SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codipar 15mg/500mg Capsules
Co-codamol 15mg/500mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Paracetamol 500mg and Codeine Phosphate 15mg.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule
red (cap) and white (body) coloured hard gelatine capsules (size 0) filled with a homogenous white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of moderate pain

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Posology

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).

Adults: The usual dose is one or two capsules every four to six hours as required up to a maximum of 8 capsules in any 24 hour period.

Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose should not exceed 240 mg.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Elderly: A reduced dosage may be necessary.

Paediatric population:

Children aged 16-18 years: 1-2 capsules every 6 hours when necessary up to a maximum of 8 capsules in 24 hours.

Children aged 12 – 15 years: 1 capsule every 6 hours when necessary up to a maximum of 4 capsules in 24 hours.

Children aged less than 12 years:

"Codeine should not be used in children below the age of 12 years 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).

Dosage needs to be adjusted according to the severity of pain and the response of the patient.

Tolerance to Codeine can develop with continued use. The incidence of unwanted effects is dose related. Doses of Codeine above 60 mg are associated with an increase in unwanted effects.

Method of administration Oral

Treatment goals and discontinuation

Before initiating treatment with Copaz/Codipar/Co-codamol, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of

adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Copaz/Codipar/Co-codamol should not be used longer than necessary

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.

This medicine 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 metabolisers.

4.4 Special warnings and precautions for use

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Copaz/Codipar/Co-codamol. Repeated use of Copaz/Codipar/Co-codamol can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Copaz/Codipar/Co-codamol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental

health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Copaz/Codipar/Co-codamol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

The efficacy and safety of this medicine in children below the age of 12 years has not been established and use in such children is contraindicated.

This medicine must be used with caution in patients with increases intracranial pressure, the debilitated, impaired hepatic or renal function and urethral stricture. (See also “Contraindications”. Note particularly that this medicine is contraindicated in patients with severe renal or hepatic impairment.)

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.

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.

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. As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine has to be administered with caution in patients with pancreatitis and diseases of the biliary tract

Risk from concomitant use of sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids:

Concomitant use of Codipar/ Co-codamol capsules and sedative medicines (such as benzodiazepines or related drugs) may result in profound sedation, respiratory depression, hypotension, coma or death. Because of these risks, concomitant prescribing with these sedative medicines or gabapentinoids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Codipar/Co-codamol capsules 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 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 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%

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of

CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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 this medicine, and to consult their doctor if symptoms persist.

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

The leaflet will state in a prominent position in the 'before taking' section

•Do not take for longer than directed by your prescriber

•Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop taking the capsules.

•Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack- not boxed):

•Do not take for longer than directed by you prescriber as taking codeine regularly for a long time can lead to addiction.

4.5 Interaction with other medicinal products and other forms of interaction

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).

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 this medicine may be enhanced by co-administration 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 this medicine 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 coadministartion with an antimuscarine drug may cause urinary retention.

The absorption of paracetamol is speeded by metaclopramide or domperidone, and absorption is reduced by colestyramine.

Codeine may delay the absorption of mexilitine, 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) and Gabapentinoids (gabapentin and pregabalin):

The concomitant use of opioids with sedative medicines (such as benzodiazepines or related drugs) or Gabapentinoids (gabapentin and pregabalin) increases the risk of profound sedation, respiratory depression, hypotension, coma or death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (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 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.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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.

If the patient is an ultra-rapid metaboliser of CYP2D6, higher levels 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.

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.

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 this medicine 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. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. 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
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Reported adverse reactions appear more common in ambulatory: rather than non- ambulatory patients. Lying down may alleviate these effects they occur. Lying down may alleviate these effects they occur.
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) and not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Adverse effects**
Blood and lymphatic system disorders	Not known	Blood disorder*, Thrombocytopenia*, Agranulocytosis*
Immune system disorder	Not known	Hypersensitivity (including skin rash)[a]
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis[c]
Psychiatric disorders	Not known	Dysphoria , Euphoria, Drug dependence (see section 4.4), Restlessness, Irritability
Nervous system disorders	Common	Dizziness, Light-headedness, Sedation, Headache
Eye Disorder	Not known	Miosis, visual disturbances
Cardiac disorders	Not known	bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Shortness of breath,
	Not known	Respiratory depression[a]
Gastrointestinal disorders	Common	Nausea vomiting Constipation
	Not known	Abdominal pain, Pancreatitis
Hepatobiliary disorders	Not known	Liver damage[b,] sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Not known	Pruritus, Rash
Renal and urinary disorders	Not known	Difficult micturition and 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]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 agranulocytosis, with the use of paracetamol-containing products, but the causal relationship has not been established.

Prolonged use of a pain killer for headaches can make them worse.

Drug dependence

Repeated use of Copaz/Codipar/Co-codamol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable) but results should not delay initiation of treatment beyond 8 hours after ingestion, as the effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

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 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 5 mg/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 effects 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 effect other sensations such as touch, vibration, vision, or hearing.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract. It is metabolised in the liver and undergoes extensive biotransformation. The major metabolites are inactive phenolic sulphate and glucuronide conjugates. An adequate supply of SH groups can prevent hepatic toxicity. Paracetamol is excreted in the urine. The elimination half life varies from about 1 to 4 hours.

Codeine is absorbed from the gastro-intestinal tract and peak plasma concentrations are produced in about 1hour. It is metabolised in the liver to morphine and norcodeines. Codeine and its metabolites are excreted almost entirely by the kidney. The plasma half line 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

Maize Starch
Sodium Lauryl sulfate
Cross carmellose sodium
Purified Talc
Magnesium Stearate
Gelatin
Titanium dioxide E171
Erythrosine E127
Red Iron Oxide E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC

6.5 Nature and contents of container

Blister strips of PVDC coated PVC /Aluminium , 10 capsules per strip
In pack size of 30, 32 or 100 capsules.

6.6 Special precautions for disposal

No special requirements for disposal

Any unused medical product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd
Dashwood House,
69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0413

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/10/2024

10 DATE OF REVISION OF THE TEXT

10/03/2026