

1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

COUGHCOD SENIOR 12,5 mg/10 mg/10 mg/125 mg/50 mg per 5 ml syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Mepyramine maleate.....12,5 mg

Codeine phosphate10 mg

Ephedrine hydrochloride10 mg

Ammonium chloride.....125 mg

Sodium citrate50 mg

Preservatives:

Methyl paraben0,1 % *m/v*

Propyl paraben.....0,01 % *m/v*

Contains alcohol: Ethanol (96 %)2,5 % *v/v*

Contains sugar: Sucrose 5,03 g

Contains sweeteners: Saccharin sodium 4,5 mg, sodium cyclamate 15 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

COUGHCOD SENIOR is a deep amber coloured syrup with blackcurrant flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COUGHCOD SENIOR is indicated for temporary relief of cough.

4.2 Posology and method of administration

Posology

Adults and children over 12 years: Take one to two medicines measures (5 ml to 10 ml) three times daily and at night or as prescribed.

COUGHCOD SENIOR should be used at the lowest effective dose for the shortest period.

Paediatric population

The safety and efficacy of COUGHCOD SENIOR in children aged under 12 years has not been established (see section 4.3).

Method of administration

Oral administration.

4.3 Contraindications

COUGHCOD SENIOR is contraindicated in:

- Patients with hypersensitivity to mepyramine maleate, codeine phosphate, ephedrine hydrochloride, ammonium chloride, sodium citrate or to any of the excipients in COUGHCOD SENIOR (see section 6.1).
- The presence of coronary thrombosis.

- Patients with ischaemic heart disease as ephedrine, as contained in COUGHCOD SENIOR, has positive inotropic and chronotropic effects on the heart, and therefore should be avoided.
- Closed-angle glaucoma.
- Patients with impaired hepatic or renal function.
- Patients who suffer from epilepsy i.e. convulsive disorders.
- Concomitant use with mono-amine oxidase inhibitors or within 14 days after cessation of such treatment.
- Respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and obstructive airways disease.
- During an asthma attack.
- In the presence of acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raised.
- Patients known to be CYP2D6 ultra-rapid metabolisers.
- Comatose patients.
- Patients at risk of paralytic ileus. In conditions where there is inhibition of peristalsis, is to be avoided.
- In acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis).
- In diarrhoea caused by poisoning.
- Hypertensive patients, as ephedrine which is contained in COUGHCOD SENIOR, increases blood pressure and should be avoided.
- Patients with hyperthyroidism as they may be hypersensitive or have an increased susceptibility to the effects of ephedrine.
- Patients with prostatic hypertrophy as acute urinary retention may be precipitated.
- In patients with phaeochromocytoma.

- In patients who have problems with breathing (see section 4.4).
- In children younger than 12 years (see section 4.4).
- Children (under 18 years of age) who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea.
- In pregnancy and lactation as sympathomimetics with vasoconstrictor effects may reduce placental perfusion (see section 4.6).

4.4 Special warnings and precautions for use

Codeine phosphate

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

General

Do not combine with other treatments for cough and colds.

Mepyramine maleate

General

Large doses of antihistamines such as mepyramine maleate, contained in COUGHCOD SENIOR, may precipitate convulsions.

COUGHCOD SENIOR should not be used in patients with epilepsy, hepatic and renal impairment (see section 4.3), these are contraindicated.

Administration of antihistamines may occasionally cause an allergic reaction.

Antihistamines, including mepyramine maleate, as contained in COUGHCOD SENIOR, may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.

COUGHCOD SENIOR may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents (see section 4.7).

Antimuscuranic effects

Because of the antimuscarinic actions of mepyramine maleate, as contained in COUGHCOD SENIOR, it should not be used in conditions such as angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyloroduodenal obstruction (see section 4.3).

Elderly patients

Elderly patients are also more susceptible to many of the adverse effects of antihistamines such as mepyramine maleate.

Codeine phosphate

Codeine toxicity

Codeine phosphate is not recommended for use in patients whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple traumas; or extensive surgical procedures. The symptoms of codeine toxicity may be increased in these settings (see section 4.3).

Disease states whereby reduced dosing is required

Codeine phosphate should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, chronic obstructive pulmonary disease

(COPD), prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, cardiac dysrhythmias, acute abdomen, gallstones, diseases of the biliary tract, or myasthenia gravis disease. Other disease states include prostatic hypertrophy, urethral stenosis, urethral stricture and convulsive disorders.

