SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Effervescent Tablets.
Codasolve 8mg/500mg/30mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500mg, codeine phosphate hemihydrate 8mg and caffeine 30mg.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.

White to off-white coloured circular flat bevelled tablets plain on both sides.

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 relieved by paracetamol, ibuprofen or aspirin alone.

This medicine is recommended for the relief of migraine, headache, backache, rheumatic pain, period pain, dental pain, strains and sprains and sciatica.

4.2 Posology and method of administration

Posology

Adults
1 to 2 tablets every 4-6 hours, up to 4 times a day. The minimum dosing interval is 4 hours. No more than 8 tablets in 24-hours.

Paediatric population:

Adolescents aged 16-18 years:
1-2 tablets every 6 hours up to 4 times a day. The minimum dosing interval is 6 hours. No more than 4 doses (8 tablets) should be given in 24 hours.

Adolescents aged 12-15 years:
1 tablet every 6 hours up to 4 times a day. The minimum dosing interval is 6 hours. No more than 4 doses (4 tablets) should be given 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).

Elderly patients:
Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing.

Renal impairment:
Patients who have been diagnose with kidney impairment must seek medical advice before taking this medication. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each interval to at least 6 hours. The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Hepatic impairment:
Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

A reduced maximum daily dose should be considered in patients who are underweight (for adults, those under 50kg) (see section 4.4 and 4.9).

Method of Administration

This medicine is for oral administration only.

This medicine should be dissolved in at least half a tumbler of water.

Treatment goals and discontinuation
Before initiating treatment with Codasolve, treatment duration and treatment goals, 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 healthcare professional.

Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage (see section 4.4 and 4.9).
Minimum dosing interval: 4 hours for adults and 6 hours for adolescents.

4.3 Contraindications

Hypersensitivity to paracetamol, codeine, caffeine, opioid analgesics or any of the other constituents.

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)

This medicine is not recommended in children and adolescents between 12 and 18 years who have breathing problems

In women who are pregnant or breastfeeding (see section 4.6)

In respiratory depression, chronic constipation

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

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. Paracetamol should be

administered only with particular caution under the following circumstances:

- Hepatocellular insufficiency
- Chronic alcoholism
- Renal failure (GFR $\leq$ 50 ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphatase dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- The elderly, adults and adolescents weighing less than 50 kg Do not exceed the stated dose.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Patients should be advised not to take other paracetamol or codeine containing products concurrently. Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

If symptoms persist for more than 3 days, consult your doctor. Keep out of the sight and reach of children.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

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.

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.

Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid since mild bronchospasms are reported in association with paracetamol (cross reaction).

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product

This medicinal product contains 403.24mg sodium per tablet, equivalent to 20.2% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 161% of the WHO recommended maximum daily intake for sodium.
Paracetamol, Codeine and Caffeine Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

The tablets also contain aspartame (a source of phenylalanine) and so should not be taken by people with phenylketonuria.

Patients should be advised not to take other paracetamol or codeine-containing products concurrently. Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

Patients taking, or who have taken, monoamine oxidase inhibitors (MAOIs) within the preceding two weeks (see section 4.5) should not take this product.

Codeine, as with other opioids should be used with caution in patients with hypotension, hypothyroidism, head injury or raised intracranial pressure.

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.

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 Codasolve. Repeated use of Codasolve 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 Codasolve 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 exibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

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.

In case of misuse and if the product is used for longer than recommended, patients may find that treatment is less effective 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.

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.

Hyperalgesia may be diagnosed if the patient misuses Codasolve 8mg/500mg/30mg Effervescent Tablets and uses long-term opioid therapy and 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.

Drug withdrawal syndrome

Addiction can cause drug withdrawal syndrome upon abrupt cessation of therapy or dose reduction.

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.

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

Concomitant use of Codasolve 8mg/500mg/30mg Effervescent Tablets and sedative medicines such as benzodiazepines or related drugs (such as pregabalin and gabapentin) 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 this medicine 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.

The label will state:

Front of Pack

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

Back of Pack

- For the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.
- For the treatment of migraine, headache, dental pain, period pain, backache, rheumatic pain, strains and sprains and sciatica.
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist.

