

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 30/500 Effervescent Tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 500mg paracetamol and 30mg codeine phosphate hemihydrate.

Excipients with known effect:

Each tablet contains 50mg of sorbitol and 388mg of sodium.  
For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Effervescent Tablets.

White bevelled-edge tablets, scored on one face.

### 4.1 Therapeutic indications

For the relief of severe 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

Do not take continuously for more than 3 days without consulting your doctor.

#### Adults:

Two tablets, to be dissolved in a glass of water, every 4 hours when necessary up to a maximum of 8 tablets in 24 hours.

#### Elderly

As for adults, however a reduced dose may be required. See warnings.

#### Children aged 16 to 18 years:

One to two tablets every 6 hours when necessary up to a maximum of four doses in 24 hours.

#### Children aged 12 to 15 years:

One tablet every 6 hours when necessary to a maximum of four doses in 24 hours.

#### Paediatric population

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).

#### Method of administration

For oral administration.

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.

#### 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 paracetamol, codeine or any of the other constituents.
- Conditions where morphine and opioids are contraindicated eg, acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure 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, particularly 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.

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.

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).

#### 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).

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

Use with caution in patients with convulsive disorders.

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

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.

#### 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 population are summarised below:

<b>Population</b>	<b>Prevalence %</b>
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.

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.

### 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.

Co-codamol 30/500 Effervescent 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.

#### 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.

#### Co-codamol contains sodium and sorbitol

Sodium: This medicinal product contains 388 mg sodium per effervescent tablet, equivalent to 19.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sorbitol: This medicine contains 50mg sorbitol per tablet. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

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 colestyramine.

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.

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).

#### 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 and opioids

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).

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.

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

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.

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.

The effects of CNS depressants (including alcohol) may be potentiated by codeine.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There is inadequate evidence of the safety of codeine in human pregnancy, but there is epidemiological evidence for the safety of paracetamol. Both substances have been used for many years without apparent ill consequences and animal studies have not shown any hazard. Nonetheless careful consideration should be given before prescribing the products for pregnant patients. A large amount of data on pregnant women indicate neither malformative, nor fetoneonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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.

Results of one case control study suggest that there might be an increased risk of malformations of the respiratory tract in the offspring of women who consumed codeine during the first four months of pregnancy. This increase was statistically not significant. Evidence of other malformations is also reported in epidemiological studies on narcotic analgesics, including codeine.

##### Breastfeeding

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

Co-codamol 30/500 Effervescent Tablets are contraindicated during breast-feeding (see section 4.3). as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

#### **4.7 Effects on ability to drive and to use machines**

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Tolerance and dependence can occur, especially with prolonged high dosage of codeine.

There have been very rare occurrences of pancreatitis.

##### Immune system disorders

Hypersensitivity including skin rash may occur.

Not known: anaphylactic shock, angioedema

##### Blood and the lymphatic system disorders

Not known: blood dyscrasias including thrombocytopenia and agranulocytosis

#### Respiratory, thoracic and mediastinal disorders

Not Known: Respiratory depression

#### Skin and subcutaneous tissue disorders

Very rare cases of serious skin reactions have been reported.

#### Psychiatric disorders:

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

#### Nervous system disorders

Not Known: Seizure, headache, somnolence, dizziness

#### Eye disorders

Not Known: Miosis

#### Gastrointestinal disorders

Not Known: Constipation, vomiting, nausea, dry mouth

#### Hepatobiliary disorders

Not known: sphincter of Oddi dysfunction.

#### General disorders and administration site conditions:

Uncommon: drug withdrawal syndrome

#### Metabolism and nutrition disorders

Not known: high anion gap metabolic acidosis.

#### Description of selected adverse reactions

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.

#### 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).

#### 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](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

### **Codeine**

Nausea and vomiting are prominent symptoms of codeine toxicity and if there is evidence of circulatory and respiratory depression, suggested treatment is gastric lavage and catharsis. If CNS depression is severe, assisted ventilation, oxygen and parenteral naloxone may be needed. 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.

In general, treatment should be symptomatic: re-establish adequate respiratory exchange by ensuring a clear airway and using mechanical ventilation.

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.

### **Paracetamol**

Patients in whom oxidative liver enzymes have been induced, including alcoholics and those receiving barbiturates and patients who are chronically malnourished, may be particularly sensitive to the toxic effects of paracetamol in overdose.

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, gastrointestinal bleeding, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is likely in adults who have taken 10g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

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 and any patient who had ingested around 7.5g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine, which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.

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

## **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 effect through  $\mu$  opioid receptors, although codeine has low affinity for those 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**

Following oral administration of two effervescent tablets (ie, a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 20.4  $\mu\text{g/ml}$  and 218.8ng/ml respectively. The mean times to maximum plasma concentrations were 0.34 hours for paracetamol 0.42 hours for codeine phosphate.

The mean AUC for the 10 hours following administration was 50.0 $\mu\text{g.ml}^{-1}.\text{h}$  for paracetamol and 450.0  $\text{ng/ml}^{-1}.\text{h}$  for codeine.

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

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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**

Sodium bicarbonate, anhydrous citric acid, anhydrous sodium carbonate, sorbitol powder, saccharin sodium, povidone, dimethicone, sodium lauryl sulphate.

## **6.2 Incompatibilities**

Not applicable

## **6.3 Shelf life**

4 years in PFPF strips  
3 years in Surlyn laminate strips.

## **6.4 Special Precautions for Storage**

Do not store above 25°C. Store in the original package.

## **6.5 Nature and contents of container**

PFPF strips in cardboard cartons.  
Pack sizes: 4, 12, 30, 60 and 100 tablets.

Surlyn laminate strips in cardboard cartons.  
Pack sizes: 4, 12, 30, 60 and 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

## **8. MARKETING AUTHORISATION NUMBER**

PL 17780/0046

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

04/03/2009

**10 DATE OF REVISION OF THE TEXT**

05/03/2026