

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 8/500mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500 mg, Codeine Phosphate 8 mg.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsules
Pink translucent capsule, marked CO COD 8

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-codamol 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).

For the relief of headaches, period pains, migraine, toothache, neuralgia, muscular and rheumatic pains.

4.2 Posology and method of administration

Posology

Adults:

1 or 2 capsules to be taken every 4 hours as required, swallowed whole with a glass of water, to a maximum of 4 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 sections 4.3 and 4.4).

Children aged 12 years to 15 years:

One capsule to be taken every 4 - 6 hours as required, swallowed whole with a glass of water, to a maximum of 4 doses in 24 hours.

Children aged 16 years to 18 years:

Dosage as for adults.

Elderly:

Dosage should be reduced in the elderly where there is impairment of hepatic function.

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 adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

The duration of treatment should be for **3 days only** and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

Method of administration

For oral administration

4.3 **Contraindications**

- Hypersensitivity to the active substances, other opioids or to any of the excipients listed in section 6.1
- 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

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 seek immediate medical advice in the event of an overdose, even if they feel well, because of the risk of delayed, serious liver damage.

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.

Renal and Hepatic impairment

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

Co-codamol 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.

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

Hepatobiliary disorders

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

Use with caution in patients with convulsive disorders.

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).

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.

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.

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).

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%

Paediatric population

Not recommended for children under 12 years of age.

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.

Label warnings:

Do not take anything else containing paracetamol while taking this medicine.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

or if leaflet present:

Immediate medical advice should be sought in the event of an overdose.

The label will state:

Front of Pack

- Can cause addiction
- Contains opioid
- For three days use only

Back of Pack

- For the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.

For relief of:

- Headaches
 - Period pains
 - Migraine
 - Toothache
 - Neuralgia
 - Muscular and rheumatic pains.
-
- If you need to take this medicine for more than three days you must see your doctor or pharmacist.
 - This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

Headlines section

- This medicine can only be used for the short term treatment of acute moderate pain when other painkillers have not worked.
- You should only take this product for a maximum of three 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 three 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 three days it can make them worse.

Section 1: What Co-codamol is and what it is used for

- For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

For the relief of:

- headaches
- period pains
- migraine
- toothache
- neuralgia
- muscular and rheumatic pains.

Section 2: What you need to know before you take Co-codamol

- This medicine contains codeine which can cause addiction if you take it continuously for more than three 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 three 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 three 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 three days. When you stop taking it you may get withdrawal symptoms such as tremor, difficulty sleeping, feeling or being sick, sweating and increased heart rate, breathing or blood pressure. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms

Section 4: Possible side effects

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

How do I know if I am addicted?

If you take the 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 the medicine you feel very unwell but you feel better if you start taking the medicine again.

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 colestyramine.

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.

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.

Sedative medicines such as benzodiazepines, gabapentinoids (gabapentin and pregabalin) or related drugs

The concomitant use of Co-codamol with sedative medicines such as benzodiazepines, gabapentinoids (gabapentin and pregabalin) or related drugs may result in respiratory depression, hypotension, profound sedation, coma or 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).

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

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 breastfeeding.

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

At normal therapeutic doses codeine and its active metabolite 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 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.

<u>System organ class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
Blood and lymphatic system disorders	Not known	Blood dyscrasias including thrombocytopenic and agranulocytosis
Immune system disorders	Not known	Hypersensitivity including skin rash may occur, anaphylactic shock, angioedema
Psychiatric disorders	Not known	Confusional state, dysphoria, euphoria
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis*
Nervous system disorders	Not known	Seizure, headache, somnolence, dizziness
Eye disorders	Not known	Miosis
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory disorders
Hepatobiliary disorders	Not known	Sphincter of Oddi dysfunction
Gastrointestinal disorders	Very rare	Pancreatitis
	Not known	Constipation, vomiting, nausea, dry mouth
Skin and subcutaneous disorders	Very rare	Cases of serious skin reactions have been reported

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

4.9 Overdose

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, phenobarbital, 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, 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 with 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

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 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations excl. psycholeptics ATC code: N02B E51

Paracetamol is an analgesic and antipyretic.

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

Paracetamol is rapidly and 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.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Light kaolin
Magnesium stearate

Capsule Shell
Gelatin
Erythrosine

Printing Ink
Shellac
Black iron oxide E172
Propylene glycol

6.2 Incompatibilities

None known

6.3 Shelf life

Securitainer – 3 years
Blister pack – 3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Securitainer or tracerpack containing 30 capsules.

Child resistant blister strips (PVC/PVdC/Glassine/aluminium foil) in packs of 32, 30 or 10 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Custom Healthcare Limited
Conway Street
Hove
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BN3 3LW
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 33446/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 July 2005

10 DATE OF REVISION OF THE TEXT

13/04/2026