# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Propain Caplets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Yellow compressed caplets with a scored line on one side, each containing paracetamol BP 400mg, codeine phosphate BP 10mg, diphenhydramine hydrochloride BP 5mg, caffeine anhydrous BP 50mg.

## 3 PHARMACEUTICAL FORM

Tablets

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Propain Caplets are 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, ibuprofen or aspirin alone.

Propain Caplets may be used in the treatment of headache, migraine, muscular pain, period pain and toothache.

### 4.2 Posology and method of administration

Before initiating treatment with Propain Caplets, treatment duration and treatment goals, should be agreed together with the patient, in accordance with pain management guidelines.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician. The duration of treatment should be as short as possible, and if no

effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

For oral administration

Adults: take 1 or 2 caplets every 4 hours as required, up to a maximum of 10 caplets in 24 hours. The suggested dosage may also be administered to the elderly (in the absence of other contra-indications).

Paediatric population:

Children aged 16-18 years: take 1 or 2 caplets every 6 hours as required, up to a maximum of 8 caplets in 24 hours.

Children aged 12 years to 15 years: take 1 caplet every 6 hours when necessary up to a maximum of 4 caplets in 24 hours.

Children aged less than 12 years:

Codeine is contraindicated 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).

## 4.3 Contraindications

- Hypersensitivity to the active substances, (paracetamol), (codeine), (diphenhydramine), (caffeine) or to any of the excipients listed in section 6.1.
- In patients with respiratory depression, chronic constipation, severe liver disease, acute alcoholism, raised intracranial pressure, head trauma, risk of paralytic ileus, acute abdomen, stenosing peptic ulcer or pyloroduodenal obstruction.
- In children aged below 12 years
- All paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)
- In women during breastfeeding (see section 4.6).
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

## 4.4 Special warnings and precautions for use

This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant agents. Patients should be warned against taking charge of

vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

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.

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 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.

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

**Paracetamol**

Dosage in excess of those recommended may cause severe liver damage.

Care is advised in the administration of paracetamol-containing product to patients with severe renal or severe hepatic impairment and in those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Patients suffering from liver or kidney disease should take paracetamol under medical supervision. The dosage in renal impairment must be reduced.

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).

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

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.

**Codeine**

The elderly are more likely to metabolise or eliminate opioid analgesics more slowly than young adults. Use with caution in the elderly, who are more likely to experience side-effects. Avoid use in elderly patients with confusion.

Codeine may cause faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction.

Dependence can develop with repeated use of codeine and therefore withdrawal symptoms may appear if the product is withdrawn abruptly.

Caution is advised when treating patients with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, shock, obstructive bowel disorders, acute abdominal conditions, recent gastrointestinal surgery, gallstones, a history of cardiac arrhythmias or convulsions. Care should be taken with patients with a history of drug abuse or emotional instability.

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

<u>Tolerance and opioid use disorder (abuse and dependence):</u>

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Propain Caplets. Repeated use of Propain Caplets 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 Propain Caplets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

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

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

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. 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.

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 this medicine and sedative medicines such as benzodiazepines or related drugs (such as pregabalin and gabapentin) may result in profound sedation, respiratory depression, hypotension, 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.

Hepatobiliary disorders

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

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic 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 summarised 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.

**Diphenhydramine**

Diphenhydramine should be used with caution in patients with myasthenia gravis, epilepsy or seizure disorders, prostatic hypertrophy, urinary retention, narrow-angle glaucoma, asthma, bronchitis and chronic obstructive pulmonary disease (COPD), moderate to severe hepatic impairment.

Avoid use of other antihistamine-containing preparations, including topical antihistamines and cough and cold medicines.

May increase the effects of alcohol, therefore alcohol should be avoided.

**Caffeine**

Excessive intake of caffeine (e.g. coffee, tea or other caffeinated drinks) should be avoided whilst taking this product.

**Propain Caplets contains:**

This medicine contains methyl (E218), ethyl (E214), propyl (E216) and butyl parabens. May cause allergic reactions (possibly delayed).

**Patients should be warned of the following via the label and leaflet:**

- Do not exceed the recommended dose.
- Do not take any other paracetamol-containing products.
- Consult your doctor if no relief is obtained with the recommended dosage.
- Keep out of the sight and reach of children.
- Do not give to children under 12.
- This product contains paracetamol.
- Immediate medical advice should be sought in the event of an overdose even if you feel well due to the risk of severe liver damage.
- Alcoholic drink should be avoided.

