery, or

climb dangerous heights, as impaired decision making could lead to accidents.

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

Codeine phosphate

Codeine phosphate, as contained in LENAZINE FORTE COUGH LINCTUS, should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, or shock. Patients with obstructive bowel disorders and myasthenia gravis also need to be cautious when taking codeine phosphate.

CYP2D6 metabolism

Codeine, as contained in LENAZINE FORTE COUGH LINCTUS, 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.

Post-operative use in children

There have been reports in the published literature that codeine as contained in LENAZINE FORTE COUGH LINCTUS, 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 LENAZINE FORTE COUGH LINCTUS, 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.

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.

Alcohol

Alcohol should be avoided whilst under treatment with codeine as contained in LENAZINE FORTE COUGH LINCTUS.

Ephedrine hydrochloride

Ephedrine hydrochloride, as contained in LENAZINE FORTE COUGH LINCTUS, should be used with care in patients with hyperthyroidism, cardiovascular disease, occlusive vascular disorders, aneurysms, diabetes mellitus or closed-angle glaucoma.

Angina pain may be precipitated in patients with angina pectoris.

Ephedrine hydrochloride, as contained in LENAZINE FORTE COUGH LINCTUS, should be avoided or used with caution in patients undergoing anaesthesia with halogenated anaesthetics and may cause an increased risk of dysrhythmias in patients receiving cardiac glycosides, quinidine or tricyclic antidepressants.

Promethazine hydrochloride

Promethazine hydrochloride, as contained in LENAZINE FORTE COUGH LINCTUS, should be used with care in patients with cardiovascular or hepatic diseases, narrow angle glaucoma, urinary retention and prostatic hypertrophy. Promethazine hydrochloride has anticholinergic properties and should be used with care in conditions such as glaucoma. Promethazine may potentiate the hypotensive effect of some anti-hypertensives.

Elderly patients are more susceptible to the many adverse effects of promethazine.
Cases of respiratory depression, including fatalities have been reported in children under two years of age.
Promethazine hydrochloride may thicken or dry lung secretions and impair expectoration. It should therefore be used with caution in patients with asthma, bronchitis or bronchiectasis.
Use with care in patients with severe coronary artery disease, narrow angle glaucoma, epilepsy or hepatic and renal insufficiency.
Caution should be exercised in patients with bladder neck or pyloro-duodenal obstruction.
The use of promethazine hydrochloride should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.
Promethazine hydrochloride may mask the warning signs of ototoxicity caused by ototoxic medicines e.g. salicylates.

Promethazine hydrochloride may also delay the early diagnosis of intestinal obstruction or raised intracranial pressure through the suppression of vomiting.

Special populations

Paediatric population

The safety and efficacy in children under 2 years of age has not yet been established.

Excipients

LENAZINE FORTE COUGH LINCTUS contains glucose which may have an effect on the glycaemic control of patients with diabetes mellitus.

LENAZINE FORTE COUGH LINCTUS contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase- isomaltase insufficiency should not take LENAZINE FORTE COUGH LINCTUS.

4.5 Interaction with other medicines and other forms of interaction

Antihistamines may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics, sedatives and antipsychotics.

Antihistamines have an additive antimuscarinic action with other antimuscarinic medicines such as atropine, and some antidepressants including tricyclic antidepressants and monoamine oxidase inhibitors.

It has been suggested that some antihistamines could mask the warning signs of damage caused by ototoxic medicines such as aminoglycoside antibiotics.

The depressant effects of codeine are enhanced by other central nervous system depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics.

The actions of codeine may affect the activities of other medicines e.g. the gastrointestinal effects of codeine may delay absorption as with mexiletine or may be counteractive as with cisapride, metoclopramide or domperidone.

Interactions with laboratory tests

Promethazine hydrochloride should be discontinued at least 72 hours before the start of skin tests as it may inhibit the cutaneous histamine response thus producing false-negative results.

Opioids may interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

Additional information on special populations

Elderly

LENAZINE FORTE COUCH LINCTUS is to be used with caution in the elderly as they are more prone to adverse effects (see section 4.8).

Use with caution in the elderly, as codeine phosphate may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and colonic obstruction. Prolonged use could aggravate irritable bowel syndrome.

Paediatric population

LENAZINE FORTE COUCH LINCTUS is contraindicated in use in children under 2 years of

age (see section 4.3).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

LENAZINE FORTE COUGH LINCTUS may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol, or any other central nervous system depressant agents.

