SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Codamol 8mg/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of Paracetamol and 8 mg of Codeine phosphate

Excipient(s) with known effect:
Methyl para hydroxy benzoate (E218): 70.0 to 75.0 %
Propyl para hydroxy benzoate (E216): 9.0 to 13.0%
Ethyl para hydroxy benzoate (E214): 14.0 to 18.0%

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White to off-white, capsule shaped biconvex tablets scored on one side and plain 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

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).

Posology

Co-codamol should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours.

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.

Do not take for more than 3 days without consulting your doctor.

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

Children aged 12 years to 18 years:
Co-codamol is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of colds (see section 4.4).

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

Method of administration
For oral administration

Treatment goals and discontinuation
Before initiating treatment with Co-codamol, 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 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.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions.
- 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
- Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembraneous colitis
- Respiratory depression
- Obstructive airways disease

4.4 Special warnings and precautions for use

The recommended dose should not be exceeded.

Paracetamol:

This medicine should not be taken with any other paracetamol-containing products. If symptoms persist, the patient should be advised to consult their doctor. The patient should be advised to seek immediate medical advice in the event of an overdose, even if they feel well, because of the risk of delayed, serious liver damage.

Use with caution in patients with convulsive disorders.
The risk-benefit of continued use should be assessed regularly by the prescriber.

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, e.g. Addison's Disease
- hypotension and shock
- myasthenia gravis
- phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine

Monitoring after prolonged use should include blood count, liver function and renal function.

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.

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

Concomitant use of Co-codamol and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to

prescribe Co-codamol concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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. Repeated use of Co-codamol 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 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).

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

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.

Risks from concomitant use of opioids and alcohol
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see section 4.5).

Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy, hypothyroidism and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

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 phosphate.

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

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

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.

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.

CYP2D6 metabolism

Codeine is metabolised by 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 populations are summarized below.

Population	**Pre valance %**
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%

Paediatric population

Not recommended for children under 12 years of age.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

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.

Leaflet:

Talk to a 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.

Label:

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

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 when you stop the tablets.
• This medicine contains paracetamol. Do not take anything else containing paracetamol while taking this medicine.
• Taking a painkiller 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.
• Do not take anything else containing paracetamol while taking this medicine.
• 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:

Talk to a doctor at once if you take too much of this medicine even if you

feel well.

Label Warnings:

The risk-benefit of continued use should be assessed regularly by the prescriber.

Important information regarding the ingredients of this medicine
Co-codamol 8mg/500mg Tablets contain para hydroxybenzoates (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.
- Uricosurics: Probenecid can reduce the loss of paracetamol from the body.
- Drugs which alter gastric emptying time (*e.g.* 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 *e.g.* 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.
- Concomitant administration of MAOI (e.g. tranylcypromine) can potentiate the central nervous effects and other side effects of unpredictable severity, Co-codamol should not be used within two weeks after the discontinuation of MAOI treatment.

- 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 can interact with the following:

- CNS depressants - enhanced sedative and/or hypotensive effect with anaesthetics, hypnotics, anxiolytics, antipsychotics, hydroxyzine, tricyclic antidepressants.
- Sedative medicines such as benzodiazepines or related drugs - The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Concomitant use of Co-codamol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).
- Antibacterials, *e.g.* 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 (*e.g.* 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 (*e.g.* atropine) - risk of severe constipation which may lead to paralytic illness, and /or urinary retention.
- Antidiarrhoeal drugs (*e.g.* loperamide, kaolin) - increased risk of severe constipation
- Antihypertensive drugs (*e.g.* guanethidine, diuretics) - enhanced hypotensive effect
- Opioid antagonists (*e.g.* buprenorphine, naltrexone, naloxone)
- Neuromuscular blocking agents - additive respiratory depressant effects.
- *Alcohol and opioids* - The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).
- 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)

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.

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 foetus, leading to withdrawal symptoms in the neonate. During labour opioids enter the foetal 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.

Patients should follow the advice of their doctor regarding the use of this product.

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.

Results of one case control study suggest that there might be an increased risk of malformations of the respiratory tract in the offspring of women who consumed codeine during the first four months of pregnancy. This increase was statistically not significant. Evidence of other malformations is also reported in epidemiological studies on narcotic analgesics, including codeine.

Breast-feeding:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding. Codeine is contraindicated in women during breastfeeding (see section 4.3).

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

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.
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 or unknown (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse effect
Blood and lymphatic system disorders	Not known	Methaemoglobinaemia, neutropenia, pancytopenia, leukopenia, thrombocytopenic purpura, haemolytic anaemia, agranulocytosis, thrombocytopenia.
Immune system disorders	Not known	Anaphylactic shock, angioedema, allergic reactions (may be caused by histamine release) – including hypersensitivity, rash, urticaria, mucosal lesions, difficulty breathing, increased sweating, redness or flushed face
Psychiatric disorders	Not known	Confusional state, dysphoria, euphoria, drowsiness, changes in mood, hallucinations, depression, trouble sleeping or nightmares, dependence, impaired mental functions, trembling, Drug dependence (see section 4.4)
Nervous system disorders	Not known	Vertigo, dizziness, CNS excitation (restlessness/excitement), convulsions, headache, raised intracranial pressure, light-headedness, confusion, drowsiness, seizure, somnolence.
Eye disorders	Not known	Blurred or double vision, miosis
Cardiac disorders	Not known	Bradycardia, palpitations, hypotension, toxic myocarditis
Gastrointestinal disorders	Not known	Constipation, GI irritation, biliary spasm,

		nausea, vomiting, loss of appetite, dry mouth, paralytic ileius, toxic megacolon, pancreatitis
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression
Hepatobiliary disorders	Not known	Chronic hepatic necrosis* Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Very rare	Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption
Renal and urinary disorders	Uncommon	Nephrotoxicity
	Not known	Ureteral spasm, antidiuretic effect, urinary retention, papillary necrosis
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome
	Not known	Tolerance, unusual tiredness or weakness, malaise, hypothermia
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis

* 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. 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.

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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.

Drug dependence

Repeated use of Co-Codamol 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).

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

- Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes or,
- Regularly consumes ethanol in excess of recommended amounts, or
- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, disseminated intravascular coagulation, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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. 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.

Further measures will depend on the severity, nature and course of clinical symptoms of paracetamol intoxication and should follow standard intensive care protocols.

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. The pupils may be pinpoint in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management
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.

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 four hours after ingestion, or eight hours if a sustained release preparation has been taken.

The opioid antagonist naloxone hydrochloride is an antidote to respiratory depression and must be administered intravenously.

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paracetamol, combinations excl. Psycholeptics
ATC Code: N02B 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

Paracetamol:

Absorption and Distribution
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 30 minutes to two hours after ingestion.

Biotransformation and Excretion
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 one hour to four hours. About 86% is excreted in the urine in 24 hours; 40-70% if free or conjugated morphine, 5-15% is free or conjugated norcodeine. Plasma protein binding is negligible at usual therapeutic concentrations but 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.

Codeine:

Absorption and Distribution
Codeine and its salts are readily absorbed from the GI tract and ingestion of codeine phosphate produces peak plasma concentrations in about one hour.

Biotransformation and Excretion
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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Potato starch

Maize starch
Talc
Povidone
Stearic acid
Magnesium stearate
Methyl para hydroxybenzoate (E218)
Propyl para hydroxybenzoate (E216)
Ethyl para hydroxybenzoate (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
Bottles: Keep the bottle tightly closed.

6.5 Nature and contents of container

Blister packs:
48, 50, 96 and 100 as POM 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.
Polypropylene/polyethylene containers: 50 and 100 as POM packs.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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