

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol Effervescent Tablets 8/500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8mg codeine phosphate hemihydrate and 500mg paracetamol.

Excipients with known effect:

Each tablet contains 438mg Sodium

Each tablet contains 5mg Aspartame

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet

White circular, flat bevelled edge tablet, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of pain, including muscular and rheumatic pains, headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains, discomfort associated with influenza, feverishness and feverish colds.

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

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine phosphate hemihydrate and paracetamol 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

One or two tablets dissolved in water every 4 to 6 hours as required, to a maximum of 8 tablets in 24 hours.

Paediatric population:

Children 16-18 years:

One or two tablets every 6 hours when necessary to a maximum of 8 tablets in 24 hours.

Children 12-15 years:

One tablet dissolved in water every 6 hours when necessary to a maximum of 4 tablets in 24 hours.

Children aged less than 12 years:

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

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

There is no current evidence for the alteration of the adult dose except where there is impaired hepatic function when dosage reduction may be necessary.

Method of administration

For oral use. The tablets should be dissolved in at least half a tumbler of water before taking.

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 limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

4.3 Contraindications

- Hypersensitivity to the active substances, other opioids 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.
- Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembranous colitis
- Respiratory depression
- Obstructive airways disease
- 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
- Conditions where morphine and opioids are contra-indicated e.g. acute alcoholism and where risk of paralytic ileus raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment).

4.4 Special warnings and precautions for use

The recommended dose should not be exceeded.

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.

Co-codamol should be used with caution in patients with:

- the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater than in those with non-cirrhotic alcoholic liver disease.
- Prolonged use of Co-codamol may cause hepatic necrosis
- 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 and/or convulsive disorders - 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
- hypotension and shock
- pheochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine
- sensitivity to the effects of opioids, e.g. the elderly and debilitated patients, with CNS depression
- Those with the potential to develop respiratory depression

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.

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).

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.

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 MAOI's or within 14 days of stopping MAOI's (see section 4.5).

Severe liver damage may occur if the maximal daily dose is exceeded, if Co-codamol is taken together with another Paracetamol containing product, or if Co-codamol is taken while consuming large amounts of alcohol.

At high dose codeine has most of the disadvantages of morphine, including respiratory depression. Codeine can produce drug dependence of the morphine type, and therefore has the potential for being abused. Codeine may impair the mental/or physical abilities required for the performance of potentially hazardous tasks.

Patients should be advised that immediate medical advice should be sought in the event of an overdose, even if they feel well, because of the risk of delayed, serious liver damage. They should be advised not to exceed the recommended dose, not to take other Paracetamol containing products concurrently, to consult their doctor if symptoms persist and to keep the product out of reach.

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).

Co-codamol should be used upon medical advice in patients with:

- Mild-to-moderate hepatocellular insufficiency
- Severe renal insufficiency.

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

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). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 phosphate hemihydrate and paracetamol.

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.

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.

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.

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%

Paediatric population

Not recommended for children under 12 years of age.

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

Concomitant administration with flucloxacillin

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 and 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.

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.

Label Warnings:

The label will state (To be displayed prominently on outer pack):

Can cause addiction

Contains opioid

Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

or if leaflet present:

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.
- Taking a painkiller for headaches too often or for too long can make them worse.

Headlines section

- This medicine can only be used for the short term of treatment of accurate moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone. Do not take less than four hours after taking other painkillers.
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days, it can make them worse.

Section 1: What co-codamol tablets are and what they are used for

It is an analgesic (painkiller) and is used for the short term treatment of acute moderate pain caused by headaches, migraine, toothache, neuralgia, period pain and rheumatic pains when other painkillers have not worked. Wait at least 4 hours after you last took other painkillers before taking this medicine.

Section 2: What you need to know before you take Co-codamol tablets

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it (see 'If you stop taking Co-codamol tablets').
- If you take a painkiller for headaches for more than three days it can make them worse.

Section 3: How to take co-codamol

This medicine should not be taken for more than 3 days. If the pain does not improve after 3 days, talk to your doctor for advice.

This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get **withdrawal symptoms** such as restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, shaking, shivering or sweating may occur if you suddenly stop taking this medicine. Contact your doctor for advice on how to stop taking Co-codamol tablets gradually to avoid withdrawal symptoms.

Section 4: Possible side effects

This will appear at the end of section 4:

How do I know if I am addicted?

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer than advised by your doctor
- You feel you need to use more than the recommended dose
- You are using the medicine for reasons other than prescribed
- When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again

The tablets contain aspartame and so should not be taken by patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

This medicinal product contains 438mg sodium per tablet, equivalent to 22% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 175% of the WHO recommended maximum daily intake for sodium.

