SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

REKOD TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg Codeine phosphate hemihydrate.

Excipient with known effect:
Each tablet contains 20.4 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Uncoated tablets.

White, SC, round biconvex tablets, REKAH engraved on one side, plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated as an analgesic for the relief of mild to moderate pain.
For the symptomatic relief of unproductive cough.

4.2 Posology and method of administration

This medicine is not intended for children below 12 years of age.

REKOD TABLETS should only be used for the treatment of acute pain (of short duration) of mild to moderate intensity, in patients above 12 years of age, and only if the pain cannot be relieved by other analgesics such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Codeine should be used at the lowest effective dose for the shortest period of time. The duration of treatment should be limited to 3 days. If no effective pain or cough relief is achieved, the patients/carers should be advised to seek the views of a physician.

Posology

Adults, adolescents and children above 12 years of age:
1-2 tablets every 4 hours and not more than 6 tablets a day.

Paediatric population:
This medicine should not be used in children under 12 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of Administration
For oral administration.

REKOD TABLETS should be swallowed whole with a glass of water and may be administered with or without food.

There is no information available regarding the crushing, splitting, or chewing of the tablets.

4.3 Contraindications

- Hypersensitivity to the active substance codeine, or other opioids, or to any of the excipients listed in section 6.1.
- Acute respiratory depression.
- Obstructive airways disease- e.g., emphysema.
- Asthma- Opioids should not be administered during an asthma attack.
- Hepatic failure.
- Head injuries or conditions where intracranial pressure is raised
- Acute alcoholism.
- Risk of paralytic ileus.
- In adolescents aged 12 to 18 who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).
- In children below the age of 12 years due to an increased risk of developing serious and life-threatening adverse reactions.
- In women during breastfeeding (see section 4.6).
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse

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

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions. 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.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with codeine.

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 drug 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.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of **REKOD TABLETS** and sedative medicines such as benzodiazepines or related drugs 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. If a decision is made to prescribe **REKOD TABLETS** concomitantly with sedative medicines, 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 caregivers to be aware of these symptoms (see section 4.5).

REKOD TABLETS should be used with caution in the following conditions:

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- There is a possible risk of CNS excitation or depression with concomitant use of opioids with Monoamine Oxidase Inhibitors (MAOIs) and use is not recommended (see section 4.5).
- Hepatic impairment - avoid if severe. Codeine may precipitate coma.
- Renal impairment.
- Hypothyroidism.
- Inflammatory bowel disease - codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure, therefore should be used with caution in diverticulitis, acute colitis, diarrhoea associated with pseudomembranous colitis or after bowel surgery.
- Convulsions - may be induced or exacerbated.
- Drug abuse or dependence (including alcoholism).
- Gall bladder disease or gall stones - opioids may cause biliary contraction. Avoid in biliary disorders.
- Gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility.
- Urinary tract surgery – following recent surgery patients will be more prone to urinary retention caused directly by spasm of the urethral sphincter, and via constipation caused by codeine.
- Phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine.
- Prostatic hypertrophy.
- Adrenocortical insufficiency, e.g., Addison's Disease.
- Hypotension and shock.
- Myasthenia gravis.
- Reduced respiratory function or history of asthma.
- Pregnancy and breast feeding (see section 4.6).
- Elderly patients may metabolise and eliminate opioid analgesics more slowly than younger patients (due to impairment of hepatic or renal function).

CYP2D6 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. 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. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized

below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children and adolescents with compromised respiratory function

Codeine is not recommended for use in children and adolescents 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.

The patients should be instructed to refer to the patient information leaflet, which contains highlighted box at the top of the leaflet informing the patient about the risk of addiction, potential for misuse, and overdose. The box includes a reference to a patient information page that elaborates on these risks. Further information about the risk of dependence and addiction can be found at the Patient Safety Information page about the risk of dependence and addiction, following link:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_he.pdf

REKOD TABLETS contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant combinations not recommended (see section 4.4):

- MAOIs (e.g. linezolid, moclobemide, selegiline) due to the possible risk of excitation or depression – avoid concomitant use and for 2 weeks after discontinuation of MAOI.