**The label will state (prominently in a rectangle):**

Front of Pack

- Can cause addiction
- Contains opioid
- For three days use only

Back of Pack

- List of indications as agreed in 4.1 of the SmPC

- If you need to take this medicine continuously for more than three days you must 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 …….(indications)
- 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 the medicine is for

- Succinct description of the indications from 4.1 of the SmPC.

Section 2: Before taking

- 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.

Section 3: Dosage

- 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: Side effects

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This

includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.go.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

**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 gastro-intestinal absorption of paracetamol may be delayed by drugs such as anticholinergic agents or opioid analgesics which decrease gastric emptying. Colestyramine may reduce the absorption of paracetamol. Metoclopramide and domperidone may potentiate the speed of absorption of paracetamol.

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.

Paracetamol is metabolised 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 criticized 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.

Paracetamol with aspirin has been noted to increase the blood concentration of unhydrolysed aspirin.

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)

**Codeine:**

The depressant effects of some of the opioids may be exaggerated and prolonged by phenothiazines, monoamine oxidase inhibitors, tricyclic antidepressants, alcohol, anaesthetics, hypnotics and sedatives. Codeine may cause a hypotensive or hypertensive effect if used with MAOI's. Opiate analgesics may interact with MAOI's and result in serotonin syndrome. Concomitant use should be avoided and codeine should not be administered until 2 weeks after MAOI's are discontinued.

Alcohol, antipsychotics, anxiolytics and hypnotics may enhance the sedative and hypotensive effects of codeine.

When codeine is given with cisapride, metoclopramide or domperidone, the gut motility properties of these drugs may be lessened due to the constipating effect of codeine.

Cimetidine may inhibit the metabolism of opiates.

The absorption of mexiletine may be delayed by codeine and as such the antiarrhythmic effect may be lessened.

Naltrexone and naloxone antagonise the analgesic, CNS and respiratory depressant effect of opioids.

The hypotensive action of diuretics and antihypertensives may be potentiated by codeine.

Use of antidiarrhoeals and antiperistaltic drugs may increase the risk of severe constipation. Concurrent use of antimuscarinics may lead to a greater risk of severe constipation which subsequently causes paralytic ileus and/or urinary retention.

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs, gabapentinoids (gabapentin and pregabalin), 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).

**Diphenhydramine**

Diphenhydramine may potentiate the sedative effects of alcohol and other CNS depressants (e.g. tranquillizers, hypnotics and anxiolytics). The effects of the anticholinergic drugs such as atropine and tricyclic antidepressants may be enhanced, therefore medical advice should be sought before taking diphenhydramine with such medicines.

MAOI's may enhance the antimuscarinic effects of diphenhydramine. The product should be used with caution with MAOIs or within 2 weeks of stopping an MAOI.

As diphenhydramine has some antimuscarinic activity, the effects of some

anticholinergic drugs (e.g. atropine, tricyclic antidepressants) may be potentiated therefore medical advice should be sought before taking diphenhydramine with such medicines.

Diphenhydramine is an inhibitor of the cytochrome p450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with drugs which are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.

Diphenhydramine should not be used in patients receiving any of the above drugs unless directed by a doctor.

**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.

Caffeine enhances the action of the ergot alkaloids in the treatment of migraine. Small doses of caffeine (5 to 10mg/kg) also appear to reduce the ED 50 for aspirin, indometacin and phenylbutazone by more than threefold.

## 4.6 Fertility, pregnancy and lactation

Not recommended in pregnancy and lactation.

**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.

There is no available data on the effect of paracetamol on fertility.

**Codeine**

In view of the possible association of codeine with respiratory depression, use of the product during pregnancy should be avoided. This includes maternal use during labour because of the potential for respiratory depression in the neonate.

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.

Codeine should not be used during breastfeeding as codeine may be excreted in breast milk and may cause respiratory depression in the infant. (see section 4.3).

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.

There is no available data on the effect of codeine on fertility.

**Diphenhydramine**

Diphenhydramine crosses the placenta. Because animal reproduction studies are not always predictive of human response and since there is inadequate experience with use of diphenhydramine in pregnant women, the potential risk for humans is unknown. Use of sedating antihistamines during the third trimester may result in reactions in the newborn or premature neonates. This drug is not recommended during pregnancy.

Diphenhydramine has been detected in breast milk, but the effect of this on breastfed infants is unknown. Diphenhydramine is not recommended for use during breastfeeding.

