

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Codamol 8/500 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Co-Codamol 8/500 mg Effervescent Tablets contain:

Paracetamol BP 500mg
Codeine Phosphate BP 8mg
Excipient(s) with known effect
Each tablet also contains sodium and sorbitol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablets

4.1 Therapeutic indications

For the relief of severe pain.

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

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).

Posology

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

Duration of treatment

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.

Adults: Two tablets, to be dissolved in a glass of water, every 4 to 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Elderly: As 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 up to a maximum of four doses in 24 hours.

Paediatric population:

Not recommended for children under 12 years of age. This is because of codeine risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of administration

For oral administration.

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. 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 substance(s) or to any of the 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
- following biliary tract surgery
- breast-feeding (see section 4.6)

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 all patients for whom it is known that 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.

For patients who experience signs and symptoms of OUD, and/or exhibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

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. This medicinal product contains 868 mg sodium per dose (two tablets), equivalent to 43.4 % of the WHO recommended maximum daily intake for sodium (2g).

The maximum daily dose of this product (eight tablets) is equivalent to 173.5% of the WHO recommended maximum for daily intake for sodium. Co-codamol is considered high in sodium. This should be taken into account for those on a low salt diet.

Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

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.

CYP2D6 metabolism

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not be obtain an adequate analgesic effect. 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 ones. 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%

The leaflet will state in the “pregnancy and breast-feeding” subsection of the section 2 “Before taking your medicine”:

Co-codamol is contraindicated in breast-feeding.

Post-operative use in children

There have been reports in the published literature that codeine given postoperatively 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.

Risks 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).

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).

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 and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

Co-codamol should be used upon medical advice in patients with:

- Severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

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

Patients should be advised to consult a doctor should symptoms persist and to keep the product out of the sight and reach of children.

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.

Caution is advised in patients with underlying sensitivity to aspirin and/or to nonsteroidal anti-inflammatory drugs (NSAIDs).

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 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 the tablets.

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.

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).

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.

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.

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

CYP2D6 inhibitors

Codeine is metabolised by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine.

Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers

Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and rifampicin should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

4.6 Fertility, Pregnancy and lactation

Careful consideration should be given prescribing the product for pregnant patients. Regular use during pregnancy may cause 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.

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.

As a precautionary measure, Co-Codamol should be avoided during the third trimester of pregnancy and during labour.

Breastfeeding

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

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 of 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 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 1968. 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 not 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

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.

- 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).

Adverse effects of paracetamol are rare:

Blood and lymphatic system disorders

Very rare: thrombocytopenia, neutropenia, leucopenia

Not known: agranulocytosis

Hepatobiliary disorders

Not known: sphincter of Oddi dysfunction

Immune system disorders

Hypersensitivity including skin rash may occur.

Not known: Anaphylactic shock, angioedema.

Psychiatric disorders

Not known: drug dependence (see section 4.4).

Vascular disorders

Not known: hypotension (with high doses).

Respiratory, thoracic and mediastinal disorders

Not known: bronchospasm (see section 4.4)

Skin and subcutaneous disorders

Very rare cases of serious skin reactions have been reported.

General disorders and administration site conditions

Uncommon: drug withdrawal syndrome

Very rare occurrence of pancreatitis.

Metabolism and nutrition disorders

Not known: High anion gap metabolic acidosis.

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

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 help if they occur.

Codeine

The effects of codeine over-dosage will be potentiated by simultaneous ingestion of alcohol and psychotic 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

Management 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.

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

Symptoms

Symptoms of paracetamol over-dosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent after 12 to 48 hours after ingestion. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin may occur and the INR may increase. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding, disseminated intravascular coagulation 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 and pancytopenia 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations

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 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

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

The mean AUC for the 10 hours following administration was 50.0 μ g/ml per hour for paracetamol and 450.0ng/ml per hour for codeine

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

Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O-demethylation leading to morphine, N-demethylation to norcodeine and after both O- and N-demethylation formation of nomorphine. Morphine and norcodeine are further transformed in glucuroconjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h (84.4 \pm 15.9%).

The O-demethylation of codeine to morphine is catalysed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine.

Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

5.3 Preclinical safety data

There are no preclinical data of relevance which are additional to that already included in other sections of the SPC.

Paracetamol

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

Citric Acid BP

Povidone BP

Sodium Saccharin BP
Sodium Cyclamate 1968 BP
Sodium Bicarbonate BP
Sodium Carbonate (Anhydrous) BP
Polyethylene Glycol USNF

6.2 Incompatibilities

Not known

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Store in a cool dry place at or below 25°C.

6.5 Nature and contents of container

Cartoned strip packs using PPFM laminate, constructed of: 40gsm MGBK paper, 12gsm LDPE, 8micron aluminium foil, 23gsm LDPE, containing either 10, 12, 16, 24, 30, 32, 36, 50, 56, 60, 100 or 112 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0166

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