Combinations to be used with caution:

Respiratory related

- Sedative medicines such as benzodiazepines or related drugs - the concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).
- Alcohol - enhanced sedative and hypotensive effect, increased risk of respiratory depression.
- Sedative antihistamines - enhanced sedative and hypotensive effect and increased risk of respiratory depression.
- Hypnotics and anxiolytics - enhanced sedative effect, increased risk of respiratory depression.

Gastrointestinal related

- Anticholinergics (*e.g.,* atropine) - risk of severe constipation which may lead to paralytic ileus, and /or urinary retention.
- Metoclopramide and domperidone – antagonise effect on GI activity.
- Antidiarrhoeal drugs (*e.g.,* loperamide, kaolin) – increased risk of severe constipation.

CNS related

- Anaesthetics - enhanced sedative and hypotensive effect.
- Tricyclic antidepressants - enhanced sedative effect.
- Antipsychotics - enhanced sedative and hypotensive effect.
- Opioid antagonists *e.g.,* buprenorphine, naltrexone, naloxone – may precipitate withdrawal symptoms.
- Quinidine - reduced analgesic effect.
- Antihypertensive drugs - enhanced hypotensive effect.

Pharmacokinetic interactions

- Ciprofloxacin - avoid premedication with opioids as they reduce plasma ciprofloxacin concentration.
- Ritonavir may increase plasma levels of opioid analgesics such as codeine.
- Mexiletine - delayed absorption of mexiletine.
- Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

During labour opioids enter the foetal circulation and may cause respiratory depression in the neonate. Respiratory malformation in neonates may be associated with exposure to codeine during pregnancy. Gastric stasis and a risk of inhalation pneumonia could occur in the mother during labour. Administration should be avoided during the late stages of labour and during the delivery of a premature infant.

Breast-feeding

Codeine is contraindicated in women during breast-feeding (see section 4.3).

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, 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.

Opioid toxicity

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Effects such as confusion, drowsiness, dizziness, hallucinations, blurred or double vision or convulsions may occur. The effects of alcohol are enhanced with this combination.
Do not drive or operate machinery if affected.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.

4.8 Undesirable effects

- **Psychiatric disorders:** frequency unknown; drug dependence (see section 4.4).
- **Immune system disorders:** (may be caused by histamine release) – including rash, urticaria, pruritus, difficulty breathing, increased sweating, redness or flushed face.
- **Nervous system disorders:** confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation

(restlessness/excitement), convulsions, mental depression, headache, or nightmares, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia.

- **Eye disorders:** - miosis, blurred or double vision.
- **Cardiac disorders:** bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia.
- **Respiratory, thoracic and mediastinal disorders:** respiratory depression with larger doses.
- **Gastrointestinal disorders:** constipation (too constipating for long-term use), biliary spasm, nausea, vomiting, dry mouth.
- **Musculoskeletal, connective tissue and bone density:** muscle rigidity.
- **Renal and urinary disorders:** ureteral spasm, antidiuretic effect, urinary retention.
- **Reproductive system and breast disorders:** decrease in libido and potency.
- **Withdrawal effects:** uncommon; abrupt withdrawal precipitates drug withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration, and increase in heart rate, respiratory rate and blood pressure. NOTE - tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.
- Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.
- Prolonged use of a painkiller for headaches can make them worse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5mg/kg.
Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code R05D A04.

Codeine is an analgesic with uses similar to those of morphine, but it is much less potent as an analgesic and has only mild sedative effects. It is also used in the treatment of cough.

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

5.2 Pharmacokinetic properties

Absorption and Distribution
Codeine and its salts are readily absorbed from the gastrointestinal tract and ingestion of codeine phosphate produces peak plasma concentrations in about one hour. Plasma half-life is between 3 to 4 hours and oral/intramuscular analgesic ration is ≅ 1:1.5.

Biotransformation
It is a metabolised by O- and N-demethylation in the liver to morphine and norcodeine.

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

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Strach, Lactose, Talc, Powdered Cellulose (Elcema), Gelatin, Magnesium Stearate, Purified Water.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the medical product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

PVC-Aluminium blisters.

Pack size: 10, 30 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Rekah Pharmaceutical Industry Ltd., 30 Hamelacha St., Holon, 5881904, Israel.

8 MARKETING AUTHORISATION NUMBER

022-09-20913-00

Revised in December 2024 according to MOH guidelines.