There is no available data on the effect of diphenhydramine on fertility.

**Caffeine**

Caffeine is not recommended for use during pregnancy.

Caffeine in breast milk may potentially have a stimulating effect on breast fed infants.

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

There is insufficient data to assess any effect of caffeine on fertility.

## 4.7 Effects on ability to drive and use machines

Propain caplets may cause drowsiness, dizziness or sedation, blurred vision, cognitive and psychomotor impairment. These can seriously affect the patient's ability to drive and use machines. If affected, do not drive or operate machinery. Avoid alcoholic drinks.

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 a '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

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to<1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data)

**Paracetamol**

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias (including thrombocytopenia and agranulocytosis) and acute pancreatitis, but these were not necessarily causally related to paracetamol.

| **Body system** | **Undesirable effect** |
|---|---|
| **Blood and lymphatic system disorders** | Not known: Thrombocytopenia*, agranulocytosis* |
| **Immune system disorders** | Very rare: Blood dyscrasias* (blood disorder), cases of serious skin reactions have been reported, anaphylaxis, cutaneous hypersensitivity reactions including (amongst others) skin rashes and angioedema. |
| | Not known: Anaphylaxis |
| **Respiratory, thoracic and mediastinal disorders** | Very rare: Bronchospasm – more likely in patients sensitive to aspirin and other NSAIDs |
| **Hepatobiliary disorders** | Very rare: Hepatic dysfunction |
| **Gastrointestinal disorders** | Not known: acute pancreatitis* |
| **Metabolism and nutrition disorders** | Not known: High anion gap metabolic acidosis** |

| | |
|---|---|
| **Skin and subcutaneous tissue disorders** | Very rare: Cutaneous hypersensitivity reactions including purpura, urticaria and angioedema.<br><br>Very rare cases of serious skin reactions have been reported. Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug induced dermatitis, acute generalised exanthematous pustulosis (AGEP). |
| **Renal and urinary disorders** | Very rare: Sterile pyuria (cloudy urine) |

*Not necessarily causally related to paracetamol.

** 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.

**Codeine**

Codeine may cause nausea, vomiting, constipation and drowsiness in sensitive patients. Other side effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, respiratory depression, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, hallucinations, dysphoria, mood changes, miosis, decreased libido and potency, rashes, urticaria and pruritus. Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.

| **Body system** | **Undesirable effect** |
|---|---|
| **Immune system disorders** | Not known: Allergic reactions (hypersensitivity) |
| **Psychiatric disorders** | Not known: Dysphoria, hallucinations, mood changes, confusion, decreased libido, nightmares, restlessness, drug dependency can occur after prolonged use of codeine (see section 4.4) |
| **Nervous system disorders** | Not known: Dizziness, hyperalgesia, light-headedness, drowsiness (somnolence) |

| | |
|---|---|
| **Eye disorders** | Not known: Miosis, blurred vision, double vision (diplopia) |
| **Ear and labyrinth disorders** | Not known: Vertigo |
| **Cardiac disorders** | Not known: Bradycardia, palpitations, tachycardia |
| **Vascular disorders** | Not known: Postural hypotension, hypotension, flushing of face |
| **Respiratory, thoracic and mediastinal disorders** | Not known: Respiratory depression |
| **Gastrointestinal disorders** | Not known: Constipation, nausea, vomiting, dry mouth, stomach cramps |
| **Hepatobiliary spasm** | Not known: Biliary spasm, sphincter of Oddi dysfunction |
| **Skin and subcutaneous tissue disorders** | Not known: Pruritus, sweating, urticaria, rash |
| **Musculoskeletal and connective tissue disorders** | Not known: Muscle rigidity |
| **Renal and urinary disorders** | Not known: Urinary retention, ureteral spasm, difficulties in micturition, dysuria, polyuria |
| **Reproductive system and breast disorders** | Not known: Decreased potency (erectile dysfunction) |
| **General disorders and administration site conditions** | Not known: Hypothermia, facial oedema |
| | Uncommon: Drug withdrawal syndrome |
| **Investigations** | Not known: Urine output decreased |

**Drug dependence**

Repeated use of Propain Caplets 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).

