SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 30/500 mg Tablets

Emcozin 30/500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Paracetamol 500 mg and Codeine Phosphate 30 mg. For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablets.

Off-white, capsule-shaped tablets. Plain on one side and embossed with “CO COD 30” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe 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

For oral administration.

Treatment goals and discontinuation

Before initiating treatment with Co-codamol or Emcozin, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician

and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

The duration of treatment should be 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. The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Adults:

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

Elderly:

Same as for adults, however a reduced dose may be required (see section 4.4).

Paediatric population:

Children aged 16-18 years: One or two tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Children aged 12 – 15 years: One 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 section 4.3 and 4.4).

Dosage should be adjusted accordingly to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciable increased incidence of undesirable side effects.

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).

4.3 Contraindications

Known hypersensitivity to paracetamol, codeine or other opioid analgesics or to any of the excipients.

Moderate to severe renal failure.

Moderate to severe liver disease.

Acute respiratory depression and obstructive airways disease.

Bronchial asthma attack or heart failure secondary to chronic lung disease.

Raised intracranial pressure or head injuries (in addition to the risk of respiratory depression and increased intracranial pressure, may affect papillary and other responses vital for neurological assessment).

Acute alcoholism.

Comatose patients.

Where there is a risk of paralytic ileus.

In acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis) or
diarrhoea caused by poisoning until the toxic material has been eliminated from the gastrointestinal tract.

Not to be used in infants.

Following biliary tract surgery; 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

Caution is advised in the administration of both paracetamol and codeine to patients with impaired kidney or liver function. The hazard of overdose with paracetamol is greater in those with alcoholic liver disease.

Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects.

Co-codamol 30mg/500mg Tablets should be given with caution or in reduced doses to elderly patients or debilitated patients or to patients with hypotension, hypothyroidism, decreased respiratory reserve, adrenocortical insufficiency, prostatic hypertrophy, shock, inflammatory or obstructive bowel disorders, urethral stricture, acute abdominal conditions, recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of cardiac arrhythmias or convulsions and in patients with a history of drug abuse or emotional instability.

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.

Avoid use during an acute asthma attack.

Care should be observed in those on concurrent CNS depressant drugs.

Opioid analgesics should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. If the use of codeine is considered essential then great care should be taken in patients taking MAOIs or within 14 days of stopping MAOIs (see section 4.5).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with intravenous busulfan (see section 4.5 Interactions). Patients should be advised that immediate medical advice should be sought in the event of an overdose, because of the risk of delayed, serious liver damage.
Care should also be observed if prolonged therapy is contemplated.

Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain, and rarely, colonic obstruction. Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Co-codamol or Emcozin. Repeated use of Co-codamol or Emcozin can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Co-codamol or Emcozin may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.

For patients who experience signs and symptoms of OUD, and/or exhibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

Before initiating treatment with Co-codamol or Emcozin and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

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 codeine.

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.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Hyperalgesia

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.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, 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.

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 painkiller for headaches too often or for too long can make them worse.
- Under 'Pregnancy and Breastfeeding':

Do not take codeine while you are breast feeding. Codeine and morphine pass into breast milk.

- In Section 3 'How to take Co-codamol tablets':

Talk to your doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

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
- Do not take more medicine than the label tells you to. If you do not get better talk to your doctor.
- Do not take anything else containing paracetamol while taking this medicine.
- Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Do not exceed the stated dose.

Patients should be advised not to take other paracetamol or codeine containing products concurrently.

If symptoms persist, consult your doctor. Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

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).

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

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.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes.

The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme- inducing drugs such as carbamazepine, phenobarbital, phenytoin, primidone or rifampicin.

Excretion of paracetamol may be reduced and plasma concentrations increased when given with probenecid.

Hepatotoxicity at therapeutic doses of paracetamol has been reported in patients receiving isoniazid.

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, hypnotics, sedatives, tricyclic antidepressants and phenothiazines. Concomitant use of Co-codamol or Emcozin with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Anaesthetics: concomitant administration of codeine and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.

Alcohol: the hypotensive, sedative and respiratory depressive effects of alcohol may be enhanced.

The hypotensive actions of diuretics and antihypertensive agents may be potentiated when used concurrently with opioid analgesics.

Concurrent use of hydroxyzine with codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

The respiratory depressant effects caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Antidepressants: The depressant effects of opioid analgesics may be enhanced by tricyclic antidepressants. MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Quinidine can inhibit the analgesic effect of codeine.

Codeine may delay the absorption of flecainide and mexiletine and thus reduce the antiarrhythmic effect of the latter.

Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Ulcer-healing drugs: Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Antihistamines: concomitant administration of codeine and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance.

Codeine potentiates the effect of hypnotics and anxiolytics.

Cytotoxic drugs: Paracetamol possibly inhibits metabolism of intravenous busulfan (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol).

Antipsychotics: enhanced sedative and hypotensive effects

Sodium oxybate: concomitant administration of codeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

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 Tc99m disofenin as opioid treatment may cause constriction of the Sphincter of Oddi and increases biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Codeine crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible association with respiratory and cardiac malformations has been reported.

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.

Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.

Breastfeeding

Paracetamol is excreted in breast milk but not in clinically significant quantities. Available published data do not contraindicate breast feeding.

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

At normal therapeutic doses codeine and its active metabolite 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

Codeine may cause drowsiness, changes in vision, including blurred or double vision. If affected patients should be advised not to drive or operate machinery. The effects of alcohol are enhanced by opioid analgesics.

