# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Zapain 30mg/500mg Capsules
Co-codamol 30mg/500mg Capsules

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Paracetamol 500 mg, and Codeine Phosphate 30mg.
For full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

Capsule.
Hard gelatin capsules, size 0 with a scarlet red cap and white body.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the relief of severe pain.

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

### 4.2 Posology and method of administration

Posology

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

*Adults:* The usual dose is one or two capsules every four to six hours as required up to a maximum of 8 capsules in any 24 hour period.

Codeine 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. Maximum daily dose should not exceed 240 mg.

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.

*Elderly*
A reduced dosage may be necessary.

*Paediatric population*

Children aged 16-18 years: 1-2 capsules every 6 hours when necessary up to a maximum of 8 capsules in 24 hours.

Children aged 12 – 15 years: 1 capsule every 6 hours when necessary up to a maximum of 4 capsules 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).

Dosage needs to be adjusted according to the severity of pain and the response of the patient.

Tolerance to Codeine can develop with continued use. The incidence of unwanted effects is dose related. Doses of Codeine above 60 mg are associated with an increase in unwanted effects.

Method of administration
Oral.

*Treatment goals and discontinuation*
Before initiating treatment with Zapain, 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*
Zapain should not be used longer than necessary.

## 4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Children under 12 years of age.

Zapain is contraindicated in patients with moderate to severe degrees of renal or hepatic impairment.

It is contraindicated in patients for whom opiate medications should not be used, such as patients with acute asthma, obstructive airway disease, respiratory depression, acute alcoholism, head injuries, raised intracranial pressure, after biliary surgery and patients suffering from diarrhoea of any cause.

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life threatening adverse reactions (see section 4.4)

In women during breastfeeding (see section 4.6)

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

## 4.4 Special warnings and precautions for use

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

**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 Zapain. Repeated use of Zapain 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 Zapain 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 Zapain 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 efficacy and safety of Zapain capsules in children below the age of 12 years has not been established and use in such children is contraindicated.

Zapain capsules must be used with caution in debilitated, patients with impaired hepatic or renal function, CNS depression, pre-existing respiratory depression or those with the potential to develop respiratory depression, urethral stricture, and biliary tract disorders (including recent biliary tract surgery).

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 acute abdominal conditions like inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

**CYP2D6 metabolism**
Codeine is metabolised by 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 metabolizer 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% |

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

Paediatric population
**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 ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

**Children with compromised respiratory function**
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity."

The hazards of paracetamol overdose are greater in those with non-cirrhotic alcoholic liver disease.

Severe liver damage may occur if the maximal daily dose of paracetamol is exceeded or if this product is taken while consuming large amounts of alcohol or with another paracetamol-containing product.

Although paracetamol might logically be presumed to be the best alternative analgesic in patients with aspirin sensitivity, cross reactions have been reported. Patients positively identified with aspirin induced asthma, or who have ever experienced an asthmatic reaction to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) or are at high risk of aspirin induced asthma should avoid all products that contain aspirin or NSAIDs indefinitely. In these

patients paracetamol should be recommended in low or moderate dose (< 1000 mg in a single dose) unless contraindicated.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with codeine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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.

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 has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Risk from concomitant use of sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids:

Concomitant use of Zapain Capsules and sedative medicines (such as benzodiazepines or related drugs) or gabapentinoids (gabapentin and pregabalin) may result in profound sedation, respiratory depression, hypotension, coma or death. Because of these risks, concomitant prescribing with these medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Zapain Capsules concomitantly with sedative medicines or gabapentinoids, 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).

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

Patients should be advised that immediate medical advice should be sought in the event of an overdose, because of the risk of delayed serious liver damage.

Patients must be advised not to exceed the recommended doses.
Patients must be advised not to take other products containing opiate derivatives or other paracetamol-containing products.
Patients should be advised to consult their doctor if symptoms persist and to keep the product out of the reach of children.

The leaflet will state in a prominent position in the ‘before taking’ section
• Do not take for longer than directed by your prescriber
• Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop taking the tablets.
• Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack- not boxed):
• Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

The label will state (boxed):
Do not take with any other paracetamol-containing products
Immediate medical advice should be sought in the event of an overdose, even if you feel well

The leaflet will state “Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.”

## 4.5 Interaction with other medicinal products and other forms of interaction

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.

Quinine or quinidine may inhibit the analgesic actions of codeine.

The CNS depressant action of Zapain may be enhanced by co-administration with any other drug which have a CNS depressant effect (eg. sedative hypnotics, phenothiazines, antipsychotics, other opioid analgesics, tranquilisers and alcohol)**.** Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Zapain and MAOIs or tricyclic antidepressants may increase the effect of either agent.

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.

Enzyme-inducing medicines, such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approximately 60 %. Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of causing lowered concentrations of paracetamol. In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme inducing agents.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and co administration with an antimuscarine drug may cause urinary retention.

The absorption of paracetamol is speeded by metoclopramide or domperidone, and absorption is reduced by colestyramine.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. Cimetidine may inhibit codeine metabolism.

Opioids may interfere with the results of plasma amylase, lipase, bilirubin, ALP, LDH, AST, and ALT tests.

The effects of codeine on the gut may interfere with diagnostic tests of gastrointestinal functions.
The anticoagulant effect of warfarin and other coumarins may be increased by long term regular daily use of paracetamol, with increased risk of bleeding. Occasional doses of paracetamol do not have a significant effect on these anticoagulants.

