SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Codamol 8mg/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Paracetamol and 8mg Codeine phosphate.

Excipient(s) with known effect:
Methyl para hydroxy benzoate (E218): 70.0 to 75.0 %
Propyl para hydroxy benzoate (E216): 9.0 to 13.0%
Ethyl para hydroxy benzoate (E214): 14.0 to 18.0%

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White to off-white, capsule shaped biconvex tablets scored on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in patients older than 12 years of age for the short term treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

For the symptomatic relief of pain including, headache, migraine, toothache, period pains, rheumatic pains, including muscle pains and backache.

4.2 Posology and method of administration

Posology

Adults over 18 years:
Co-codamol should be used at the lowest effective dose for the shortest period of time. One or two tablets to be swallowed with water. The dose should not be repeated more frequently than every four to six hours and not more than four times in any 24 hour period. Maximum dose is 8 tablets (4.0gm of paracetamol and 64mg of codeine in divided doses) per 24 hours.

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

Paediatric population:

Children aged 16 years to 18 years:
The recommended dose for children 16 years and older is 1 to 2 tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Children aged 12 years to 15 years:
The recommended dose for children 12 years to 15 years is 1 tablet which may be repeated every 6 hours when necessary up to a maximum dose of 4 tablets in any 24 hour period.

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).
Co-codamol is contraindicated in children below the age of 12 years for the symptomatic treatment of cold (see sections 4.3).

Children aged 12 years to 18 years:
Co-codamol is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of colds (see section 4.4).

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

Method of administration
For oral administration

Treatment goals and discontinuation
Before initiating treatment with Co-codamol, a 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).

Duration of treatment
The duration of treatment should be as short as possible limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

4.3 Contraindications

- Hypersensitivity to the active substances, other opioids or to any of the excipients listed in section 6.1.
- In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions.
- 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
- Respiratory depression
- Obstructive airways disease
- Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembraneous colitis

4.4 Special warnings and precautions for use

Paediatric population
Not recommended for children under 12 years of age.

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 non-cirrhotic alcoholic liver disease.

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

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

Use with caution in patients with convulsive disorders.

Co-codamol should be used with caution in patients with:

- hepatic function impairment (avoid if severe) and those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
- Prolonged use of co-codamol may cause hepatic necrosis.

- renal function impairment
- hypothyroidism (risk of depression and prolonged CNS depression is increased)
- inflammatory bowel disease - risk of toxic megacolon
- Opioids should not be administered during an asthma attack
- convulsions - may be induced or exacerbated
- drug abuse, dependence (including alcoholism), enhanced instability, suicidal ideation or attempts - predisposed to drug abuse
- head injuries or conditions where intracranial pressure is raised
- gall bladder disease or gall stones - opioids may cause biliary contraction
- gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility
- prostatic hypertrophy or recent urinary tract surgery
- adrenocortical insufficiency, e.g. Addison's Disease
- hypotension and shock
- myasthenia gravis
- phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

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).

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.

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, 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.

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.

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.

Sleep-related breathing disorders
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.

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

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 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, shallow breathing, small pupils, nausea, vomiting, constipation, lack of appetite and somnolence. 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 summarized 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 Populations:

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 with any other paracetamol-containing products.
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:
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

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.
- Headaches, migraine, toothache, neuralgia, period pains and rheumatic pains
- Do not take less than four hours after taking other painkillers.
- If you need to use this medicine for more than three days, you should 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. Do not take less than four hours after taking other painkillers.

- 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 Tablets are and what they are used for

It is an analgesic (painkiller) and is used 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. Do not take less than four hours after taking other painkillers.

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

- 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.

If you stop taking the tablets

- 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. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms such as tremor, difficulty sleeping, feeling or being sick, sweating and increased heart rate, breathing or blood pressure.

