SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kapake 30mg/500mg Capsules/Co-Codamol 30mg/500mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

	per capsule
Paracetamol	500mg
Codeine Phosphate Hemihydrate	30mg

Excipients with known effect: Each capsule contains Cochineal Red A (E124).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Hard gelatin capsule (size 0) with a red cap and a white body; both are marked in black ink with “G 30/500”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in adults.

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

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).

Posology

Adults:
One or two capsules every four hours as required.

Maximum of eight capsules daily.

A lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be

appropriate in patients with an increased risk of hepatotoxicity (see section 4.4).

Paediatric population:
Children aged 12 and over:
One capsule to be taken every six hours as required, up to a maximum of four capsules in any 24-hour period.

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

Elderly:
The adult dose is appropriate, however, a reduced dose may be required (see section 4.4).

Codeine should be used at the lowest effective dose for the shortest period of time.

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

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

Method of administration

For oral use.

4.3 Contraindications

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

Conditions where morphine and opioids are contraindicated, such as raised intracranial pressure or head injury, respiratory depression, obstructive airway disease, acute asthma, acute alcoholism and following biliary surgery.

This product is also contraindicated in patients with severe renal or hepatic impairment (see section 4.4).

Kapake/Co-Codamol 30mg/500mg Capsules are also contraindicated in patients receiving monoamine oxidase inhibitors or who have received these agents within the previous two weeks (see section 4.5).

This product is contraindicated in women during breast-feeding (see section 4.6) and also in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

Kapake/Co-Codamol 30mg/500mg Capsules are contraindicated 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).

Kapake/Co-Codamol 30mg/500mg Capsules are not recommended for children under 12 years of age.

4.4 Special warnings and precautions for use

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are 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% to 2%

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Kapake/Co-Codamol 30mg/500mg Capsules and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Kapake/Co-Codamol 30mg/500mg Capsules concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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).

Kapake/Co-Codamol 30mg/500mg Capsules should be used with caution in the elderly and debilitated as these patients may be more sensitive to the effects of opioids, those with prostatic hypertrophy, inflammatory or obstructive bowel disorders, convulsive disorders, hypothyroidism, myasthenia gravis, urethral stenosis or Addison's disease.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.

There is a risk of hepatotoxicity in association with paracetamol, even at doses within the normal therapeutic range, in patients who are at particular risk of such adverse effects. These include: patients who are underweight (adults or adolescents less than 50kg) or of low body mass index, malnourished, dehydrated, those with chronic alcoholism, co-existing renal or hepatic impairment, concomitantly taking hepatotoxic drugs and those with conditions that may predispose to glutathione deficiency or depletion. For some patients considered to be at higher risk, a lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be appropriate (see section 4.2).

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.

Opioid analgesics should be given with caution or in reduced doses to patients with renal or hepatic impairment (and avoided if the impairment is severe).

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

Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed serious liver damage. Patients should be advised not to take opiate derivatives or other paracetamol-containing products concurrently.

Do not exceed the recommended dose. If symptoms persist, consult your doctor. Keep 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 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.

Kapake/Co-Codamol 30mg/500mg Capsules contain Cochineal Red A (E124) and may cause allergic reactions.

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Kapake/Co-Codamol 30mg/500mg Capsules are contraindicated in patients receiving monoamine oxidase inhibitors or who have received these agents within the previous two weeks (see section 4.3).

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs (including anxiolytics, hypnotics, antidepressants and antipsychotics) increases the risk of sedation, respiratory depression, coma and death because of additive central nervous system (CNS) depressant effects. The dose and duration of concomitant use should be limited (see section 4.4). Alcohol should be avoided.

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

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Concurrent use of codeine with CYP2D6 inhibitors, such as quinidine, fluoxetine and paroxetine, may result in a reduction or loss of analgesic effect of codeine.

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 risk factors (see section 4.4).

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The metabolism of paracetamol is increased in patients taking enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

This product should not be used during pregnancy.

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

Administration during labour may depress respiration in the neonate.

Breast-feeding

Codeine should not be used during breast-feeding (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.

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.

4.7 Effects on ability to drive and use machines

Codeine may impair mental and/or physical abilities, therefore it may affect the ability to drive and operate machinery.

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 effects of paracetamol are rare but hypersensitivity including skin rash and angioedema may occur. Very rare cases of serious skin reactions have been reported. There have been reports of blood dyscrasias including thrombocytopenia, leucopenia, neutropenia and agranulocytosis, but these were not necessarily causally related to

paracetamol. There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs. 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. The frequency of high anion gap metabolic acidosis is not known (cannot be estimated from the available data).

The most common adverse effects to codeine are dizziness, drowsiness, nausea and vomiting. These effects are often more common in the ambulatory patient and thus may be alleviated if the patient lies down. Other side effects to codeine which may occur include constipation, urinary retention, light headedness, headache, respiratory depression (with high doses), dyspnoea, hallucination, confusion, euphoria, dysphoria, miosis, bradycardia, abdominal pain (rarely codeine-induced pancreatitis has been reported in patients with a history of cholecystectomy), allergic reactions, urticaria and pruritus.

Regular prolonged use of codeine is known to lead to drug dependence (see section 4.4). Drug withdrawal syndrome may occur when treatment is stopped.

Prolonged use of a painkiller for headaches can make them worse.

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

Paracetamol Overdose

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, phenobarbitone, 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 of Paracetamol Overdose

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 of Paracetamol Overdose

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 National Poisons Information Service (NPIS) or a liver unit.

Codeine Overdose

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

Symptoms of Codeine 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.

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 of Codeine Overdose

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 has analgesic and antipyretic effects that do not differ significantly from that of aspirin. Its anti-inflammatory action is weak and it has practically no anti-platelet effect. The mechanism of action is unclear although it is believed to exert its action by inhibition of prostaglandin synthesis.

Codeine is a centrally acting weak analgesic. Codeine exerts its effects through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes to two hours after oral administration. 90-100% of administered drug can be recovered in the urine within the first day. Practically none is excreted unchanged, most is conjugated in the liver with glucuronic acid or sulphuric acid.

Codeine and its salts are rapidly absorbed from the GI tract with peak plasma levels occurring about one hour after oral administration. Codeine is metabolised in the liver and excreted in the urine mainly as a conjugate of glucuronic acid. Approximately 10% of administered codeine is demethylated to form morphine.

Concurrent administration of both drugs does not interfere with the normal metabolic processes of each agent.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell constituents:
Cochineal red A (E124)
Brilliant blue (E133)
Titanium dioxide (E171)
Gelatin

Overprint ink constituents:
Shellac glaze
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC (250µm)/aluminium (20µm) blisters and/or polypropylene tablet containers with polyethylene caps: 2 years.

PVC (250µm)/child-resistant aluminium (20µm aluminium/15µm PVC) blisters: 3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC (250um)/aluminium (20um) blisters and/or PVC (250um)/child-resistant aluminium (20um aluminium/15um PVC) blisters and/or polypropylene tablet containers with polyethylene caps.

Pack sizes: 1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 16, 20, 21, 24, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 200, 224, 250, 300, 400, 500 and 1000 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Galen Limited
Seagoe Industrial Estate
Craigavon
BT63 5UA
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 27827/0010

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 June 1999
Date of latest renewal: 20 February 2009

10 DATE OF REVISION OF THE TEXT

14/02/2025