SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 30mg/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30mg of Codeine Phosphate and 500mg of Paracetamol (as the active ingredients).

Each Co-codamol 30mg/500mg Tablet contains 0.3455mg of sodium.

Excipient: Sodium metabisulphite (E223)

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White to off white capsule shaped biconvex uncoated plain tablets, debossed with '30' on one side and 'BL' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cocodamol 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

Adults: One to two tablets not more frequently than every 4 hours, up to a maximum of 8 tablets in any 24 hour period.

Older People: As Adults, however a reduced dose may be required. See warnings.

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 12 years to 18 years:
The recommended codeine dose for children 12 years and older should be 1 to 2 tablets every 6 hours when necessary up to a maximum dose of codeine of 240 mg daily. The dose is based on the body weight (0.5-1mg/kg).

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)

Dosage needs to be adjusted according to the severity of pain and the response of the patient.

Tolerance to Codeine can develop with continued use. The incidence of unwanted effects is dose related. Doses of Codeine above 60mg are associated with an increase in unwanted effects.

Method of administration: oral

4.3 Contraindications

Hypersensitivity to paracetamol or codeine or sodium metabisulfite which is rare.

Hypersensitivity to any of the other constituents.

Conditions where morphine and opioids are contraindicated e.g:
• Acute asthma
• obstructive airway disease
• Respiratory depression
• Acute alcoholism
• Head injuries
• Raised intra-cranial pressure
• Following biliary tract surgery
• moderate to severe degrees of renal or hepatic impairment.
• Patients suffering from diarrhoea of any cause and
• Patients who have taken 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 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

Each Co-codamol 30mg/500mg Tablet contains 0.3455mg of sodium.

This sodium content should be taken into account when prescribing for patients in whom sodium restriction is indicated.

Co-codamol tablets must be used with caution in patients with increased intracranial pressure, acute abdominal conditions the elderly, the debilitated, impaired hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, and urethral stricture. (See also “Contraindications”). Overdosage in patients with non-cirrhotic alcoholic liver disease can be hazardous. The hazard of paracetamol overdose is greater in those with alcoholic liver disease.

Cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Drug dependence of the morphine type can be produced by the Codeine, and the potential for drug abuse with codeine must be considered. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

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. Keep the product out of the reach and sight of children.

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.

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 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%

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

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine. Quinine or quinidine may inhibit the analgesic actions of codeine.

The CNS depressant action of Co-codamol may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Co-codamol and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine. Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Concomitant administration of codeine with an anti-diarrhoel agent increases the risk of severe constipation, and co-administration with an antimuscarine drug may cause urinary retention.

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 colestyramine.

Codeine may delay the absorption of mexilitine, and cimetidine may inhibit codeine metabolism.

Opioids may interfere with the results of plasma amylase, lipase, bilirubin, ALP, LDH, AST, and ALT tests.

The effects of codeine on the gut may interfere with diagnostic tests of gastro-intestinal functions.

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.

4.6 Fertility, pregnancy and lactation

Cocodamol is not recommended during pregnancy or lactation. Codeine crosses the placenta and is found in breast milk.

There is inadequate evidence of the safety of codeine in human pregnancy, but there is epidemiological evidence for the safety of paracetamol. Both substances have been used for many years without apparent ill consequences and animal studies have not shown any hazard. Nonetheless careful consideration should be given before prescribing the products for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

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

Codeine should not be used during breast-feeding (see section 4.3)
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. Effect on ability to drive and use machines

Codeine may cause visual disturbances

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 can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, sedation, shortness of breath, confusion, drowsiness andconstipation. 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.
In addition, miosis, visual disturbances, headache, bradycardia, respiratory depression, difficult micturition and urinary retention, and allergic reaction (including skin rash) can occur.

Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function.

Euphoria, dysphoria, constipation, abdominal pain, and pruritus can occur as reactions to Co-codamol.

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

Adverse effects of paracetamol are rare:
Immune system disorders
-Hypersensitivity including skin rash may occur.
-Not known: Anaphylactic shock, angioedema

Very rare cases of serious skin reactions have been reported.

There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

• Regular prolonged use of codeine/DHC 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 rare occurrence of pancreatitis.

Ear and Labyrinth disorders: deafness has been reported in patients after long term use of high doses of codeine-paracetamol

Long-term usage of high doses of codeine + paracetamol can be rarely associated with ototoxicity leading to sensorineural hearing loss.

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

4.9 Overdose

Codeine

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 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 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

a. Is on long term treatment with carbamazepine, phenobarbital, 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, haemorrhage, hypoglycaemia, cerebral oedema 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.

Treatment

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 severe hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations

ATC Code: NO2B E51

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

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

5.2 Pharmacokinetic properties

Following oral administration of two tablets (ie, a dose of paracetamol 1000mg and codeine 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 15.96mg/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 49.05mg.ml $^{-1}$.h for paracetamol and 885.0 ng/ml $^{-1}$.h for codeine.

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch
Microcrystalline cellulose
Sodium starch glycollate Type A
Sodium metabisulfite (E223)
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.

6.5 Nature and contents of container

Opaque PVDC (40gsm) coated PVC and 20µm aluminium laminated to 15µm PVC blisters, which are placed in an outer carton along with leaflet.

The pack size in which the product may be packed are 8's, 10's, 16's, 20's, 30's 32's and 100's tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd,
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