Codeine phosphate is metabolised by the liver and should not be used in patients with hepatic disease because increased bioavailability after oral administration or cumulative effects may occur (see section 4.3).

Renal disease also significantly alters the pharmacokinetics of codeine (see section 4.3).

Elderly

The dosage should be reduced in elderly and debilitated patients.

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.

The risk-benefit of continued use should be assessed regularly by the prescriber.

Physical dependence and withdrawal syndrome

Therapy with an opioid such as codeine phosphate, as contained in COUGHCOD SENIOR, may cause physical dependence with withdrawal syndrome.

Use with caution in those with a history of substance abuse. Discontinuation should be carried out gradually in patients who may have developed physical dependence to avoid precipitating withdrawal symptoms.

Alcohol and other central nervous system depressants.

COUGHCOD SENIOR may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants (see section 4.7).

Asthma

Use with caution or in reduced doses in asthma and decreased respiratory reserve, avoid use during an acute asthma attack (see section 4.3).

Biliary tract disorders

Opioid analgesics should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic (see section 4.3), this includes inflammatory or obstructive bowel disorders.

Monoamine oxidase inhibitor (MAOI)

Patients taking a monoamine oxidase inhibitor (MAOI) with opioid analgesics, such as codeine phosphate contained in COUGHCOD SENIOR, has been associated with very severe and sometimes fatal reactions (see sections 4.3 and 4.5).

CYP2D6 metabolism

Codeine phosphate 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. 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 that codeine phosphate 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 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 (see section 4.3).

Patients with compromised respiratory function

Codeine phosphate is not recommended for use in patients 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 (see section 4.3).

Ephedrine hydrochloride

Disease states

COUGHCOD SENIOR, containing ephedrine hydrochloride should not be used in patients who may be particularly susceptible to their effects; particularly those with hyperthyroidism (see section 4.3). Great care is also needed in patients with cardiovascular disease such as ischaemic heart disease, dysrhythmia or tachycardia, occlusive vascular disorders including arteriosclerosis, hypertension, or aneurysms. Anginal pain may be precipitated in patients with angina pectoris.

Care is also required when ephedrine hydrochloride is given to patients with diabetes mellitus. The use of COUGHCOD SENIOR in patients with close-angle glaucoma and phaeochromocytoma is contraindicated (see section 4.3).

Sympathomimetics with beta₂ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful. In patients with prostatic enlargement, COUGHCOD SENIOR may increase difficulty with micturition.

Anaesthesia and other medicines

COUGHCOD SENIOR contains ephedrine hydrochloride and should be avoided or used with caution in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics, as they may induce ventricular fibrillation. An increased risk of dysrhythmias may also occur if ephedrine as contained in COUGHCOD SENIOR is given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants (see section 4.5).

Monoamine oxidase inhibitors

Many sympathomimetics interact with monoamine oxidase inhibitors and should not be given to patients receiving such treatment or within 14 days of its termination. It is advisable to avoid sympathomimetics, as contained in COUGHCOD SENIOR, when taking MAOIs (see sections 4.3 and 4.5).

Antihypertensive therapy

COUGHCOD SENIOR, contains ephedrine hydrochloride, increases blood pressure and therefore special care is advisable in patients receiving antihypertensive therapy.

Interactions of ephedrine hydrochloride with alpha- and beta-blocking medicines may be complex. Propranolol and other beta-adrenoceptor blocking medicines antagonise the effects of beta₂ adrenoceptor stimulants (beta₂ agonists) such as salbutamol. The use of COUGHCOD SENIOR in patients with hypertension is contraindicated (see section 4.3).

Concomitant medicines

Adverse metabolic effects of high doses of beta₂ agonists as contained in COUGHCOD SENIOR, may be exacerbated by concomitant administration of high doses of corticosteroids; patients should therefore be monitored carefully when the 2 forms of therapy are used together. Hypokalaemia associated with high doses of beta₂ agonists may result in increased susceptibility to digitalis-induced cardiac dysrhythmias.

Hypokalaemia may be enhanced by concomitant administration of aminophylline or other xanthines, corticosteroids, or by diuretic therapy.