Section 4: Possible Side effects

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. 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

Important information regarding the ingredients of this medicine

Co-codamol 8mg/500mg Tablets contain para hydroxybenzoates (E218, E214 and E216), which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol can interact with the following:

- Drugs which alter gastric emptying time (e.g. cimetidine, ethyl alcohol, oral steroid contraceptives). These drugs reduce or delay peak paracetamol blood levels.
- The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
- Drugs which interfere with the metabolism of paracetamol by competition with metabolic pathways or substrates e.g. anticonvulsants (phenytoin), hepatic enzyme inducers, alcohol, barbiturates, tricyclic antidepressants. A poor diet (low protein) may also have a similar effect on the risk of serious paracetamol toxicity to hepatic enzyme inducers. Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which may be prolonged.
- 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.
- Alcohol can increase the hepatotoxicity of paracetamol overdosage and may have contributed to the acute pancreatitis reported in one patient who had taken an overdosage of paracetamol.

Codeine phosphate can interact with the following:

- *CNS depressants* - enhanced sedative and/or hypotensive effect with alcohol, anaesthetics, hypnotics, anxiolytics, antipsychotics, hydroxyzine, tricyclic antidepressants.
- 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). 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).
- *Antibacterials*, e.g. ciprofloxacin, - avoid premedication with opioids as reduced plasma ciprofloxacin concentration.
- *MAOIs* - use only with extreme caution.
- *Cyclizine*,
- *Mexiletine* - delayed absorption.
- *Metoclopramide and domperidone* - antagonise GI effects.
- *Cisapride* - possible antagonism of GI effects.
- *Dopaminergics* (e.g. selegiline) - possible risk of hyperpyrexia and CNS toxicity. This risk is greater with pethidine but with other opioids the risk is uncertain.
- *Ulcer-healing drugs:* cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.
- Anticholinergics (e.g. atropine) - risk of severe constipation which may lead to paralytic illness, and /or urinary retention.
- *Antidiarrhoeal drugs* (e.g. loperamide, kaolin) - increased risk of severe constipation.
- *Antihypertensive drugs* (e.g. guanethidine, diuretics) - enhanced hypotensive effect.
- *Opioid antagonists* (e.g. buprenorphine, naltrexone, naloxone).
- *Neuromuscular blocking agents* - additive respiratory depressant effects.
- *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.

Risk benefit must be considered because opioid analgesics cross the placenta. Studies in animals have shown opioids to cause delayed ossification in mice and increased resorption in rats.

Regular use during pregnancy may cause physical dependence in the fetus, leading to withdrawal symptoms in the neonate. During labour opioids enter the fetal circulation and may cause respiratory depression in the neonate. Administration should be avoided during the late stages of labour and during the delivery of a premature infant.

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

Breast-feeding:

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

Codeine is contraindicated in women during breast-feeding (see section 4.3). Co-codamol Tablets 8/500mg 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.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid

analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

Opioid analgesics can impair mental function and can cause blurred vision and dizziness or sedation. Patients should make sure they are not affected before driving or operating machinery.

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

Most reports of adverse reactions to paracetamol relate to overdosage with the drug.
At the recommended dosage, paracetamol may cause the following side effects:
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).

MedDRA system Organ Class	**Frequency**	**Adverse Effects**
Blood and lymphatic system disorders	Not known	There have been reports of blood dyscrasias including methaemoglobinaemia, neutropenia, pancytopenia, leukopenia, thrombocytopenic purpura, haemolytic anaemia and agranulocytosis, but these

		were not necessarily causality related to paracetamol.
Immune system disorders	Not known	Hypersensitivity, Allergic reactions - rare but may include skin rash, drug fever, mucosal lesions.
Psychiatric disorders	Not known	Drowsiness, Impaired mental functions, Confusional state, dysphoria, euphoria
Nervous system disorders	Not Known	Seizure, headache, somnolence, dizziness
Eye disorders	Not Known	Miosis
Respiratory, thoracic and mediastinal disorders	Not Known	Respiratory depression
Cardiac disorders	Not known	toxic myocarditis
Gastrointestinal disorders	Very rare	Pancreatitis
Hepatobiliary disorders	Not known	Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year, and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol, nor was the control of their disease improved after paracetamol withdrawal.
Skin and subcutaneous disorders	Very Rare	Cases of skin reactions have been reported, including serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption.
Renal and urinary disorders	Not known	Nephrotoxicity following therapeutic doses of paracetamol is uncommon, but papillary necrosis has been reported after prolonged administration.
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.

