SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 15/500 Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg paracetamol and 15mg codeine phosphate hemihydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Co-codamol 15/500 Tablets are white to off-white capsule-shaped tablets, marked PRO 15 and scored on one side with a plain reverse.

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

Adults:
Two tablets every four to six hours when necessary, up to a maximum of eight tablets in 24 hours.

Elderly:

The adult dose is appropriate (please refer to section 4.4 for additional information on elderly patients).

Paediatric population
Children aged 16 to 18 years:
One to two tablets every 6 hours when necessary, up to a maximum of eight tablets in 24 hours.

Children aged 12 to 15 years:
One tablet every six hours when necessary, up to a maximum of four tablets 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 section 4.3 and 4.4).

Do not take for more than 3 days without consulting your doctor.
The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Method of administration
For oral administration. The tablets are to be taken whole.
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Treatment goals and discontinuation
Before initiating treatment with 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).

4.3 Contraindications

- Hypersensitivity to the active substances or any of the other excipients listed in section 6.1.
- Conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure, hepatocellular insufficiency and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or 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 Co-codamol. Repeated use of 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 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 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.

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 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..

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

Concomitant use of co-codamol 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 co-codamol 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).

Sleep related breathing disorders including central sleep apnoea

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.

Risks from concomitant use of opioids and alcohol

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (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 metabolisers in different populations are summarised 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%

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 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

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.

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.

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/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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 ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

Use with caution in patients with convulsive disorders.

Patients should be advised not to exceed the recommended dose and not take other paracetamol-containing products concurrently.

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

Co-codamol 15/500 Tablets should be used upon medical advice in patients with:

- Mild-to-moderate hepatocellular insufficiency
- Severe renal insufficiency

  Monitoring after prolonged use should include blood count, liver function and renal function.

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

- Do not take for longer than your doctor tells you to.
- This medicine contains paracetamol. Do not take anything else containing paracetamol while taking this medicine.
- 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 your prescriber as taking codeine regularly for a long time can lead to addiction.
- Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine even if you feel well.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of CNS depressants (including other opioid analgesics, tranquilisers, sedative hypnotics and alcohol) may be potentiated by codeine. When such therapy is contemplated, the dose of one or both agents should be reduced.

Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression.

Concomitant use of Co-codamol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

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).

Concomitant administration of MAOI (e.g. tranylcypromine) can potentiate the central nervous effects and other side effects of unpredictable severity, Co-codamol should not be used within two weeks after the discontinuation of MAOI treatment.

<u>Sedative medicines such as benzodiazepines or related drugs:</u>
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 duration of concomitant use should be limited (see section 4.4).

<u>Alcohol and opioids</u>
The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

Concurrent use of MAO inhibitors or tricyclic antidepressants with codeine may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Concurrent use of anticholinergics and codeine may produce paralytic ileus.

Isoniazid may increase the risk of hepatotoxicity with therapeutic doses of paracetamol. Antiepileptics, such as carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol and increase the risk of hepatotoxicity.

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Codeine
There is inadequate evidence of the safety of codeine in human pregnancy. Animal studies with codeine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Paracetamol
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.

Co-codamol
As a precautionary measure, it is preferable to avoid the use of co-codamol during 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.

Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount.

Co-codamol 15/500 Tablets is contraindicated during breast-feeding (see section 4.3), as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility
There are no data on the effects of co-codamol on human fertility. Fertility was unaffected following paracetamol or codeine treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

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

- 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.

The information below lists reported adverse reactions, ranked using the following frequency classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system
Not known: blood dyscrasias including thrombocytopenia and agranulocytosis

Immune system disorders
Not known: anaphylactic shock, angioedema, allergic reactions (hypersensitivity) including skin rash

Respiratory, thoracic and mediastinal disorders
Not Known: Respiratory depression

Hepatobiliary disorders
Not known: sphincter of Oddi dysfunction

Psychiatric disorders
Not Known: Confusional state, dysphoria, euphoria, drug dependence (see section 4.4)

Nervous system disorders
Not known: dizziness, light-headedness, seizure, headache, somnolence

Eye disorders
Not Known: Miosis

Ear and labyrinth disorders
Not known: ototoxicity leading to sensorineural hearing loss.

Gastrointestinal disorders
Not known: pancreatitis, constipation, nausea, vomiting, dry mouth

Skin and subcutaneous tissue disorders
Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders
Not known: high anion gap metabolic acidosis.

Renal and urinary disorders
Not known: urinary retention

General disorders and administration site conditions
Uncommon: drug withdrawal syndrome

Description of selected adverse reactions

Drug dependence
Repeated use of 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).

High anion gap metabolic acidosis
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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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:
- is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes, or
- regularly consumes ethanol in excess of recommended amounts, or

- is likely to be glutathione depleted 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, disseminated intravascular coagulation, 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). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. 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. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

Further measures will depend on the severity, nature and course of clinical symptoms of paracetamol intoxication and should follow standard intensive care protocols.

Codeine

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

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 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.

The opioid antagonist naloxone hydrochloride is an antidote to respiratory depression and must be administered intravenously.

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paracetamol, combinations excl. Psycholeptics
ATC Code: N02B E51

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

Codeine is a centrally acting weak analgesic. Codeine exerts its effects 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

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration in plasma reaches a peak in 30-60 minutes. Plasma half-life is 1-4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids, plasma protein binding is variable.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86% is excreted in the urine in 24 hours; 40-70% if free or conjugated morphine, 5-15% is free or conjugated norcodeine.

The bioavailabilities of paracetamol and codeine, when given as the combination, are similar to those when they are given separately.

5.3 Preclinical safety data

<u>Paracetamol</u>
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

Pregelatinised starch
Maize starch
Povidone
Potassium sorbate
Microcrystalline cellulose
Stearic acid
Purified Talc
Magnesium stearate
Croscarmellose sodium (type A)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

PVC (250µm)/20µm Aluminium child resistant foil / 15µm PVC blister packs
Or
PVC (250µm)/35gsm glassine/9µm Aluminium child resistant foil blister packs

Pack sizes: 100 tablets.

6.6 *Special precautions for disposal*

No special requirements

7. MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
12 New Fetter Lane
London
EC4A 1JP
United Kingdom

Trading as
Zentiva, 12 New Fetter Lane, London, EC4A 1JP, UK

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PL 17780/0500

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10 DATE OF REVISION OF THE TEXT

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