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:
Headlines section (to be prominently displayed)

- This medicine can only be used for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

- 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 PARACETAMOL, CODEINE & CAFFEINE TABLETS ARE AND WHAT THEY ARE USED FOR

This medicine can be used in patients over 12 years of age for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

They are used to relieve migraine, headache, dental pain, period pain, strains and sprains, backache, rheumatic pain and sciatica.

Section 2: WHAT YOU NEED TO KNOW BBEFORE YOU TAKE PARACETAMOL CODEINE & CAFFEINE 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.
- If you take a painkiller for headaches for more than three days it can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Section 3: HOW TO TAKE PARACETAMOL, CODEINE & CAFFEINE TABLETS

- Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist 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. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: POSSIBLE SIDE EFFECTS

- Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday – Friday) or fill in a paper form available from your local pharmacy.

How do I know if I am addicted?

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

- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. Cholestyramine should not be administered within one hour of taking paracetamol. 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.

Paracetamol is metabolized in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or induce this route(e.g. barbiturates, such as phenobarbitone, tricyclic antidepressants, alcohol, carbamazepine, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes),causing hepatotoxicity, particularly in overdose (see section 4.9).

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced because probenecid reduces the clearance of paracetamol by 50% since it prevents the conjugation of paracetamol with glucuronic acid.
There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics, but its validity has been criticised and evidence of a clinically relevant interaction appears to be lacking. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

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)
Caffeine
Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers. Caffeine may enhance the tachycardia effect of some decongestants.

Codeine
Codeine may antagonize the effects of metoclopramide and domperidone on gastrointestinal motility.
Codeine potentiates the central depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

Opioid analgesics should be given with care to patients receiving monoamine
oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

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.

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOI) and result in serotonin syndrome.

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.

4.6 Fertility, pregnancy and lactation Pregnancy

Use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate.

The safety of paracetamol-caffeine-codeine during pregnancy has not been established relative to the possible adverse effects of foetal development and should be avoided during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

The patient should be advised of the risk of neonatal opioid withdrawal syndrome, and it should be ensured that appropriate treatment will be available.

Paracetamol

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.

Lactation

Codeine-containing products must not be used while breast feeding unless prescribed by a doctor. (See section 4.3) 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.

In nursing mothers, who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia and difficulty breast feeding or

breathing. In severe cases respiratory depression and death can occur. The lowest effective dose should be used, for the shortest possible time. Nursing mothers should be informed about carefully monitoring the infant during treatment for any sign and symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breast feeding, breathing difficulties, and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed.

Although significant caffeine toxicity has not been observed in breastfed infants, caffeine may have a stimulating effect on the infant.

Due to the caffeine content of this product it should not be used if you are pregnant or breast feeding.

Fertility

There are no data available regarding the influence of Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Effervescent Tablets on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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 taking 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:

o The medicine has been taken to treat a medical or dental problem and

o You have taken it according to the information provided with the medicine and

o It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post- marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system.

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10),

uncommon (≥1/1,000, <1/100), rare (≥1/10,000, 363 <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Paracetamol

Body System	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Not Known
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome/toxic epidermal necrolysis	Not Known Not Known
	Allergies (not including angioedema)	Rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Not Known
Hepatobiliary disorders	Hepatic dysfunction	Not Known
Skin and subcutaneous tissue disorders	Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema Very rare cases of serious skin reactions have been reported Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), druginduced dermatitis, acute generalized exanthematous pustulosis (AGEP)	Very rare Very rare
Renal and urinary disorders	Sterile pyuria (cloudy urine)	Very rare
Metabolism and nutrition disorders	High anion gap metabolic acidosis**	Not Known

Description of selected adverse reactions

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

**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.

Caffeine

Body System	Undesirable effect	Frequency
Central nervous system	Nervousness Dizziness	Not known

When the recommended paracetamol-caffeine-codeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Codeine

Adverse reactions identified during post-marketing use are listed below by MedDRA system organ class. The frequency of these reactions is not known.