Concurrent use with centrally acting muscle relaxants may increase the risk of respiratory depression.

Sedative medicines (such as benzodiazepines or related drugs) and Gabapentinoids (gabapentin and pregabalin):
The concomitant use of opioids with sedative medicines (such as benzodiazepines or related drugs) or Gabapentinoids (gabapentin and pregabalin) increases the risk of profound sedation, respiratory depression, hypotension, coma or death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

## 4.6. Fertility, pregnancy and lactation

Pregnancy

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

Codeine should not be used during breastfeeding (see section 4.3).

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

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.

Fertility:
No data available

## 4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if Copaz causes dizziness or sedation. Codeine may cause visual disturbances.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

## 4.8 Undesirable effects

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention:
Uncommon (≥1/1,000 to <1/100)
Not known (cannot be estimated from the available data)
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.
A tabulated list of adverse reactions is outlined below:

| System Organ Class | Frequency | Adverse Effects |
|---|---|---|
| Blood and lymphatic system disorders | Not known | Thrombocytopenia, agranulocytosis |
| Immune system disorders | Not known | Anaphylactic reaction, hypersensitivity |
| Metabolism and nutrition disorders | Not known | High anion gap metabolic acidosis[3] |
| Psychiatric disorders | Not known | Dysphoria, euphoria, Drug dependence (see section 4.4) |
| Nervous system disorders | Not known | Dizziness, sedation, headache |
| Ear and labyrinth disorders | Not known | Deafness[1] |
| Respiratory thoracic and mediastinal disorders | Not known | Bronchospasm, dyspnoea |
| Gastro-intestinal | Not known | Nausea, vomiting, constipation, abdominal |

| | | |
|---|---|---|
| disorders | | pain, pancreatitis[2] |
| Hepatobiliary disorders | Not known | Sphincter of Oddi dysfunction |
| Skin and subcutaneous tissue disorders | Not known | Pruritus, rash, urticaria |
| General disorders and administration site conditions | Uncommon | Drug withdrawal syndrome |

[1]Deafness has been reported in patients after long term use of high doses of codeine-paracetamol.

[2]Drug-induced pancreatitis associated with paracetamol has been reported in literature to be a rare reaction only occurring in patients taking in excess of the recommended doses. Literature reports have also associated cases of pancreatitis with codeine.

[3]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.

In addition, miosis, visual disturbances, respiratory depression, difficult micturition and urinary retention can occur.

Allergic reactions (including skin rash), urticaria and pruritus can occur as reactions to Zapain.

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

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

There have been some reports of blood dyscrasias - thrombocytopenia and agranulocytosis, with the use of paracetamol-containing products, but the causal relationship has not been established.

Anaphylaxis, angioedema and toxic epidermal necrolysis have also been associated with the use of paracetamol.

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.

Long-term usage of high doses of codeine + paracetamol can be rarely associated with ototoxicity leading to sensorineural hearing loss.

Prolonged use of a pain killer for headaches can make them worse.

*Drug dependence*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

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.

**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, 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**
The effects in over dosage 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 patients for at least four hours after ingestion.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics,

ATC code: N02AJ06

Paracetamol has analgesic and antipyretic actions. It is a weak inhibitor of prostaglandin biosynthesis. Single or repeated therapeutic doses of paracetamol do not affect the cardiovascular or respiratory systems. Gastric irritation, erosion, or bleeding is not produced by paracetamol. There is minimal effect on platelets, no effect on bleeding time or excretion of uric acid.

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 affects the CNS and the gut, including analgesia, drowsiness, mood changes, respiratory depression, reduced gastrointestinal motility, nausea or vomiting, changes in the endocrine and autonomic nervous system. Codeine's effect on pain relief is selective, and it does not affect other sensations such as touch, vibration, vision, or hearing.

## 5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol 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 varies from about 1-4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent. A minor hydrolated metabolite which is usually produced in very small amounts by mixed function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage .

Codeine and its salts are absorbed from the gastro-intestinal tract and peak plasma concentrations are produced in about 1 hour. It is metabolised in the liver to morphine and norcodeines. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half life is between 3 and 4 hours.

## 5.3. Preclinical Safety Data

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

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. List of Excipients

Maize Starch
Sodium Lauryl Sulphate
Talc
Magnesium Stearate
Croscarmellose Sodium
Gelatin
Titanium dioxide E171 (capsule)
Erythrosin E127 (capsule)
Red Iron Oxide E172 (capsule)

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf-Life

36 months.

### 6.4. Special Precautions for Storage

Do not store above 25°C.

### 6.5 Nature and Content of Container

Polyethylene capsule container with low density polyethylene child resistant closure.
OR
Aluminium foil over PVC/PVDC film blisters.

In pack sizes of 50, 56, 100 or 112 capsules

### 6.6. Instruction for Use, Handling and Disposal

No special requirements for disposal
Any unused medical or waste material should be disposed of in accordance with local requirements

## 7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd
Dashwood House,
69 Old Broad Street,

London,
EC2M 1QS,
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**

PL 12762/0033

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

Date of first authorisation: 03 March 2009

## 10 DATE OF REVISION OF THE TEXT

10/03/2026