Adverse effects of opioid treatment which have been reported include:

MedDRA system Organ Class	**Frequency**	**Adverse Effects**
Immune system disorders	Not known	Allergic reactions (may be caused by histamine release) - including rash, urticaria, difficulty breathing, increased sweating, redness or flushed face, angioedema, anaphylactic shock.
Psychiatric disorders	Not known	Drowsiness, changes in mood, hallucinations, mental depression, trouble sleeping, or nightmares, trembling.
Nervous system disorders	Not known	Light headedness, confusion, vertigo, dizziness, CNS excitation (restlessness/ excitement), convulsions, headache, raised intracranial pressure, tolerance or dependence
Eye disorders	Not known	blurred or double vision, miosis.
Cardiac disorders	Not known	bradycardia, palpitations, hypotension.
Gastrointestinal disorders	Not known	constipation, GI irritation, biliary spasm, nausea, vomiting, loss of appetite, dry mouth, paralytic ileius or toxic megacolon. Pancreatitis
Hepatobiliary disorders	Not known	Sphincter of Oddi dysfunction
Renal and urinary disorders	Not known	Antidiuretic effect, urinary retention.
Reproductive system and breast disorders	Not known	Ureteral spasm
General disorders and administration site conditions.	Not known	Unusual tiredness or weakness, malaise, hypothermia

- Effects of withdrawal - abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, nausea, vomiting, sweating and increase in heart rate, respiratory rate and blood pressure.
  NOTE - tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.
- Regular prolonged use of codeine is known to lead to addiction, and symptoms of restlessness and irritability may result when treatment is stopped.
- Prolonged use of a painkiller for headaches can make them worse.
- 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.

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 the 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

a. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b. Regularly consumes ethanol in excess of recommended amounts.

Or

c. Is likely to be glutathione deplete 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 pinpoint 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Paracetamol has analgesic and antipyretic properties but is has no useful anti inflammatory properties.

Codeine phosphate is a weak analgesic and is used in the treatment of cough and diarrhoea.

Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.

Codeine is much less potent than morphine and it is inadequate against severe pain even in the largest tolerable doses. It does not cause appreciable respiratory depression but does have antitussive and constipating effects. 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.

Codeine produces its analgesic effects by binding to μ opioid receptors. Codeine also binds weakly to κ opioid receptors which mediates spinal analgesia, sedation and miosis.

5.2 Pharmacokinetic properties

Codeine:

Absorption and Distribution:
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.

Biotransformation and Excretion:
It is metabolised in the liver; and codeine and its metabolites are entirely excreted almost by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life is reported to be 3-4 hours after administration by mouth.

***Paracetamol**:*

Absorption and Distribution:
Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30-60 minutes. Plasma half-life is 1-4 hours
Paracetamol is relatively uniformly distributed throughout most body fluids, plasma protein binding is variable.

Biotransformation and excretion
It is metabolised in the liver and excreted in the urine, mainly as the glucuronide and sulphate conjugates. The elimination half-life varies from about 1 – 4 hours. About 86% is excreted in the urine in 24 hours; 40-70% is free or conjugated morphine, 5-15% is free or conjugated norcodeine. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

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
Potato starch
Maize starch
Talc
Povidone

Stearic acid
Magnesium stearate
Methyl para hydroxybenzoate (E218)
Propyl para hydroxybenzoate (E216)
Ethyl para hydroxybenzoate (E214)

6.2 Incompatibilities
None

6.3 Shelf life
Al/PVC Blisters: 4 years
Containers: 3 years

6.4 Special precautions for storage
Do not store above 25ºC.
Blisters: Store in the original package

6.5 Nature and contents of container
Blister packs:
8, 10, 12, 16, 20, 24, 28, 30, 32 as Pharmacy packs
Blister strips consist of a 35gsm paper/9µ soft tempered aluminium foil lid and 250µ PVC film base in cartons.
Or
Blister strips consist of a 250µ hard aluminium foil laminated to 15 µ rigid PVC film and 250µ PVC film base in cartons.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
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8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0477

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 10/06/2015
Renewal of the authorisation: 02/10/2025

10 DATE OF REVISION OF THE TEXT
04/06/2026