Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kapake 30 mg/500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient	Per tablet
Paracetamol	500 mg
Codeine Phosphate	30 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Oblong, white uncoated tablets marked 'K2' both sides of a score line on one side, the other side is plain and unmarked. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment 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

Posology

Adults:
One or two tablets to be taken every four hours as required up to a maximum of eight tablets in any 24 hour period.

Paediatric population:
Children aged 12 and over:
One tablet to be taken every six hours as required, up to a maximum of four tablets 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 dosage may need to be reduced and should be titrated to the individual's need and overall medical condition (see section 4.4).

Renal impairment

Kapake 30mg/500mg Tablets should be used with caution in patients with mild to moderate renal impairment as a reduced dose and/or prolonged dosing interval may be necessary. Use is contraindicated in patients with severe renal impairment (see sections 4.3 and 4.4).

Hepatic impairment

Kapake 30mg/500mg Tablets should be used with caution in patients with mild to moderate hepatic impairment as a reduced dose and/or prolonged dosing interval may be necessary. Use is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Treatment goals and discontinuation

Before initiating treatment with Kapake 30mg/500mg Tablets, 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

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

The duration of treatment should be as short as possible and 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.

In all patients over 16 years of age, the maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician: (see section 4.4)

- Weight less than 50kg
- Dehydration
- Malnutrition
- Chronic alcoholism

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 contraindicated in patients with severe renal or severe hepatic impairment (see sections 4.2 and 4.4).

Kapake 30mg/500mg Tablets 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 breastfeeding (see section 4.6) and also in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

Kapake 30mg/500mg Tablets 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 30mg/500mg Tablets are not recommended for children under 12 years of age.

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 Kapake 30mg/500mg Tablets. Repeated use of Kapake 30mg/500mg Tablets 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 Kapake 30mg/500mg Tablets 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 Kapake 30mg/500mg Tablets 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.

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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%

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Kapake 30mg/500mg Tablets 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 30mg/500mg Tablets 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 30mg/500mg Tablets 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. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Dependence of the morphine type may be produced especially with prolonged use of high doses of codeine.

There is a risk of hepatotoxicity in association with paracetamol use, 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. Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment (see section 4.2).

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Opioid analgesics should be given with caution or in reduced doses to patients with mild to moderate renal or hepatic impairment (and avoided if the impairment is severe). Kapake 30mg/500mg Tablets are contraindicated in patients with severe renal or severe hepatic impairment (see sections 4.2 and 4.3).

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

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.

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

Hyperalgesia
As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

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.

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 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.

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 30mg/500mg Tablets 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) and gabapentinoids (gabapentin and pregabalin) increases the risk of profound sedation, respiratory depression, hypotension, 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 (e.g. baclofen) 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, 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.

Breast-feeding
Codeine should not be used during breast-feeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

4.7 Effects on ability to drive and use machines

Patients receiving this medication should be advised not to drive or operate machinery if affected by dizziness or sedation.

4.8 Undesirable effects

Reported adverse reactions are often more common in the ambulatory patient and thus may be alleviated if the patient lies down.

In this section, the following terms and frequencies are applied: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Post marketing data

Paracetamol:

System Organ Class	**Adverse Effect**	**Frequency**
Blood & lymphatic system disorders	Thrombocytopenia	Not known
	Neutropenia	
	Leucopenia	
	Agranulocytosis	
Immune system disorders	Hypersensitivity, including skin rash	Not known
Skin & subcutaneous tissue disorders	Serious skin reactions*	Very Rare
	Angioedema	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm**	Not known
Metabolism and nutrition disorders	High anion gap metabolic acidosis Pyroglutamicacidosis, in patients with pre-disposing factors for glutathione depletion	Not known

* Very rare cases of serious skin reactions have been reported.
**There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Codeine:

System Organ Class	**Adverse Effect**	**Frequency**
Immune system disorders	Allergic reactions	Not known
Psychiatric disorders	Drug dependence (see section 4.4)	Not known
	Hallucination	
	Confusion	
	Euphoria	
	Dysphoria	
Nervous system disorders	Light headedness	Not known
	Headache	
	Dizziness	
	Drowsiness	
Eye disorders	Miosis	Not known
Cardiac disorders	Bradycardia	Not known
Skin & subcutaneous tissue disorders	Urticaria	Not known
	Pruritis	Not known

Renal and urinary disorders	Urinary Retention	Not known
Respiratory, thoracic and mediastinal disorders	Respiratory depression (with high doses)	Not known
	Dyspnoea	
Gastrointestinal disorders	Constipation	Not known
	Abdominal pain	
	Nausea	
	Vomiting	
	Pancreatitis*	Rare
Hepatobiliary disorders	Sphincter of Oddi dysfunction	Not known

* Rarely codeine-induced pancreatitis has been reported in patients with a history of cholecystectomy.

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.

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

Drug dependence
Repeated use of Kapake 30mg/500mg Tablets 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).
Description of selected adverse reactions

High anion gap metabolic acidosis
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.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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.

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 Centre (NPIC) 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
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: Analgesics, 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

Microcrystalline cellulose
Sodium starch glycolate (type A)
Magnesium stearate
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

High density polypropylene containers with low density polyethylene caps and/or cold-form aluminium blisters: 2 years.

PVC/aluminium blisters and/or PVC/child-resistant aluminium blisters: 3 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

High density polypropylene containers with low density polyethylene caps and/or cold-form aluminium blisters and/or PVC aluminium blisters and/or PVC/child-resistant aluminium blisters.

Pack sizes: 2, 4, 6, 10, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 150, 200, 250 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited
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1 Burlington Road
Dublin 4
D04 C5Y6
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8 MARKETING AUTHORISATION NUMBER

PA1418/020/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 October 1993

Date of last renewal: 26 October 2008.

10 DATE OF REVISION OF THE TEXT

August 2026