Sodium citrate

Sodium citrate, as contained in COUGHCOD SENIOR, should not be administered to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria.

Sodium containing salts should be administered extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, or aldosteronism.

Sodium citrate may enhance intestinal aluminium absorption in renal patients which may lead to increased, harmful serum aluminium levels. It has therefore been suggested that patients with renal failure taking aluminium compounds to control phosphate absorption should not be prescribed COUGHCOD SENIOR.

Excipients:

COUGHCOD SENIOR contains 5,03 g of sucrose per 5 ml of syrup. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take COUGHCOD SENIOR.

4.5 Interaction with other medicines and other forms of interaction

Mepyramine maleate

Central nervous system depressants: Alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and antipsychotics. May enhance the sedative effects of CNS depressants.

Anticholinergics:

Atropine and some antidepressants (both tricyclics and MAOIs). May have an additive antimuscarinic action with other antimuscarinic medicines.

Aminoglycoside antibacterials. Some sedating antihistamines such as mepyramine maleate as contained in COUGHCOD, could mask the warning signs of damage caused by these ototoxic medicines may be masked.

Allergen tests: Antihistamines such as mepyramine maleate as contained in COUGHCOD may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.

Codeine phosphate

Contraindicated combinations

Monoamine oxidase inhibitors (MAOIs) (e.g. moclobemide, selegiline, linezolid): Due to the possible risk of excitation or depression, avoid concomitant use and for 14 days after discontinuation of MAOIs (see sections 4.3 and 4.4).

Concomitant combinations not recommended

Alcohol or central nervous system depressants: The depressant effects of opioid analgesics are enhanced.

Cimetidine: Inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine phosphate.

Cisapride, metoclopramide or domperidone: The reduction in intestinal motility caused by codeine phosphate may delay the absorption or antagonise the gastrointestinal effects of other medicines.

Opioid antagonists (e.g. buprenorphine, naltrexone, naloxone): May precipitate withdrawal symptoms.

Ritonavir: May increase plasma levels of opioid analgesics such as codeine phosphate.

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

Anti-dysrhythmics: mexiletine, quinidine: Codeine phosphate delays the absorption of mexiletine. The analgesic activity of codeine phosphate is likely to be significantly impaired by quinidine which impairs codeine phosphate metabolism.

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

Antihistamines: Concomitant administration of codeine phosphate and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Antipsychotics: Enhanced sedative and hypotensive effect.

Tranquillisers: As an opioid analgesic, codeine phosphate may potentiate the sedative effects of tranquilisers such as barbiturates, general anaesthetics, anxiolytics and hypnotics, sedatives and alcohol.

Interference with laboratory tests: 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.

Antimuscarinics: Codeine phosphate, as contained in COUGHCOD SENIOR, may increase the risk of antimuscarinic side effects such as dry mouth, urine retention and constipation.

Rifampicin: Metabolism of codeine is accelerated by rifampicin leading to reduced effect.

Ephedrine hydrochloride

Antidepressants: With tricyclics, administration of adrenaline and noradrenaline may cause hypertension and dysrhythmias (but local anaesthetics with adrenaline appear to be safe); with MAOIs administration of inotropics such as dopamine and dopexamine may cause hypertensive crisis; also with MAOIs administration of dexamphetamine and other amphetamines, dexfenfluramine, diethylpropion, ephedrine, fenfluramine, isometheptene, methylphenidate, pemoline, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine may cause hypertensive crisis.

Antiepileptics: Increased plasma concentration of phenytoin and possibly of phenobarbitone and primidone.

Antihypertensives: Sympathomimetics in anorectics and cold and cough remedies antagonise hypotensive effects of adrenergic neuron blockers; possible risk of hypertension with apraclonidine and adrenaline or noradrenaline; hypotensive effect of some other antihypertensives may be enhanced by dexfenfluramine and fenfluramine.

Doxapram: Risk of hypertension.

Oxytocin: Hypertension with vasoconstrictor sympathomimetics.

Cyclopropane, halothane, or other halogenated anaesthetics: They may induce ventricular fibrillation.

Cardiac glycosides, quinidine: Increased risk of dysrhythmias.

Ergot alkaloids: There is an increased risk of vasoconstrictor or pressor effects with ergotamine or methysergide. Concurrent use of ergotamine not recommended (risk of gangrene).

