SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-codamol 8/500 Effervescent Tablets / Soluble Paracetamol and Codeine Tablets / Paracetamol & Codeine Effervescent Tablets (Co-codamol).
Co-codamol Effervescent Tablets

2.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 500mg paracetamol and 8mg 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 Tablet
Flat white tablet with bevelled edges

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone such as headaches, migraine, neuralgia, toothache, dysmenorrhoea and rheumatic 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 and the elderly:

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.

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 healthcare professional.

Treatment goals and discontinuation

Before initiating treatment with Co-Codamol treatment duration and treatment goals should be agreed together with the patient, in accordance with pain management guidelines.

4.3 Contraindications

- Hypersensitivity to paracetamol, codeine phosphate or any of the other constituents.
- 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).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. 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.

Care is advised in the administration of paracetamol to patients with severe renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease. Do not exceed the recommended dose.

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).

The recommended dose should not be exceeded. This medicine should not be taken with any other paracetamol-containing products. If symptoms persist, the patient should be advised to consult their doctor. The patient should be advised to see immediate medical advice in the event of an overdose, even if they feel well, because of the risk of delayed, serious liver damage.

Use with caution in patients with convulsive disorders.

The label will state:

Front of pack
- Can cause addiction
- For three days use only
- For pain relief

Back of pack

- For the short term treatment of acute moderate pain when other painkillers have not worked. Wait at least 4 hours after you last took other painkillers before taking this medicine.
- Headache, migraine, toothache, neuralgia, period pains and rheumatic pains
- If you need to take this medicine for more than 3 days you should see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. If you take this medicine for headaches for more than 3 days it can make them worse.

The leaflet will state:

Important things you should know about co-codamol
- This medicine can only be used the short term treatment of acute moderate pain when other painkillers have not worked
- You should only take this product for a maximum of 3 days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it
- If you take this medicine for headaches for more than 3 days it can make them worse

Section 1: What co-codamol is and what it is used for
- It is an analgesic (painkiller) and is for the short term treatment of acute moderate pain caused by headaches, migraine, toothache, neuralgia, period pain and rheumatic pains when other painkillers have not worked. Wait at least 4 hours after you last took other painkillers before taking this medicine.

Section 2: Before you take co-codamol
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it
- If you take a painkiller for headaches for more than 3 days it can make them worse

Section 3: How to take co-codamol
- Do not take for more than 3 days. If you need to use this medicine for more than 3 days you must speak to your doctor or pharmacist
- This medicine contains codeine and can cause addiction if you take it continuously for more than 3 days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: Possible side effects
This will appear at the end of section 4
How do I know if I am addicted?
If you take this medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:
- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose
- When you stop taking this medicine you feel very unwell but you feel better if you start taking the medicine again

<u>CYP2D6 metabolism</u>

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%

Paediatric population

Not recommended for children under 12 years of age.

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.

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.

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 8/500 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.

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

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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 daily 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dose. 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 if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Codeine can cause respiratory depression and withdrawal syndrome in newborns.

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.

Codeine has been used for many years without apparent ill consequence and animal studies have not shown any hazard.

Patients should follow the advice of their doctor regarding the use of this product.

Breastfeeding

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Codeine should not be used during breastfeeding (see section 4.3). Co-codamol 8/500 Effervescent Tablets are contraindicated during breast-feeding.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

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 (≥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).

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, drowsiness, confusion 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 lymphatic system disorders

Not Known: agranulocytosis, thrombocytopenia

Respiratory, thoracic and mediastinal disorders

Not Known: Respiratory depression

Skin and subcutaneous disorders

Very rare cases of serious skin reactions have been reported.

Psychiatric disorders

Not Known: Confusional state, dysphoria, euphoria

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.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Symptoms
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 deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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 haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding 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 serious hepatic dysfunction beyond 24h from ingestion should be discussed with the 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.

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: Anilides, Paracetamol combinations

ATC Code: N02B E51

Paracetamol is a well-established analgesic and antipyretic.

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

5.2 Pharmacokinetic properties

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% is free or conjugated morphine and 10-20% is free or conjugated Norcodeine.

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.

6.1 List of excipients

Sorbitol
Saccharin sodium
Sodium hydrogen carbonate (sodium bicarbonate)
Polyvidone (povidone)
Sodium lauryl sulfate
Anhydrous citric acid
Anhydrous sodium carbonate
Dimeticone (dimethicone)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Paper/PE/Aluminium/PE (PPFP laminate) - 48 months.
Paper/PE/Aluminium/Copolymer (Surlyn laminate) – 36 months

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Individually packed into paper, polyethylene, aluminium foil and polyethylene or ionomer laminate strips in cardboard carton.

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(S)

PL 17780/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/03/2009

10 DATE OF REVISION OF THE TEXT

13/04/2026