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.

Excipient with known effect: Also contains 0.345 mg of sodium and 0.56 mg of sodium metabisulfite (E223)

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet

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

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

4.2 Posology and method of administration

Posology

Co-codamol should be used at the lowest effective dose for the shortest period of time.

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

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

Paediatric population:

Children aged 16 years to 18 years:
The recommended codeine dose for children 16 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 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. 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)

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 substance(s) or to any of the excipients listed in section 6.1.

- Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembraneous colitis
- Obstructive airway disease
- respiratory depression
- 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

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.

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.

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:
Immediate medical advice should be sought in the event of an overdose, even if you feel well.
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.

Important information regarding the ingredients of this medicine
This medicinal product contains 0.345 of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Sodium metabisulfite in this product may severe hypersensitivity reactions and Bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol can interact with the following:

- 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.
- Codeine Phosphate can interact with the following:
- 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.

4.6 Fertility, pregnancy and lactation

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

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 Effects 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.
- 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 tolerance. Symptoms of restlessness and irritability may result when treatment is then 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:

Symptoms: Pallor, nausea, vomiting, anorexia and abdominal pain in the first 24 hours. 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, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is likely in adults who have taken 10g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

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 and any patient who had ingested around 7.5g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.

Opioids:
Symptoms: cold clammy skin, confusion, convulsions, severe drowsiness, tiredness, low blood pressure, pinpoint pupils of eyes, slow heart beat and respiratory rate coma.

Treatment: Treat respiratory depression or other life-threatening adverse effects first. Empty the stomach via gastric lavage or induction of emesis. The opioid antagonist naloxone (0.4-2mg subcutaneous) can be given and repeated at 2-3 minute intervals to a maximum of 10mg. Naloxone may also be given by intramuscular injection or intravenous infusion. The patient should be monitored as the duration of opioid analgesic may exceed that of the antagonist.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations

ATC Code: NO2B 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. It differs from morphine in that for normal medical use serious dependence is not frequently associated with codeine and large doses produce excitement rather than depression. 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 also binds weakly to κ opioid receptors which mediates spinal analgesia, sedation and miosis.

5.2 Pharmacokinetic properties

Codeine and its salts are readily absorbed from the GI tract and ingestion of codeine phosphate produces peak plasma concentrations in about one hour. 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 is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes-2 hours after ingestion. 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.

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

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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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0235

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/05/2011

10 DATE OF REVISION OF THE TEXT

26/10/2016