Body System	Undesirable effect	Frequency
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine (see section 4.4)	Not Known
Gastrointestinal disorder	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis	Not Known
Nervous system disorder	Dizziness, worsening of headache with prolonged use, Hyperalgesia drowsiness.	Not Known
General disorders and administration	Drug withdrawal syndrome	Uncommon
Renal and urinary disorders	Difficulty with micturition	Not Known
Skin and subcutaneous tissue disorder	Pruritus, sweating	Not Known
Hepatobiliary disorders	Sphincter of Oddi dysfunction	Not Known

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

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Codeine

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

Symptoms

An overdose of codeine is characterised, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

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.

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g 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 overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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.

Caffeine

Symptoms

Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Management

Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose, but can be considered for up to four hours after the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

Summary

Treatment of overdose with this medicine requires assessment of plasma paracetamol levels for antidote treatment, with signs and symptoms of codeine and caffeine toxicity being managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics: codeine and paracetamol. ATC code: NO2BE51

Paracetamol is a well-established analgesic, caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action. Codeine phosphate has moderate analgesic and weak cough-suppressant effects. 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.
Paracetamol is a well-established analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.
Caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action. Caffeine stimulates all levels of the CNS, although its cortical effects are milder and shorter than those of amphetamines.
Analgesia adjunct: caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhancing pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.
Caffeine enhances and prolongs the analgesic activity of paracetamol up to 3 hours.
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.

5.2 Pharmacokinetic properties

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. After oral administration, concentration of paracetamol in plasma reaches a peak in 10-60 minutes depending on pharmaceutical form.

Caffeine is rapidly but irregularly absorbed after oral administration; absorption is pH related. Maximum plasma concentrations are achieved within one hour and the plasma half-life is about 4.9 hours, but there are large inter-individual and intraindividual
differences ranging between 1.9-12.2 hours.

Codeine phosphate is well absorbed from the gastrointestinal tract after oral administration with peak plasma concentration being reached in approximately 1 hour after ingestion.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids and

exhibits variable protein binding.

Caffeine administered orally is practically fully bioavailable and distributes into all body fluids. The mean plasma protein binding of caffeine is 35%. Maximum plasma concentrations are reached after 30-40 minutes.

Codeine distributes widely throughout the body and exhibits low plasma protein binding with a plasma half-life of approximately 2.5 to 3 hours.

Biotransformation

Paracetamol is mainly metabolised in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinone imine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Caffeine is almost completely metabolised in the liver by oxidation, demethylation and acetylation, and is excreted in the urine. The major metabolites are 1-methylxantine, 7-methylxantine, 1,7-dimethylxantine (paraxantine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6-formylamino 3-methyluracil (AMFU).

Codeine is metabolised in the liver by the hepatic enzyme Cytochrome P450 2D6 (CYP2D6) to form morphine, and Cytochrome (CYP3A4) to form norcodeine, which are further metabolized by conjugation with glucuronic acid.

Elimination

Less than 5% is excreted as unmodified *paracetamol*; the elimination half-life varies from 1 to 4 hours. Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulfate conjugates (20-30%). In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. and the plasma half-life is 1-4 hours. Excretion is almost exclusively renal, in the form of conjugated metabolites.

Caffeine and its metabolites are primarily eliminated by the kidneys. Plasma half-life = 4-10 hours. In 48 hours, 45% of a dose is excreted in the urine as l-methylxanthine and l-methyluric acid.

85% of an oral dose of *codeine* is excreted in the urine within 24 hours, 40-70% of this being free or conjugated codeine, 5-15% free or conjugated morphine, 10-20% free or conjugated norcodeine, and trace amounts may be free or conjugated normorphine.

5.3 Preclinical safety data

There are no pre-clinical 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

Citric Acid (anhydrous)

Povidone (K30)

Sodium Hydrogen Carbonate

Saccharin Sodium

Sodium Carbonate Anhydrous

Simeticone

Polysorbate 80

Aspartame (E951)

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Strip formed from 4 ply laminate (paper/LDPE/aluminium/LDPE).

Pack sizes of 16, 24 or 32 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
2nd Floor, Connect 38,
1 Dover Place,
Ashford, Kent, England,
TN23 1FB.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 51463/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/01/2025

10 DATE OF REVISION OF THE TEXT

23/03/2026