

Product Summary

1. Trade Name of the Medicinal Product

Zapain Caplets and/or Co-Codamol 30/500 Caplets

2. **Qualitative and Quantitative Composition**

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

3. **Pharmaceutical Form**

Tablet

4. CLINICAL PARTICULARS

- 4.1. **Therapeutic indications**

For the relief of severe pain

- 4.2. **Posology and method of administration**

Method of administration: Oral.

Adults The usual dose is one or two caplets every four hours as required. The total daily dose should not exceed 240 mg codeine phosphate (8 caplets in a day).

Elderly A reduced dosage may be necessary.

Children Not recommended in children below the age of 12 years.

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.

- 4.3. **Contraindications**

Hypersensitivity to either paracetamol or codeine, or any of the excipients of Zapain caplets.

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.

4.4 Special warnings and precautions for use

The efficacy and safety of Zapain caplets in children below the age of 12 years has not been established, and use in such children is contraindicated.

Zapain caplets must be used with caution in patients with increases intracranial pressure, acute abdominal conditions, the elderly, the debilitated, impaired hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, and urethral stricture. (See also "Contraindications". Note particularly that Zapain is contraindicated in patients with severe renal or hepatic impairment.)

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. Drug dependence of the morphine type can be produced by the Codeine, and the potential for drug abuse with codeine must be considered. 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 risk-benefit of continued use should be assessed regularly by the prescriber.

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. Interactions 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.

4.6. Pregnancy and lactation

Zapain is not recommended during pregnancy or lactation.

Codeine crosses the placenta and is found in breast milk.

Use during pregnancy may lead to withdrawal syndromes in neonates, and use during labour may cause neonatal respiratory depression.

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.

4.8. Undesirable effects

The commonest side effects of codeine are nausea, vomiting, light headedness, dizziness, sedation, shortness of breath and constipation. Some of these side effects appear more commonly in ambulatory rather than non-ambulatory patients. Lying down may alleviate these effects if they occur. In addition, miosis, visual disturbances, headache, bradycardia, respiratory depression, difficult micturition and urinary retention, and allergic reaction (including skin rash) can occur.

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

Euphoria, dysphoria, constipation, abdominal pain, 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 some reports of blood dyscrasias- Thrombocytopenia and agranulocytosis, with the use of paracetamol- containing products, but the causal relationship has not been established.

Regular prolonged use of codeine/DHC is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

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

4.9. Overdose

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 10 g or more of paracetamol. Excess quantities of a toxic metabolite become irreversibly bound to liver tissue, and immediate treatment is essential. Patients ingesting 7.5 g 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 350 mg or a child more than 5 mg/kg.

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

Pharmacological Properties

5.1. Pharmacodynamic Properties

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 an analgesic with similar uses to morphine, but only mild sedative effects. 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 gastro-intestinal tract. It is metabolised in the liver and undergoes extensive biotransformation. The major metabolites are inactive phenolic sulphate and glucuronide conjugates. An adequate supply of SH groups can prevent hepatic toxicity. Paracetamol is excreted in the urine. The elimination half life varies from about 1 to 4 hours.

Codeine is 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. The plasma half life is between 3 and 4 hours.

5.3. Preclinical Safety Data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Maize Starch sifted
Methylcellulose
Talc
Calcium Stearate
Povidone
Purified Water
Hypromellose
Macrogol 3350

6.2. Incompatibilities

None relevant.

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 foil over PVC/PVDC film blisters.

In pack sizes of 56, 100 or 112 caplets.

6.6. Instruction for Use, Handling and Disposal

None.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
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Croydon CR0 0XT
United Kingdom

8. MARKETING AUTHORIZATION NUMBER

PL 12762/0034

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

03/03/2009

10 DATE OF REVISION OF THE TEXT

03/03/2009