SUMMARY OF PRODUCT CHARACTERISTICS

COD ACAMOL® 15/325

TABLETS

BOXED WARNINGS

WARNING: Death related to ultra-rapid metabolism of codeine to morphine respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (see section 4.3 contra indications and section 4.4.Special warnings and precautions for use).

1. NAME OF THE MEDICINAL PRODUCT

COD ACAMOL® 15/325

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Paracetamol 325 mg
Codeine phosphate 15 mg

Excipients with known effect:
Each tablet contains 78.66 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Light blue round flat tablets with white flakes and beveled edges, Scored in half on one side, debossed "IKA' on the other side.
There is no information regarding chewing or crushing the tablets.
The tablets may be divided.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Relief of mild to moderate pain.
Relief of fever and cough associated with fever.
For usage in children see section 4.4 "Special warnings and precautions for use".

4.2. Posology and method of administration

Method of administration: Oral

Adults and Adolescents above the age of 12 Years
1-2 tablets every 4-6 hours, as needed.
Dosage should not exceed 8 tablets in 24 hours.

This product should only be taken for a maximum of 3 days at a time. If needed to be taken for longer than 3 days the physician should be consulted
If this medicine is taken for headaches for more than three days it can make them worse.

4.3. Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Children under 12 years of age.
- Cod Acamol is contraindicated in patients with moderate to severe degrees of renal or hepatic impairment.
- It is contraindicated in patients for whom opiate medications should not be used, such as patients with acute asthma, obstructive airway disease, respiratory depression, acute alcoholism, head injuries, raised intracranial pressure, after biliary surgery, patients suffering from diarrhoea of any cause, and patients who have taken MAOIs within 14 days.
- In all paediatric patients (0-18 years of age) 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 women during breastfeeding (see section 4.6)
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolizers (see section 4.4).

4.4. Special warnings and precautions for use

The efficacy and safety of Cod Acamol tablets in children below the age of 12 years has not been established, and use in such children is contraindicated.

Cod Acamol tablets must be used with caution in patients with increases intracranial pressure, debilitated, impaired hepatic or renal function, and urethral stricture. (See also "Contraindications". Note particularly that Cod Acamol is contraindicated in patients with severe renal or hepatic impairment.)

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal

effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy, hypothyroidism and those with acute abdominal conditions like inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.
Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGM A), particularly in patients with severe renal impairment, sepsis, malnutrition, and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol.
Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of opioids causes 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 online, 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 Cod Acamol 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 Cod Acamol 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).

CYP2D6 metabolism
Codeine is metabolized 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 metabolizer 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 metabolizer 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 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.

Overdosage in patients with non-cirrhotic alcoholic liver disease can be hazardous. The hazard of paracetamol overdose is greater in those with alcoholic liver disease.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Drug dependence of the morphine type can be produced by the Codeine, and the potential for drug abuse with codeine must be considered. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

Patients must be advised not to exceed the recommended doses.

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking Cod Acamol, and to consult their doctor if symptoms persist.

The cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

Children

Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.[2]

Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.

Children and adolescents (aged below 18 years) with conditions associated with breathing problems must not use codeine (see Contraindications).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see Contraindications).

Rare but serious skin reactions

Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.

Anyone who develops a skin rash or reaction while using paracetamol should **stop the drug** and seek medical attention right away. Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free.

4.5. Interaction with other medicinal products and other forms of interaction

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.

Quinine or quinidine may inhibit the analgesic actions of codeine.

The CNS depressant action of Cod Acamol may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Cod Acamol and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and coadministration with an antimuscarine drug may cause urinary retention.

The absorption of paracetamol is speeded by metoclopramide or domperidone, and absorption is reduced by cholestyramine.

Codeine may delay the absorption of mexiletine, and cimetidine may inhibit codeine metabolism.

Opioids may interfere with the results of plasma amylase, lipase, bilirubin, ALP, LDH, AST, and ALT tests.

The effects of codeine on the gut may interfere with diagnostic tests of gastro-intestinal functions.

The anticoagulant effect of warfarin and other coumarins may be increased by long term regular daily use of paracetamol, with increased risk of bleeding. Occasional doses of paracetamol do not have a significant effect on these anticoagulants.

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).

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

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

4.6. Fertility, pregnancy and lactation

Pregnancy:

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

Breast-feeding:

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant.[9]

If the patient is an ultra-rapid metabolizer 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.

Fertility:

No data available

4.7. Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if Cod Acamol causes dizziness or sedation. Codeine may cause visual disturbances.