The rate of metabolism of some other medicines is increased by ephedrine hydrochloride.

Other adrenoceptor stimulants: Concurrent use of ephedrine hydrochloride, as contained in COUGHCOD SENIOR, with theophylline may result in increased nausea, nervousness, and insomnia.

Corticosteroids: Ephedrine hydrochloride, as contained in COUGHCOD SENIOR, has been shown to increase the clearance and prolong the half-life of dexamethasone in asthmatic patients.

Urinary acidifiers/alkalinisers: Effects of ephedrine hydrochloride may be reduced by acidification and increased by alkalinisation of the urine.

4.6 Fertility, pregnancy and lactation

COUGHCOD SENIOR should not be used in pregnancy and lactation (see section 4.3).

Pregnancy

COUGHCOD SENIOR is contraindicated and should not be used in pregnancy (see section 4.3).

Codeine phosphate

Codeine phosphate, as contained in COUGHCOD SENIOR crosses the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing, and yawning) in the neonate (see section 4.8).

The administration of COUGHCOD SENIOR during labour may cause respiratory depression in the newborn infant and may prolong labour.

Ephedrine hydrochloride

Ephedrine hydrochloride readily crosses the placenta and this is associated with an increase in foetal heart rate and beat-to-beat variability.

Lactation

COUGHCOD SENIOR is contraindicated and should not be used in lactation.

Codeine phosphate

Codeine phosphate, as contained in COUGHCOD SENIOR, is distributed into breast milk.

Breastfed infants of mothers taking codeine phosphate may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultra-rapid metaboliser of codeine phosphate. It is advised that breastfeeding mothers taking codeine phosphate should be informed of the potential risk of morphine overdose and the need to monitor breastfed infants for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Breastfeeding mothers, themselves, may also develop overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation.

Ephedrine hydrochloride

The use of ephedrine hydrochloride in lactation has been associated with irritability and disturbed sleep in the infant. Breastfeeding should be regarded as a contraindication for ephedrine administration.

Fertility

There is no fertility data.

4.7 Effects on ability to drive and use of machines

COUGHCOD SENIOR has major influence on the ability to drive and use machines.

Since adverse reactions such as drowsiness, impaired concentration and blurred vision have been reported in patients receiving COUGHCOD SENIOR, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that

COUGHCOD SENIOR does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) *Tabulated list of adverse reactions*

Mepyramine maleate

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Blood and the lymphatic system disorders | | Blood dyscrasias, including agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia | |
| Immune system disorders | | | Rashes and hypersensitivity reactions (including bronchospasm, angioedema anaphylaxis and cross-sensitivity to related medicines) |
| Metabolism and nutrition disorders | | Anorexia | |
| Psychiatric disorders | | Hallucinations, irritability, nightmares, euphoria, elation | Confusion, paradoxical stimulation especially at high doses and in children or the elderly, sleep disturbances as insomnia, depression |
| Nervous system disorders | Sedation, varying from slight drowsiness to deep sleep, and including inability to concentrate, drowsiness, dizziness, fatigue, lassitude, headache, psychomotor impairment | Nervousness, ataxia, heaviness and weakness of the hands | Convulsions, paraesthesias, extrapyramidal effects, tremor |
| Eye disorders | Blurred vision | | |
| Ear and labyrinth disorders | | Tinnitus | |
| Cardiac disorders | | Palpitations, dysrhythmias, tachycardia | |
| Vascular disorders | | | Hypotension |
| Respiratory, thoracic and | Tightness of the chest, thickened | | |

| | | | |
|--------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------|---------------------------|
| mediastinal disorders | respiratory-tract secretions | | |
| Gastrointestinal disorders | Dryness of the mouth, increased gastric reflux, constipation, colic | Nausea, vomiting, diarrhoea, epigastric pain | |
| Hepatobiliary disorders | | Jaundice | |
| Skin and subcutaneous tissue disorders | | Photosensitivity | Rash, sweating, hair loss |
| Musculoskeletal and connective tissue disorders | | | Myalgia |
| Renal and urinary disorders | Difficulty in micturition, urinary retention | | |