Patients should be warned not to drive a motor vehicle, operate dangerous machinery or climb dangerous heights, as impaired decision making could lead to accidents.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

Codeine Phosphate

System organ class	Frequent	Less Frequent	Frequency unknown
Blood and lymphatic system disorders		Splenomegaly, lymphadenopathy	
Metabolism and nutrition disorders			Hyperglycaemia, anorexia, loss of appetite
Psychiatric disorders		Euphoria Restlessness and confusion	Mood changes, hallucinations
Nervous system disorders	Drowsiness	Deepening coma with high doses, increased intracranial pressure. Convulsion may occur,	Headache, dizziness

System organ class	Frequent	Less Frequent	Frequency unknown
		especially in infants and children with high doses	
Eye disorders	Miosis		
Ear and labyrinth disorders		Ringing or buzzing in the ears	Vertigo
Cardiac disorders		Bradycardia, palpitations	Tachycardia
Vascular disorders		Circulatory failure, hypotension, orthostatic hypotension	Hypothermia
Respiratory, thoracic and mediastinal disorders	Respiratory depression		
Gastrointestinal disorders	Constipation	Nausea, vomiting and dry mouth	Abdominal pain, including pancreatitis
Hepato-biliary disorders		Biliary spasm	
Skin and subcutaneous tissue disorders		Pruritus, urticaria, sweating	
Musculoskeletal and connective tissue disorders		Muscle rigidity has been reported following high doses	
Renal and urinary disorders		Difficulty in micturition, ureteric and anti-diuretic effect	
Reproductive system and breast disorders			Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido
General disorders and administration site conditions		Facial flushing, hypothermia	

Ephedrine hydrochloride

System organ class	Frequent	Less Frequent	Frequency unknown
Metabolism and nutrition disorders			Altered metabolism including disturbances of glucose metabolism

System organ class	Frequent	Less Frequent	Frequency unknown
Psychiatric disorders		Psychotic states	
Nervous system disorders	Anxiety, restlessness, insomnia, headache	Tremor, fear	Confusion, irritability, weakness
Cardiac disorders	Tachycardia, palpitations	Reflex bradycardia, cardiac dysrhythmias, angina pain, cardiac arrest	Dyspnoea
Vascular disorders		Vasoconstriction with resultant hypertension, hypotension with dizziness and fainting	
Respiratory, thoracic and mediastinal disorders		Chest discomfort or pain	
Gastrointestinal disorders	Nausea	Decrease in appetite and vomiting	Hypersalivation
Skin and subcutaneous tissue disorders			Sweating
Musculoskeletal and connective tissue disorders		Muscle cramps	
Renal and urinary disorders			Difficulty in micturition, urinary retention
General disorders and administration site conditions		Flushing	

Promethazine hydrochloride

System organ class	Frequent	Less Frequent	Frequency unknown
Blood and lymphatic system disorders		Agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia	
Immune system disorders			Allergy and anaphylaxis
Metabolism and nutrition disorders		Anorexia	
Psychiatric disorders		Depression, euphoria, confusion	
Nervous system disorders	Sedation, headache, dizziness, lassitude and inco-	Paradoxical central nervous system stimulation especially at high doses in children or elderly	Convulsions, extrapyramidal effects, tremor, sleep disturbances,

System organ class	Frequent	Less Frequent	Frequency unknown
	ordination		muscular weakness, tinnitus, incoordination, tingling and cerebral stimulation (in infants and children)
Eye disorders	Blurred vision		
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders		Tachycardia	
Vascular disorders		Hypotension and dizziness	
Respiratory, thoracic and mediastinal disorders	Tightness of the chest		
Gastrointestinal disorders	Dryness of the mouth and constipation	Nausea, vomiting, diarrhoea, epigastric pain, anorexia or increased appetite and gastrointestinal disturbances	
Hepato-biliary disorders			Jaundice
Skin and subcutaneous tissue disorders		Photosensitivity and angioedema	Sweating
Musculoskeletal and connective tissue disorders			Myalgia, muscle twitching, heaviness and weakness of hands
Renal and urinary disorders	Difficulty in micturition, dysuria		
General disorders and administration site conditions			Lassitude

b) Description of selected adverse reactions

Regular prolonged use of codeine phosphate, as contained in LENAZINE FORTE COUGH LINCTUS, is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.

Tolerance and some of the most common side effects – drowsiness, nausea, and vomiting, and confusion – generally develops with long term use.

Ephedrine hydrochloride, as contained in LENAZINE FORTE COUGH LINCTUS, may act as stimulant in children with nocturnal enuresis and cause sleeplessness. It may have sedative effects in some children.

The elderly are more sensitive to the cardiovascular effects of ephedrine hydrochloride.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are 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

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9 Overdose

Symptoms

Codeine phosphate

Poisoning with codeine phosphate, as contained in LENAZINE FORTE COUGH LINCTUS produces central nervous system depression with exhilaration, excitation, miosis and slow breathing, and in children, convulsions followed by, respiratory depression, vomiting,

drowsiness, reduced levels of consciousness, somnolence, cyanosis, hypotension, and deepening coma, lack of appetite, constipation, nausea, pinpoint pupils, dry mouth, sweating and facial flushing are symptoms of overdose. High doses of codeine may produce hypotension, circulatory failure, sedation, or excitement and, in children, convulsions may occur.