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

The information below lists reported adverse reactions, ranked using the following frequency classification:

common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100) ; very rare (<1/10,000) and not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse effects
Blood and lymphatic system disorders	Not known	Thrombocytopenia, Agranulocytosis*
Immune system disorder	Not known	Hypersensitivity (including skin rash)
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[d]

Psychiatric disorders	Not known	Dysphoria Euphoria Drug dependence (see section 4.4),
Nervous system disorders	Common Not known	Dizziness[c] Light-headedness[c] Sedation[c] Headache
Eye Disorder	Not known	Miosis visual disturbances
Cardiac disorders	Not known	Bradycardia
Ear and labyrinth disorders	Not known	Hearing loss
Respiratory, thoracic and mediastinal disorders	Common Not known	Shortness of breath[c] Respiratory depression[a]
Gastrointestinal disorders	Common Not known	Nausea[c] Vomiting[c] Constipation[c] , Abdominal pain,
Hepatobiliary disorders	Not known	Liver damage[b]
Skin and subcutaneous tissue disorders	Not known	Pruritus
Renal and urinary disorders	Not known	Difficult micturition Urinary retention
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome

[a] Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function.

[b] Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

[c] Some of these side effects appear more common in ambulatory: rather than non- ambulatory patients. Lying down may alleviate these effects they occur.

[d]Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

* There have been some reports of blood dyscrasias- Thrombocytopenia and argranulocytosis, with the use of paracetamol- containing products, but the causal relationship has not been established.[9]

Prolonged use of a pain killer 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.

Paracetamol

Symptoms

Symptoms of overdosage with paracetamol in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. In 12 to 48 hours liver damage may become apparent, together with abnormalities of glucose metabolism, and metabolic acidosis.

Liver damage has occurred in adults taking 10g or more of paracetamol. Excess quantities of a toxic metabolite become irreversibly bound to liver tissue, and immediate treatment is essential. Patients ingesting 7.5g or more of paracetamol in 4 hours should be referred to hospital urgently.

Overdose with paracetamol can commonly cause acute hepatic necrosis with severe liver damage and may lead to fulminant hepatic failure, which is usually fatal. In severe overdose hepatic failure may progress to encephalopathy, coma and death. Even in the absence of severe liver damage, acute renal failure due to acute tubular necrosis may develop without hepatic failure.

There are no specific early signs of severe poisoning with paracetamol. Consciousness is not usually impaired, and maximum abnormality of liver function tests is delayed for at least three days. Liver damage is caused by conversion of paracetamol to a highly reactive metabolite. Necrosis does not occur unless hepatic glutathione is depleted.

Early treatment of paracetamol overdose with agents which facilitate glutathione synthesis, for example N-acetylcysteine and methionine, can prevent liver damage, renal failure, and death. Treatment must be started within 8 to 10 hours, and is not effective if delayed beyond 15 hours.

Cardiac arrhythmias and pancreatitis have been reported.

Codeine

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 pinpoint 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 350mg 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: Opioids in combination with non-opioid analgesics,

ATC code: N02AJ06

Paracetamol (N02B E51) has analgesic and antipyretic actions. It is a weak inhibitor of prostaglandin biosynthesis. Single or repeated therapeutic doses of paracetamol do not affect the cardiovascular or respiratory systems. Gastric irritation, erosion, or bleeding is not produced by paracetamol. There is minimal effect on platelets, no effect on bleeding time or excretion of uric acid.

Codeine (N02A A59) 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.
Codeine affects the CNS and the gut, including analgesia, drowsiness, mood changes, respiratory depression, reduced gastrointestinal motility, nausea or vomiting, changes in the endocrine and autonomic nervous system. Codeine's effect on pain relief is selective, and it does not affect other sensations such as touch, vibration, vision, or hearing.

5.2. Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half- life varies from about 1-4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent. A minor hydrolated metabolite which is usually produced in very small amounts by mixed function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Codeine and its salts are absorbed from the gastro-intestinal tract and peak plasma concentrations are produced in about 1 hour. It is metabolized in the liver to morphine and norcodeines. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life is between 3 and 4 hours.

5.3. Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose, lactose monohydrate, gelatin, sodium starch glycolate , magnesium stearate, colloidal silicon dioxide, col. FD&C blue No. 1 lake 12%.

6.2. Incompatibilities

None relevant

6.3. Shelf life

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

6.4. Special precautions for storage

Store in a dry place below 25°C.

6.5. Nature and contents of container

PVC/aluminium blister
Pack size of 10 tablets.

6.6. Special precautions for disposal and other handling

None

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel LTD
124 Dvora HaNevi'a St., Tel Aviv Israel

8. REGISTRATION NUMBER

040.04.22978

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