Codeine phosphate

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|-------------------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blood and the lymphatic system disorders | | Splenomegaly, lymphadenopathy | |
| Immune system disorders | | | Maculopapular rash |
| Metabolism and nutrition disorders | | | Hyperglycaemia, anorexia, loss of appetite |
| Psychiatric disorders | | Nervousness, hallucinations, nightmares or unusual dreams, trouble in sleeping, medicine dependence | Mental depression, restlessness, confusion, mood changes, euphoria, dysphoria, addiction, sleep disturbances |
| Nervous system disorders | | Trembling or uncontrolled muscle movements, feeling faint or lightheadedness | Convulsions (especially in infants and children), dizziness, drowsiness, headache (prolonged use of a painkiller for headaches can make them worse) raised intracranial pressure |
| Eye disorders | | | Blurred or double vision or other changes in vision, miosis |
| Ear and labyrinth disorders | | Ringing or buzzing in the ears | Vertigo |
| Cardiac disorders | | | Bradycardia, palpitations, tachycardia |

| | | | |
|-------------------------------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Vascular disorders | | Increased blood pressure | Postural hypotension, facial flushing. Large doses produce hypotension, oedema |
| Respiratory, thoracic and mediastinal disorders | | Atelectasis, bronchospastic allergic reaction, allergic laryngeal oedema, allergic laryngospasm | Dyspnoea. Large doses produce respiratory depression |
| Gastrointestinal disorders | Constipation, nausea, vomiting | Dry mouth, paralytic ileus or toxic megacolon, gastrointestinal irritation, acute pancreatitis, abdominal pain | |
| Hepatobiliary disorders | | Hepatotoxicity | Biliary spasm (may be associated with altered liver enzyme values) |
| Skin and subcutaneous tissue disorders | | Contact dermatitis, burning erythematovesicular plaques, maculopapular rash | Allergic reactions such as skin rashes, urticaria, pruritus, sweating and facial oedema |
| Musculoskeletal and connective tissue disorders | | | Muscle fasciculation, rigidity |
| Renal and urinary disorders | | | Micturition difficulties, ureteric spasm, antidiuretic effect, urinary retention |
| Reproductive system and breast disorders | | | Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido |
| General disorders and administrative site conditions | | False sense of well-being, general feeling of discomfort or illness, weakness, fever, medicine tolerance | Malaise, tiredness, hypothermia |

Ephedrine hydrochloride

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|--------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Metabolism and nutrition disorders | | | Reduced appetite, altered metabolism including changes in blood sugar concentrations |
| Psychiatric disorders | Anxiety | | Fear, confusion, psychotic states, irritability, tolerance with dependence with prolonged administration |
| Nervous system disorders | Insomnia, restlessness | Headache, nervousness, drowsiness, giddiness, tremor, seizure | |
| Cardiac disorders | Palpitations, tachycardia, precordial pain, dysrhythmias | Myocardial infarction | Dyspnoea |
| Vascular disorders | | | Impaired circulation to the extremities, hypertension |
| Respiratory, thoracic and mediastinal disorders | | Chest discomfort or pain | |
| Gastrointestinal disorders | Nausea | Heartburn, thirst | Vomiting, hypersalivation, dry mouth |
| Skin and subcutaneous tissue disorders | | Sweating | |
| Musculoskeletal and connective tissue disorders | | Muscle cramps | |
| Renal and urinary disorders | | | Difficulty in micturition in large doses, urinary retention |

Ammonium chloride

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|-------------------------------------------------------------|----------|----------------------------------|--------------------------------------------------------------------|
| Metabolism and nutrition disorders | | Acidosis, hypokalaemia | |
| Nervous system disorders | | Headache, progressive drowsiness | |
| Respiratory, thoracic and mediastinal disorders | | Hyperventilation | |
| Gastrointestinal disorders | | Nausea, vomiting, thirst | |
| General disorders and administrative site conditions | | | Weakness |

Sodium citrate

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|-------------------------------------------|----------|----------------|--------------------------------------------------------------------|
| Metabolism and nutrition disorders | | Hypernatraemia | |

Post marketing experience

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|----------------------------------|----------|---------------|--------------------------------------------------------------------|
| Gastrointestinal disorder | | | Risk of abdominal pain, including pancreatitis have been reported |

b) Description of selected adverse reactions

Regular prolonged use of codeine phosphate, as contained in COUGHCOD SENIOR, 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 COUGHCOD SENIOR, 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.

