SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 15mg/500mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Co-codamol 15mg/500mg tablet contains paracetamol 500mg, codeine phosphate hemihydrate 15mg.

Excipients with known effect:

Lactose monohydrate (18 mg/tablet)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet
Co-codamol 15mg/500mg tablets are white to almost white, capsule-shaped, biconvex, bevelled edged tablets, with 'CC2' on one side and 'score line' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of moderate pain.

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

4.2 Posology and method of administration

Posology

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).

Adults

Two tablets not more frequently than every 4 to 6 hours, up to a maximum of 8 tablets in any 24 hour period.

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 8 tablets in 24 hours.

Children aged 12 to 15 years

One tablet every 6 hours when necessary to a maximum of 4 tablets in 24 hours.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Paediatric population:

Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see section 4.3 and 4.4).

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to paracetamol or codeine which is rare.
- Hypersensitivity to the active substances, soya or peanut or to any of the other 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 patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

CYP2D6 metabolism

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. 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 summarized below:

Population	Prevalence %
African/Ethiopian	29%
African/Ethiopian	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%

Codeine/Paracetamol is contraindicated in breast-feeding

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Paracetamol and Codeine Phosphate 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 Paracetamol and Codeine Phosphate concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Risks from concomitant use of opioids and alcohol
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see section 4.5).
Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, particularly the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.
Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.
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 pain killer 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.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

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 <active>.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)
Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Alcohol and opioids
The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Careful consideration should be given before prescribing the product for pregnant patients.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that Appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

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.

As a precautionary measure, use of Paracetamol and Codeine Phosphate should be avoided during the third trimester of pregnancy and during labour.

Breast-feeding

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.

Paracetamol and Codeine Phosphate tablets should not be used during breastfeeding (see section 4.3).

Fertility

There are no data on the effects of Paracetamol and Codeine Phosphate tablets on human fertility. Fertility was unaffected following paracetamol and codeine treatment in animal studies (see section 5.3).

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 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

Codeine phosphate 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 phosphate.

– 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.

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).

Adverse effects of paracetamol are rare:

Undesirable effects

Blood and lymphatic system disorders Very rare Not known	Thrombocytopaenia, neutropenia, Leucopenia Agranulocytosis
Immune system disorders Rare Not known	Hypersensitivity including skin rash may occur. anaphylactic shock, angioedema
Metabolism and nutrition disorders Not known	High anion gap metabolic acidosis*
Respiratory, thoracic and mediastinal disorders Not known	bronchospasm (see section 4.4).
Skin and subcutaneous disorders Very rare	Very rare occurrence of pancreatitis, Very rare cases of serious skin reactions have been reported.
Psychiatric disorders Not known	Drug dependence (see section 4.4)
General disorders and administration site conditions Uncommon	Drug withdrawal syndrome

* 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.

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 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 medical help if they occur.

Codeine Phosphate

The effects of Codeine 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 coingested, 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 4 hours after ingestion, or 8 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 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. Also 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 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.

*Managemen*t

Immediate treatment is essential in the management of Paracetamol overdose. Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate 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 concentrations 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 indigestion.

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 24 hours from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Codeine, combinations excl. Psycholeptics.

ATC Code: N02AA59

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 tablets (i.e. a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 15.96μg/ml and 212.4ng/ml respectively.

The mean times to maximum plasma concentrations were 0.88 hours for paracetamol and 1.05 hours for codeine.

The mean AUC for the 9 hours following administration was 49.05μg/ml per hour for paracetamol and 885.0ng/ml per hour for codeine.

The bioavailabilities of paracetamol and codeine, 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, Ndemethylation to norcodeine and after both O- and N-demethylation formation of normorphine. Morphine and norcodeine are further transformed in glucuroconjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h (84.4±15.9%).

The O-demethylation of codeine to morphine is catalyzed 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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized maize starch

Stearic acid

Povidone K-30

Lactose monohydrate

Powdered cellulose

Talc

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Paracetamol/Codeine phosphate 500mg/15mg tablets are available in HDPE bottle pack and Blister pack of PVC and Aluminium foil. Such HDPE bottle and blisters are packaged into cardboard carton.

Carton containing 30, 50 or 100 tablets in blister

Carton containing 100 tablets in bottle

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lyrus life sciences Limited

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