**Diphenhydramine**

Drowsiness is seen with all of the older antihistamines such as diphenhydramine especially in high dosage. Also seen are headache, psychomotor impairment, antimuscarinic effects (e.g. urinary retention), dry mouth, blurred vision and gastro-intestinal disturbance. Other less common side effects that have been reported with antihistamines are: palpitations, arrhythmias, hypotension, hypersensitivity reactions (inc. bronchospasm, angioedema and anaphylaxis), rashes and photosensitivity, extrapyramidal effects, confusion, depression, sleep disturbance, tremor, convulsion, sweating, myalgia, paraesthesia, blood disorder, liver dysfunction and hair loss.

| **Body system** | **Undesirable effect** |
|---|---|
| **Blood and lymphatic system disorders** | Not known: Agranulocytosis |
| **Immune system disorders** | Not known: Hypersensitivity reactions including rash, urticaria, dyspnoea and angiodema |
| **Psychiatric disorders** | Not known: Confusion, paradoxical excitation (e.g. increased energy, restlessness, nervousness), depression, sleep disturbances<br><br>*The elderly are more prone to confusion and paradoxical excitation |
| **Nervous system disorders** | Common: Sedation, drowsiness, disturbance in attention, unsteadiness, dizziness<br><br>Not known: Convulsions, headache, paraesthesia, dyskinesias |
| **Eye disorders** | Not known: Blurred vision |
| **Cardiac disorders** | Not known: Tachycardia, palpitations, arrhythmias |
| **Respiratory, thoracic and mediastinal disorders** | Not known: Thickening of bronchial secretions |
| **Gastrointestinal disorders** | Common: Dry mouth<br><br>Unknown: Gastrointestinal |

| | |
|---|---|
| | disturbance including nausea, vomiting |
| **Musculoskeletal and connective tissue disorders** | Not known: Muscle twitching |
| **Renal and urinary disorders** | Not known: Urinary difficulty, urinary retentions |
| **General disorders and administration site conditions** | Common: Fatigue |

**Caffeine**

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects.

| **Body system** | **Undesirable effect** |
|---|---|
| **Central nervous system** | Not known: Dizziness, headache, nervousness, tremor |
| **Cardiac disorders** | Not known: Palpitation |
| **Psychiatric disorders** | Not known: Insomnia, restlessness, anxiety and irritability |
| **Gastrointestinal disorders** | Very rare: Gastrointestinal disturbances |

**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: 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.

**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 depleted 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, 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.

**Codeine**

**Symptoms**
Central nervous system depression may develop as well as respiratory depression. The pupils may be pin-point in size and nausea and vomiting are common. Possible but unlikely effects are hypotension and tachycardia. The effects in overdosage of codeine are potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

**Management**
If coma or respiratory depression is present give naloxone, preferably intravenously, at a dose of 0.4 to 2mg for adults and 0.01mg/kg body weight for children. Repeat the dose if there is no response within two minutes. Large doses (4mg) of naloxone may be required in a seriously poisoned patient. Intramuscular naloxone is an alternative in the event that IV access is not possible, or if the patient is threatening to self-discharge when it may help reduce the risk of respiratory arrest. Failure of a definite opioid overdose to respond to large doses of naloxone suggests that another CNS depressant drug or brain damage is present.

Observe the patient carefully for recurrence of CNS and respiratory depression. Repeated doses of naloxone may be required. If so, intravenous infusion of naloxone may be useful. An infusion of 60% of the initial dose per hour is a useful starting point. A 200 microgram/ml solution for infusion using an IV pump can be used and the dose adjusted to clinical response. Infusions are not a substitute for frequent review of the patient's clinical state.

A clear airway, adequate ventilation and oxygenation should be established without delay if consciousness is impaired.
Consider activated charcoal (50g for adults; 10-15g for children) if an adult presents within 1 hour of ingestion of more than 350mg, or a child more than 5mg/kg, provided the airway can be protected.

Observe patient for at least 4 hours after ingestion. Other supportive measures should be taken as indicated by the patient's progress.

**Diphenhydramine**

Overdose is likely to result in effects similar to those listed under adverse reactions.

Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse.

Treatment should be supportive and directed towards specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

**Caffeine**

Symptoms:
CNS stimulation: Anxiety, nervousness, agitation, jitteriness, tremors, convulsions, restlessness, insomnia, excitement, irritability, headaches, muscle twitching, confusion.
Cardiac: Tachycardia, cardiac arrhythmia.
Gastric: Abdominal or stomach and epigastric pains, vomiting
Other: Diuresis, facial flushing.

The symptoms of caffeine overdose may be masked by the depression of consciousness associated with possible codeine overdose when associated with this combination.

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.