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: <https://www.sahpra.org.za/Publications/Index/8>.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

Mepyramine maleate

Overdosage with sedating antihistamines, like mepyramine maleate as contained in COUGHCOD SENIOR, is associated with antimuscarinic, extrapyramidal, and CNS effects. When CNS stimulation predominates over CNS depression, which is more likely in

children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, CNS depression is more common with drowsiness, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse.

Codeine phosphate

Poisoning with codeine phosphate, as contained in COUGHCOD SENIOR produces central nervous system depression with exhilaration, miosis and slow breathing, and in children, convulsions, followed by vomiting, drowsiness, respiratory depression and cyanosis, coma, reduced levels of consciousness, somnolence, 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.

Administration should be stopped immediately in cases of overdosage.

Ephedrine hydrochloride

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

Treatment

Mepyramine maleate

Treatment is symptomatic and supportive.

Codeine phosphate

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

Intravenous injection: 0,8 to 2 mg repeated at intervals of 2 to 3 minutes to a maximum of 10 mg.

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

Subcutaneous or intramuscular injection: As 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 COUGHCOD SENIOR 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 ($< 2,8 \text{ mmol.L}^{-1}$) 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: Cough and cold preparations, cough suppressants and expectorants

ATC code: R05FB02

Mechanism of action

COUGHCOD SENIOR is a combination medicine containing mepyramine maleate, codeine phosphate, ephedrine hydrochloride, ammonium chloride and sodium citrate.

Mepyramine maleate

Mepyramine is a sedating antihistamine with antimuscarinic and sedative properties.

Codeine phosphate

Codeine is an opioid analgesic and has mild sedative effects.

Codeine depresses the cough reflex, partly by a direct effect on a cough centre in the medulla. The exact mechanism is not entirely clear. It has been suggested that the usual doses of opioids produce their major effect on the patient's subjective reactions to the cough, rather than on the frequency and intensity of coughing.

Ephedrine hydrochloride

Ephedrine is a sympathomimetic with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity and has pronounced stimulating effects on the CNS.

When given by mouth in therapeutic doses, ephedrine constricts the peripheral vessels, thus increasing blood pressure. It also relaxes bronchioles.

Ammonium chloride

Ammonium chloride is an expectorant in productive cough and has an irritant effect on mucous membranes.

Sodium citrate

Sodium citrate is a buffering or alkalinising medicine.

5.2 Pharmacokinetic properties***Mepyramine maleate*****Absorption**

Mepyramine is absorbed after oral administration. H₁ antagonists are well absorbed from the GI tract.

Distribution

Following oral administration, peak plasma concentrations are achieved in 2 to 3 hours, and effects usually last 4 to 6 hours.

Codeine phosphate

Absorption

Codeine phosphate is absorbed from the gastrointestinal tract.

Metabolism

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.

Distribution

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.

Elimination

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

Ephedrine hydrochloride

Absorption

Ephedrine is rapidly and completely absorbed after oral administration.

Metabolism

Small amounts of metabolites are produced by hepatic metabolism.

Distribution

Ephedrine is extensively distributed throughout the body with accumulation in the liver, lungs, kidneys, spleen and brain.

Elimination

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.

Ammonium chloride

Absorption

Ammonium chloride is absorbed from the gastrointestinal tract.

Metabolism

The ammonium ion is converted into urea in the liver.

Distribution

The anion thus liberated into the bloodstream and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine.

Elimination

This is followed by a transient diuresis.

Sodium citrate

Absorption

Sodium citrate is systemically absorbed.

Metabolism

Sodium citrate is metabolised after absorption to bicarbonate.

Elimination

Sodium citrate is renally eliminated, causing metabolic alkalosis and urine alkalinisation in sufficient doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Blackcurrant essence, citric acid monohydrate, Clark's caramel, ethanol (96%), invert syrup, methyl paraben, phosphoric acid (for pH-adjustment), propyl paraben, purified water, saccharin sodium, sodium cyclamate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool, dark place at or below 25 °C.

Keep in original packaging until required for use.

6.5 Nature and contents of container

COUGHCOD SENIOR is obtainable in 100 ml amber glass bottles.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

G1071 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION

Date of registration: Old Medicine

10 DATE OF REVISION OF TEXT

29 June 2023

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

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| Namibia: NS1 14/10.1/0125 |
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