

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zapain 30mg/500mg Tablets and/or Co-Codamol 30mg/500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol Ph. Eur 500mg, and Codeine Phosphate BP 30mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Caplet-shaped, white film-coated tablet.

Each film coated tablet is of 16.6 mm – 18.4 mm x 7.1 mm -7.9 mm x 5.8 mm - 6.5 mm.

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 tablets every four to six hours when needed, up to a maximum of 8 tablets 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: one to two tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Children aged 12 – 15 years: one tablet every 6 hours when necessary up to a maximum of 4 tablets in 24 hours.

Children aged less than 12 years:

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

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

Doses of Codeine above 60mg 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 of Zapain tablets 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, patients suffering from diarrhoea of any cause, and patients who have taken MAOIs within 14 days.

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

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 tablets in children below the age of 12 years has not been established, and use in such children is contraindicated.

Zapain tablets must be used with caution in patients with increases intracranial pressure, debilitated, impaired hepatic or renal function and urethral stricture. (See also “Contraindications”. Note particularly that Zapain is contraindicated in patients with severe renal or hepatic impairment.)

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 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.

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 tablets 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 tablets 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).

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.

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.”

Overdosage in patients with non-cirrhotic alcoholic liver disease can be hazardous. The hazard of paracetamol overdose is greater in those with alcoholic liver disease.

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.

Patients must be advised not to exceed the recommended doses.

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking Zapain, and to consult their doctor if symptoms persist.

The cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

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/dihydrocodeine (DHC) 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 you prescriber as taking codeine/DHC regularly for a long time can lead to addiction.

4.5 Interaction with other medicinal products and other forms of interaction

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 coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics 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 the antidepressant or codeine.

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 coadministration with an antimuscarine drug may cause urinary retention.

The absorption of paracetamol is speeded by metaclopramide or domperidone, and absorption is reduced by cholestyramine.

Codeine may delay the absorption of mexilitine, and 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.

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).

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

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:

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

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.

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 Zapain 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

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

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

System organ class	Frequency	Adverse effects
Blood and lymphatic system disorders	Not known	Thrombocytopenia, Agranulocytosis*
Immune system disorder	Not known	Hypersensitivity (including skin rash)
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis ^d

Psychiatric disorders	Not known	Dysphoria Euphoria Drug dependence (see section 4.4),
Nervous system disorders	Common	Dizziness ^c Light-headedness ^c Sedation ^c
	Not known	Headache
Eye Disorder	Not known	Miosis visual disturbances
Cardiac disorders	Not known	bradycardia
Ear and labyrinth disorders	Not known	Hearing loss
Respiratory, thoracic and mediastinal disorders	Common	Shortness of breath ^c
	Not known	Respiratory depression ^a
Gastrointestinal disorders	Common	Nausea ^c vomiting ^c Constipation ^c ,
	Not known	Abdominal pain, pancreatitis
Hepatobiliary disorders	Not known	Liver damage ^b , sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Not known	Pruritus
Renal and urinary disorders	Not known	Difficult micturition Urinary retention
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome

^a Codeine can cause respiratory depression particularly in overdose and in patients with compromised respiratory function.

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

^c Some of these side effects appear more common in ambulatory: rather than non-ambulatory patients. Lying down may alleviate these effects they occur.

^d 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.

*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.

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

Drug dependence

Repeated use of Zapaïn 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

Symptoms of overdosage with paracetamol in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. In 12 to 48 hours liver damage may become apparent, together with abnormalities of glucose metabolism, and metabolic acidosis.

Liver damage has occurred in adults taking 10g or more of paracetamol. Excess quantities of a toxic metabolite become irreversibly bound to liver tissue, and immediate treatment is essential. Patients ingesting 7.5g or more of paracetamol in 4 hours should be referred to hospital urgently.

Overdose with paracetamol can commonly cause acute hepatic necrosis with severe liver damage and may lead to fulminant hepatic failure, which is usually fatal. In severe overdose hepatic failure may progress to encephalopathy, coma and death. Even in the absence of severe liver damage, acute renal failure due to acute tubular necrosis may develop without hepatic failure.

There are no specific early signs of severe poisoning with paracetamol. Consciousness is not usually impaired, and maximum abnormality of liver function tests is delayed for at least three days. Liver damage is caused by conversion of paracetamol to a highly reactive metabolite. Necrosis does not occur unless hepatic glutathione is depleted.

Early treatment of paracetamol overdose with agents which facilitate glutathione synthesis, for example N-acetylcysteine and methionine, can prevent liver damage, renal failure, and death. Treatment must be started within 8 to 10 hours, and is not effective if delayed beyond 15 hours.

Cardiac arrhythmias and pancreatitis have been reported.

Codeine

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

Symptoms

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg or a child more than 5mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: N02AJ06

Paracetamol (N02B E51) 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 (N02A A59) 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 hydrolysed metabolite which is usually produced in very small amounts by mixed function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdose and cause liver damage.

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

Methylcellulose

Talc

Calcium Stearate

Povidone

Purified Water

Hypromellose
Macrogol 3350

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 container with low density polyethylene child resistant closure
OR

Aluminium-Polyethylene Terephthalate (PET) foil over PVC/PVDC film
blisters

In pack sizes of 50, 56, 100 or 112 tablets.

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(S)

PL 12762/0034

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

Date of first authorisation: 22 November 1999

Date of latest renewal: 03 March 2009

10 DATE OF REVISION OF THE TEXT

03/03/2026