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

The information below lists reported adverse reactions, ranked using the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The frequency and severity of side effects are determined by dosage, duration of treatment and individual sensitivity. Symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headaches can make them worse.

Tolerance and some of the most common side effects – drowsiness, nausea and vomiting, and confusion – generally develops with long term use.

Immune system disorders: maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate; fever, splenomegaly and lymphadenopathy also occurred.

Endocrine disorders: hyperglycaemia

Metabolism and nutrition disorders: anorexia

Frequency unknown: 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.

Psychiatric disorders: hallucinations, nightmares, confusion, restlessness, mood changes, mental depression, dysphoria, euphoria (The euphoric activity of codeine may lead to its abuse and dependence).

Frequency unknown: Drug dependence (see section 4.4).

Nervous system disorders: convulsions (especially in infants and children), dizziness, headache, drowsiness, light-headedness.

Eye disorders: miosis, blurred or double vision, other visual disturbances Ear and labyrinth disorders: vertigo

Cardiac disorders: orthostatic hypotension, palpitations, tachycardia and bradycardia Vascular disorders: Postural hypotension, facial flushing. Large doses produce hypotension.

Respiratory, thoracic and mediastinal disorders: dyspnoea, larger doses produce respiratory depression.

Gastrointestinal disorders: nausea, vomiting, constipation, dry mouth and stomach cramps. There have been very rare occurrences of pancreatitis.

Hepatobiliary disorders: biliary spasm (may be associated with altered liver enzyme values), Frequency unknown: sphincter of Oddi dysfunction.

Skin and subcutaneous tissue disorders: allergic reactions such as urticaria, pruritus, skin rash, sweating and facial oedema.

Musculoskeletal and connective tissue disorders: uncontrolled muscle movements, muscular rigidity may occur after high doses.

Renal and urinary disorders: urinary retention, uretic spasm, difficulties in micturition (dysuria, increased frequency, decrease in amount) An antidiuretic effect may also occur with codeine.

Reproductive system and breast disorders: sexual dysfunction, erectile dysfunction, decreased potency, decreased libido.

General disorders and administration site conditions: malaise, tiredness, hypothermia, uncommon: drug withdrawal syndrome.

<u>Drug dependence</u>

Repeated use of Co-codamol or Emcozin can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

The paracetamol component of Co-codamol 30/500 mg Tablets is relatively free of side-effects but immune system disorders, hypersensitivity including skin rash, urticaria, anaphylactic shock or angioedema may occur. Very rare cases of serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption have been reported.

Haematological side-effects including thrombocytopenia, agranulocytosis, neutropenia, pancytopenia and leucopenia have occurred in isolated cases, but these were not necessarily causally related to paracetamol.

Renal damage may occur rarely with long term use.

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

Paracetamol

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are sweating, 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, hypotension, cerebral oedema, gastrointestinal bleeding, coma and death. Prothrombin time may increase with deteriorating liver function.

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.

Liver damage is possible in adults who have taken 10 g 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.

Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has any of the following risk factors:

- is on long term treatment with carbamazepine, phenobarbital, 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.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any patient who has ingested around 7.5 g or more of paracetamol in the proceeding 4 hours should undergo gastric lavage. 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 at least 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 serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Codeine

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.

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

Symptoms

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large.

Symptoms of codeine overdosage include cold clammy skin, skeletal muscle flaccidity, confusion, convulsions, dizziness, drowsiness, nervousness or restlessness, miosis, bradycardia, dyspnoea, unconsciousness, circulatory failure and deepening coma. The pupils may be pinpoint in size; Nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

In severe overdose with codeine, apnoea, circulatory collapse, cardiac arrest and death may occur (from respiratory failure).

Management
This should include general symptomatic and supportive measures including a clear airway and the institution of controlled ventilation 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.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Intensive support therapy may be required to correct respiratory failure and shock due to the effects of codeine.

In addition the specific narcotic antagonist, naloxone hydrochloride, may be used to rapidly counteract the severe respiratory depression and coma. Naloxone has a short half-life so large and repeated doses may be required in a seriously poisoned patient. A dose of 0.4-2 mg is given intravenously or intramuscularly to adults, this is repeated at intervals of 2-3 minutes if necessary. Up to a total of 10 mg of naloxone may be given. In children doses of naloxone of 5-10 mcg/kg bodyweight may be given intravenously or intramuscularly. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

Codeine is not dialysable.

General supportive measures must be available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol has analgesic and antipyretic actions.

Codeine phosphate is an analgesic of the opioid class. Opioid analgesics bind with stereospecific receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to it. It has been hypothesised that alterations in release of various neurotransmitters from afferent nerves sensitive to painful stimuli may be partially responsible for the analgesic effect.

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.

The drugs are additive and some workers suggest there may be synergy between the constituents.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma levels occurring about 30 minutes to 2 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 unchanged.

The elimination half-life of paracetamol varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic doses.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by O-and N-demethylation in the liver to morphine, and norcodeine and other metabolites. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Most of the excretion products appear in the urine within six hours and up to 80% 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.

Codeine is not extensively bound to plasma proteins. The plasma half-life varies from about 3 to 4 hours.

5.3 Preclinical safety data

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

Each tablet contains:
Maize starch
Colloidal anhydrous silica
Povidone
Potassium sorbate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

Blister pack strips, constructed from 250 micron PVC film lidded with Glassine paper and aluminium foil containing 10, 20, 30, 50 or 100 tablets per strip.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Palla Pharma (UK) Holding Limited

10 Norwich Street,

London,

EC4A 1BD

United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 52635/0003

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