Promethazine hydrochloride

Overdosage may be fatal, especially in infants and children. It is associated with antimuscarinic, extrapyramidal, gastrointestinal and central nervous system (CNS) effects. In infants and children central nervous system (CNS) stimulation predominates over central nervous system (CNS) depression, causing ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, central nervous system (CNS) depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse.

Ephedrine hydrochloride

The effects of ephedrine hydrochloride, as contained in LENAZINE FORTE COUGH LINCTUS in overdose include nausea, vomiting, fever, palpitations, tachycardia, hypertension, paranoid psychosis, respiratory depression, convulsions and coma.

Treatment

In the event of overdosage the stomach should be emptied by aspiration and lavage. Activated charcoal and laxatives may also be used.

Intensive supportive therapy may be required to treat respiratory failure and shock. Treatment should be symptomatic and supportive.

Codeine Phosphate

In acute overdosage with respiratory depression or coma, naloxone is indicated using one of the following dose regimens:

Naloxone hydrochloride is used as an antagonist to codeine phosphate in dosages of 0,4 mg to 2 mg intravenously which may be repeated at intervals of 2 to 3 minutes, if necessary, up to 10 mg.

Child: 10 µg/kg and, if no response, subsequent doses of 100 µg/kg.

Subcutaneous or intramuscular injection: As intravenous injection but only if the intravenous route is not feasible. The onset of action is slower with subcutaneous or intramuscular injection.

Continuous intravenous infusion: 2 mg diluted in 500 ml of intravenous infusion solution at a rate adjusted according to the patient's response.

Ephedrine hydrochloride

The treatment of ephedrine overdose with LENAZINE FORTE COUGH LINCTUS may require intensive supportive treatment. Slow intravenous injection of labetalol 50 to 200 mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia (< 2,8 mmol/L^{-1}) due to compartmental shift of potassium predisposes to cardiac dysrhythmias and may be corrected by infusing potassium chloride in addition to propranolol and correcting respiratory alkalosis, when present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 10.1: Antitussives and expectorants

Pharmacotherapeutic group: Combinations

ATC code: R05DA20

Mechanism of action

Codeine phosphate is a narcotic analgesic agent.

Ephedrine hydrochloride is sympathomimetic with bronchodilator and central nervous system stimulant properties.

Promethazine hydrochloride is a phenothiazine derivative with antihistamine and sedative properties.

5.2 Pharmacokinetic properties

Absorption

Codeine phosphate:

Codeine is well absorbed from the gastrointestinal tract following oral administration.

Ephedrine hydrochloride:

Ephedrine is rapidly and completely absorbed from the gastrointestinal tract.

Promethazine hydrochloride:

Promethazine hydrochloride is readily absorbed from the gastrointestinal tract.

Distribution

Codeine phosphate

Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. The plasma half-life has been reported to be between 3 and 4 hours after an oral dose.

Ephedrine hydrochloride

Ephedrine is extensively distributed throughout the body with

accumulation in the liver, lungs, kidneys, spleen and brain.

Promethazine hydrochloride

After oral therapy, therapeutic effects are identifiable at 15-30 minutes and peak plasma concentrations at 2 to 3 hours. Estimates of

terminal half-life in blood plasma are in the range of 4-6 hours. It is extensively plasma protein bound.

Biotransformation

Codeine phosphate

Codeine is metabolised by O- and N-Demethylation in the liver to morphine and norcodeine. Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism.

Ephedrine hydrochloride

Small amounts of metabolites are produced by hepatic metabolism.

Promethazine hydrochloride

Undergoes extensive first pass metabolism in the liver, with only 25 % of the oral dose reaching the systemic circulation unchanged.

Elimination

Codeine phosphate

Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

Ephedrine hydrochloride

Ephedrine has been variously reported to have a plasma half-life ranging from 3 to 6 hours depending on urinary pH; elimination is enhanced and half-life accordingly shorter in acid urine.

It is excreted largely unchanged in the urine with up to 95 % being excreted in the urine.

Promethazine hydrochloride

Is eliminated mainly as metabolites, predominantly by the faecal (via biliary) route, with 10 % as the sulphoxide metabolite being excreted in the urine over a 72-hour period.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caramel 48000 or dye Lennon brown no. 112, chloroform spirit, flavour sweet orange essence, glycerol, hydrochloric acid (for pH adjustment), liquid glucose, methyl hydroxybenzoate, purified water, saccharin sodium, sucrose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and keep container well closed.

Keep in original packaging until required for use.

6.5 Nature and contents of container

100 ml is packed into a round, amber glass bottle and sealed with a round, flat topped white polypropylene screw-on child-lock cap with an expanded polyethylene liner and translucent polyethylene tamper evident band. The bottle is packed in an outer cardboard carton.

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

8. REGISTRATION NUMBER(S)

G0533 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Old medicine

10. DATE OF REVISION OF THE TEXT

11 December 2023

Botswana: B9322460 S3

Namibia: NS1 15/2.8/0125

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