Co-codamol Effervescent Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol can interact with the following:

- 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.
- Cholestyramine reduces paracetamol absorption.
- Drugs which interfere with the metabolism of paracetamol by competition with metabolic pathways or substrates e.g. anticonvulsants (phenytoin, phenobarbital, carbamazepine), 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 overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. It also increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.
- Other paracetamol containing products
- 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 risk factors (see section 4.4)

Codeine Phosphate can interact with the following:

- CNS depressants - enhanced sedative and/or hypotensive effect with alcohol, 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.
- Antibacterials, e.g. ciprofloxacin, - avoid premedication with opioids as reduced plasma ciprofloxacin concentration
- MAOIs (e.g. tranylcypromine) - use only with extreme caution as they may increase the effect of either the antidepressant or codeine. 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.
- 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.
- 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).

Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression.

4.6 Fertility, Pregnancy and lactation Pregnancy

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor fetoneonatal 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. There is a risk of gastric stasis and of inhalation pneumonia in mothers during labour.

Codeine can cause respiratory depression and withdrawal syndrome in newborns.

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. Codeine has been used for many years without apparent ill consequence and animal studies have not shown any hazard.

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.

Breast-feeding

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding. Codeine should not be used during breastfeeding (see section 4.3). Cocodamol Tablets 8/500mg are contraindicated during 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

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 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 offense to drive under the influence of this medicine
- However, you would not be committing an offense (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. Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.

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

A tabulated list of adverse reaction is outlined below:

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

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Tolerance and dependence can occur, especially with prolonged high dosage of codeine.

System organ class	Frequency	Undesirable effect
Blood and lymphatic disorders	Not known	Blood dyscrasias including methaemoglobinaemia, neutropenia, pancytopenia, leukopenia, thrombocytopenic purpura, haemolytic anaemia, agranulocytosis, thrombocytopenia
Immune system disorders	Not known	Hypersensitivity including skin rash may occur; anaphylactic shock, angioedema, urticaria, mucosal lesions, difficulty breathing, increased sweating, redness or flushed face.
Psychiatric system disorders	Not known	Confusional state, drowsiness, changes in mood, hallucinations, depression, trouble sleeping or nightmares, impaired mental functions, trembling, drug dependence (see section 4.4), dysphoria, euphoria
Nervous system disorders	Not known	Vertigo, dizziness, CNS excitation (restlessness/excitement), convulsions, seizure, somnolence, headache, raised intracranial pressure
Eye disorders	Not known	Blurred vision, double vision, miosis
Respiratory thoracic and mediastinal disorders	Not known	Bronchospasm ¹ , dyspnoea, Respiratory depression
Cardiac disorders	Not known	Bradycardia, palpitations, hypotension, toxic myocarditis
Gastro-intestinal disorders	Not known	Constipation, nausea, vomiting, GI irritation, biliary spasm, loss of appetite, dry mouth, paralytic ileus, toxic megacolon, abdominal pain
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known	Chronic hepatic necrosis [*] , Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Very Rare	Cases of serious skin reactions have been reported, including Toxic Epidermal

		Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption
	Not known	Pruritus, rash, urticarial, fixed drug eruption
Renal and urinary disorders	Uncommon	Nephrotoxicity
	Not known	Ureteral spasm, antidiuretic effect, urinary retention, papillary necrosis
Metabolism and nutrition disorders	Not Known	High anion gap metabolic acidosis*
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome
	Not known	Tolerance, unusual tiredness or weakness, malaise, hypothermia

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.

¹There have been cases of bronchospasm with Paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

*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.

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).

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.

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

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient:

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

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion.

Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, 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 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 pin-point 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 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations

excl. psycholeptics ATC Code: N02B E51

Paracetamol has analgesic and antipyretic properties but it has no useful anti-inflammatory properties.

Codeine phosphate is a centrally acting weak analgesic.

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

Absorption and Distribution

Codeine is absorbed from the gastro-intestinal tract and peak plasma-codeine concentrations are found in about one hour.

Biotransformation and Excretion

It is metabolised by O- and N- demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The elimination half-life has been reported to be between 3 and 4 hours after administration by mouth. About 86% is excreted in the urine in 24 hours, 40-70% if free or conjugated morphine, 5-15% is free or conjugated norcodeine.

Paracetamol

Absorption and Distribution

Paracetamol is rapidly and almost completely absorbed from the GI tract with peak plasma concentrations occurring about 30-60 minutes. Plasma half-life is 1-4 hours 2 hours after ingestion.

Biotransformation and Excretion

It is metabolised in the liver and excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1-4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids, plasma protein binding is variable. 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 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 overdose and cause liver damage.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate, citric acid, sodium carbonate, povidone, simeticone, sodium saccharin, aspartame (E951), polysorbate 80.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in a dry place and protect from light.

6.5 Nature and contents of container

4 layer paper/PE/aluminium/PE blisters.

Pack sizes: 100 tablets.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
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