SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Codamol 8mg/500mg Tablets

Boots Paracetamol and Codeine Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Paracetamol and 8mg Codeine phosphate.
For the full list of excipients, see section 6.1.

SUMMARY OF PRODUCT CHARACTERISTICS

3 PHARMACEUTICAL FORM

Tablets

Clean, white tablets, bevelled edged, debossed with ‘8’ and broken breakline on one side and ‘BL’ 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:
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.

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

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).

Method of administration

For oral administration

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.

4.3. Contraindications

- Hypersensitivity to the active substances 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
- 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

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 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, eg 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.

<u>CYP2D6 metabolism</u>

Codeine is metabolised by 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 poplations are summarized below

Population	Prevalance %
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."

The label will state:

Front of Pack

- ***Can cause addiction***
- ***For three days use only***

Back of Pack

List of indication as agreed in 4.1 of the SmPC
If you need to takethis medicine for more than three days continuously, 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 the medicine is for

Succinct description of the indications from 4.1 of the SmPC

Section 2: Before taking

- 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: Dosage

- 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

Section 4: 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 at: www.mhra.gov.uk/yellowcard. 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 parahydroxybenzoates (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:

Analgesics- Diflunisal increases blood concentrations of paracetamol.

Antibacterials- Isoniazid may increase the risk of hepatotoxicity with therapeutic doses of paracetamol.

Drugs which alter gastric emptying time (eg cimetidine, ethyl alcohol, oral steroid contraceptives). These drugs reduce or delay peak paracetamol blood levels.

Metoclopramide or domperidone increases the speed of absorption of paracetamol.

Colestyramine reduces paracetamol absorption.

Drugs which interfere with the metabolism of paracetamol by competition with metabolic pathways or substrates eg 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.

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.

Uricosurics- Probenecid can reduce the loss of paracetamol from the body.

Codeine phosphate can interact with the following:

Alcohol- the effects of alcohol may be enhanced.

CNS depressants - enhanced sedative and/or hypotensive effect with alcohol, anaesthetics, hypnotics, anxiolytics, antipsychotics, hydroxyzine, tricyclic antidepressants.

Antibacterials, *eg* 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 (*eg* 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. Anticholinergics (*eg* atropine) - risk of severe constipation which may lead to paralytic illness, and /or urinary retention.

Antidiarrhoeal drugs (*eg* loperamide, kaolin) - increased risk of severe constipation.

Antihypertensive drugs (*eg* guanethidine, diuretics) - enhanced hypotensive effect.

Opioid antagonists (*eg* buprenorphine, naltrexone, naloxone).

Neuromuscular blocking agents - additive respiratory depressant effects.

Interference with laboratory tests
Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Paracetamol:
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

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

Codeine:

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.

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

Opioid analgesics can impair mental function and can cause blurred vision and dizziness. 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

At the recommended dosage, paracetamol may cause the following side effects:

Allergic reactions - rare but may include skin rash, drug fever, mucosal lesions.

Effects on CNS - drowsiness, impaired mental functions

Effects on GI system - 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. Acute pancreatitis has been reported. 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.

Effects on CVS - toxic myocarditis.

Effects on blood - 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.

Effects on GU system - Nephrotoxicity following therapeutic doses of paracetamol is uncommon, but papillary necrosis has been reported after prolonged administration.

Other effects - Most reports of adverse reactions to paracetamol relate to overdosage with the drug. Very rare cases of serious skin reactions have been reported.

Adverse effects of opioid treatment which have been reported include:

Allergic reactions (may be caused by histamine release) - including rash, urticaria, difficulty breathing, increased sweating, redness or flushed face.

Effects on CNS - confusion, drowsiness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental

depression, headache, trouble sleeping, or nightmares, raised intracranial pressure, tolerance or dependence.

Effects on GI system - constipation, GI irritation, biliary spasm, nausea, vomiting, loss of appetite, dry mouth, paralytic ileius or toxic megacolon.

Effects on CVS - bradycardia, palpitations, hypotension.

Effects on sensory system -blurred or double vision.

Effects on GU system - ureteral spasm, antidiuretic effect.

Other effects - trembling, unusual tiredness or weakness, malaise, miosis, 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.

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

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

Codeine:

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 triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid overdosage with dilation of the pupils occurring as hypoxia develops.
Nausea and vomiting are common Other opioid overdose symptoms include hypothermia, confusion, convulsions, severe dizziness, severe drowsiness, hypotension and tachycardia (possible but unlikely), nervousness or restlessness, excitement, hallucinations, bradycardia, circulatory failure, slow or troubled breathing, severe weakness, convulsions, especially in infants and children. Rhabdomyolysis, progressing to renal failure, has been reported in overdosage with opioids.

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Treatment
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. In acute overdosage with respiratory depression or coma, the specific opioid antagonist naloxone is indicated using one of the recommended dose regimens– repeated doses may be required in a seriously poisoned patient as naloxone is a competitive antagonist with a short half-life. Patients should be observed closely for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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 particulars

Paracetamol:
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 30 minutes to two hours after ingestion. It is metabolised in the liver and excreted in the urine, mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about one hour to four hours. At usual therapeutic concentrations plasma protein binding is negligible.

Codeine:
Codeine is well absorbed from the gastrointestinal tract following oral administration. It is metabolised in the liver to morphine~~,~~ and norcodeine which are both excreted in the urine partly as conjugates with glucuronic acid. Most of the excretion products appear in the urine within 6 hours and up to 86% of the dose is excreted in 24 hours. About 70% of the dose is excreted as free codeine, 10% as free and conjugated morphine and a further 10% as free or conjugated norcodeine. Only traces are found in the faeces. The plasma half life is between approximately three and four hours.

5.3. Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which is additional to that already included in the other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch
Maize starch
Talc

Povidone
Stearic acid
Magnesium stearate

Methyl para hydroxy benzoate (E218)
Propyl para hydroxy benzoate (E216)
Ethyl para hydroxy benzoate (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

Bristol Laboratories Ltd,
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Berkhamsted
HP4 1EG
UK

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