Treatment:
Treatment is primarily symptomatic and supportive. Acute toxicity is unlikely to occur with the low levels of caffeine in this product.
CNS symptoms can be treated with intravenous diazepam, phenobarbitone or phenytoin.
For cardiac symptoms monitoring of ECG is required.
Diuresis should be treated by maintaining fluid and electrolyte balance.
Gastric symptoms can be treated using antacids.

If acute poisoning is suspected treatment generally includes emesis with ipecacuanha syrup and/or gastric lavage if caffeine has been ingested within 4 hours in amounts over 15mg/kg bodyweight. However whilst treatment of this nature would be beneficial in reducing absorption of caffeine, consideration would need to be given to the level on consciousness of the patient in view of the sedating effect of codeine in this product combination.

Administration of activated charcoal may be useful within the first 4 hours if precautions are taken to minimize aspiration. Magnesium sulphate cathartic may also be helpful.

To enhance elimination haemoperfusion is usually more effective than dialysis.

**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

**Paracetamol**
Pharmacotherapeutic classification: Other Analgesics and Antipyretics – Anilides
ATC code: N02B E51
Paracetamol has analgesic (mainly peripheral) and antipyretic properties.

**Codeine**
Pharmacotherapeutic classification: Opioids – Natural opium alkaloids ATC code: N02AA59
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.

**Diphenhydramine**
Pharmacotherapeutic classification: Antihistamines for Systemic Use – aminoalkyl ethers ATC code: R06AA02

Diphenhydramine hydrochloride is an ethanolamine-derivative antihistamine. It is an antihistamine with anti-cholinergic and sedative effects. It acts by inhibiting the effects of H1-receptors.

Diphenhydramine hydrochloride is an antihistamine with sedative, antiemetic, anti-cholinergic and local anaesthetic properties. These actions are considered useful in those conditions for which Propain is indicated.

**Caffeine**
Pharmacotherapeutic classification: Psychostimulants, Agents used for ADHD and Nootropics – Xanthine derivatives ATC code: N06BC01
Caffeine is a CNS stimulant.

## 5.2 Pharmacokinetic properties

### Paracetamol

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine, mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life ranges from 1 to 4 hours. Plasma protein binding is negligible at therapeutic concentrations, although this is dose dependent.

### Codeine

Codeine Phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after one hour. Codeine is metabolised in the liver by O- and N-demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours.

**Diphenhydramine**
Diphenhydramine hydrochloride is rapidly absorbed following oral administration.

Apparently it undergoes first-pass metabolism in the liver and only about 40-60% of an oral dose reaches systematic circulation as unchanged diphenhydramine.

It is rapidly distributed throughout the whole body. Peak plasma concentrations are attained within 1-4 hours. The sedative effect also appears to be maximal within 1-3 hours after administration of a single dose.
It is positively correlated with the plasma drug concentration.

Diphenhydramine is approx 80-85% bound to plasma proteins.
Diphenhydramine is rapidly and almost completely metabolised. The drug is

metabolised principally to diphenylmethoxyacetic acid and is also dealkylated.

The metabolites are conjugated with glycine and glutamine and excreted in urine.
Only about 1% of a single dose is excreted unchanged in urine.

The elimination half-life ranges from 2.4-9.3 hours in healthy adults. The terminal elimination half-life is prolonged in liver cirrhosis.

**Caffeine**
Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. Caffeine passes readily into the CNS and into saliva. In adults, caffeine is metabolised almost completely via oxidation, demethylation and acetylation and is excreted in the urine as various metabolites with only about 1% being excreted unchanged. Elimination half life is approximately 3 to 6 hours in adults.

### 5.3 Preclinical safety data

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

There are no pre-clinical data of relevance to the prescriber which are additional to that covered in other sections of the SPC.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Magnesium Stearate

Maize Starch

Talc

Methyl, ethyl, propyl and butyl parabens

Spirit of Chloroform

Gelatin

Quinoline yellow (E104)

Erythrosine (E127)

Purified Water

### 6.2 Incompatibilities

Not applicable in terms of solid medication.

### 6.3 Shelf life

36 Months.

### 6.4 Special precautions for storage

None.

### 6.5 Nature and contents of container

Blister: Lidding material - 35gsm Glassine paper/ad/9 micron soft temper Aluminium/compatible heat seal. Base material - 250 micron uPVC.

Pack sizes: 12, 16, 24, 32

### 6.6 Special precautions for disposal

None.

## 7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,

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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0017

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 March 2000

## 10 DATE OF REVISION OF THE TEXT

31/03/2026