Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 15 mg/500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Paracetamol: 500 mg
Codeine phosphate hemihydrate: 15 mg

Excipient with known effect:
Each film-coated tablet contains 0.32 mg of lecithin (derived from soya).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

White to off-white oblong-shaped, biconvex, film-coated tablet with break line on one side and plain on other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-codamol 15 mg/500 mg Film-coated Tablets is indicated in adult and adolescent 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
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.

Adults:
Two tablets to be taken every four hours as required, up to a maximum of eight tablets in any 24-hour period.

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

Renal impairment:
It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:

In patients with hepatic impairment or Gilbert's Syndrome, the paracetamol dose should be reduced or the dosing interval prolonged. The daily dose of paracetamol should not exceed 2 g/day unless directed by a physician.

The maximum daily dose of paracetamol should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in patients aged 16 years and over in the following situations, unless directed by a physician:
• Weight less than 50 kg
• Chronic alcoholism
• Dehydration
• Chronic malnutrition.

Paediatric population:
Children aged 16 and over:
Two tablets to be taken at intervals not less than six hours as required, up to a maximum of eight tablets in any 24-hour period.

Children aged 12 to 15 years:
One tablet to be taken at intervals not less than six hours as required, up to a maximum of four tablets in any 24-hour period.

Children under 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).

Method of administration
For oral administration.
The break line on the tablet is present to facilitate breaking for ease of swallowing.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

This product is contraindicated in patients with raised intracranial pressure or head injury, respiratory depression, acute asthma and acute alcoholism.

Co-codamol 15 mg/500 mg Film-coated 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).

Co-codamol 15 mg/500 mg Film-coated Tablets should not be given to patients following biliary tract surgery (see section 4.4).

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.

Co-codamol 15 mg/500 mg Film-coated 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).

Co-codamol 15 mg/500 mg Tablets are not recommended for children under 12 years of age.

4.4 Special warnings and precautions for use

Paracetamol should be administered only with particular caution under the following circumstances:

- Glutathione deficiency
- Chronic alcoholism
- Dehydration
- Chronic malnutrition
- The elderly
- Adults and adolescents weighing less than 50 kg
- Renal impairment (GFR ≤50 ml/min)
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia

- Concomitant treatment with medicinal products affecting hepatic function
- Hepatic impairment
- Gilbert's Syndrome (familial non-haemolytic jaundice).

Hepatotoxicity at therapeutic doses of paracetamol

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9).

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.

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

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an 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 nausea, vomiting, constipation, lack of appetite, confusion, somnolence, shallow breathing and small pupils. 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 Co-codamol 15 mg/500 mg Film-coated 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 Co-codamol 15 mg/500 mg Film-coated 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).

Co-codamol 15 mg/500 mg Film-coated 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 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.

Co-codamol 15 mg/500 mg Film-coated Tablets should be given with caution or in reduced doses to patients with hypothyroidism, hypotension or myasthenia gravis due to codeine component.

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms such as restlessness and irritability, once the drug is stopped.

Codeine increases smooth muscle tone which may result in spasm, raised biliary tract pressure and biliary colic. Codeine should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic.

Co-codamol 15 mg/500 mg Film-coated Tablets should not be used in patients who have recently had an operation on liver, gallbladder or bile duct (biliary tract) (see section 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 other paracetamol- or codeine-containing products concurrently.

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.

Important information about some of the ingredients:
This medicinal product contains lecithin (derived from soya). If you are allergic to peanut or soya, do not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Codeine is contraindicated in patients receiving monoamine oxidase inhibitors or who have received these agents within the previous two weeks (see section 4.3).

Codeine may potentiate the depressant effects of other central nervous system (CNS) depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics.

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

Paracetamol clearance is increased in women taking oral hormonal contraceptives.

Paracetamol is metabolised in the liver and can consequently enter into interactions with other medicinal products which follow the same metabolic route or which are able to inhibit or induce the route. In the case of chronic alcohol abuse and the use of drugs, which induce hepatic enzymes such as barbiturates and tricyclic antidepressants, an overdose of paracetamol can take a more severe course as a result of the increased and more rapid formation of toxic metabolites.

Caution is required with the concomitant intake of enzyme-inducing drugs (see sections 4.4 and 4.9).

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

The absorption of paracetamol may be accelerated by drugs such as metoclopramide.

In the case of concomitant treatment with probenecid, the dose of paracetamol must be reduced as probenecid reduces the clearance of paracetamol by 50 % since it prevents the conjugation of paracetamol with glucuronic acid.

Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

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
Co-codamol 15 mg/500 mg Film-coated Tablets should not be used during pregnancy.

Paracetamol
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity to paracetamol. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Codeine
Use of codeine during pregnancy may lead to withdrawal symptoms in neonates, and use during labour may cause neonatal respiratory depression.

Breastfeeding
Co-codamol 15 mg/500 mg Film-coated Tablets must not be used during breast-feeding (see section 4.3).

Paracetamol
Paracetamol is excreted in breast milk but not in a clinically significant amount.

Codeine
Codeine should not be used during breastfeeding. 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.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

Fertility
No available data on fertility.

4.7 Effects on ability to drive and use machines

Co-codamol 15 mg/500 mg Film-coated Tablets 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. 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 may be an offence to drive while under the influence of this medicine.

4.8 Undesirable effects

The following undesirable effects have been reported following the use of paracetamol:

blood dyscrasias including thrombocytopenia, leucopenia, neutropenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Hypersensitivity, including skin rash and angioedema, may also occur.
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.
High anion gap metabolic acidosis has also been reported, with frequency 'not known' (cannot be estimated from the available data).

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

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.

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:
Paracetamol overdose can result in liver damage which may be fatal. Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk factors include
If the patient

1. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes, or
2. Regularly consumes ethanol in excess of recommended amounts, or
3. 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, or patients may be asymptomatic. 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 one 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 24 hours 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paracetamol, combinations, excluding psycholeptics
ATC Code: N02B E51

Paracetamol has analgesic and antipyretic effects that do not differ significantly from those 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 with uses similar to those of morphine, although it is much less potent as an analgesic and has only mild sedative effects. It is used for the relief of cough and pain. Codeine exerts its effects through μ opioid receptors, although codeine has a low affinity for these receptors, and its analgesic effect is due to its conversion to morphine; approximately 10% of administered codeine is demethylated to form 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 gastrointestinal 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 absorbed rapidly from the gastrointestinal 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

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

There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Starch
Povidone (K-30)
Microcrystalline Cellulose PH102
Maize Starch
Crospovidone XL 10
Colloidal Anhydrous Silica
Magnesium Stearate
Opadry AMB white OY-B-28920:
Polyvinyl Alcohol Part Hydrolyzed
Titanium dioxide
Talc
Lecithin (Soya)
Xanthan Gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 Tablets are packed in Alu – PVC/PVdC blister pack. One such blister is packed in a carton along with leaflet (10 x 10's).

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd.
12 Hamilton Drive
The Rock Road
Blackrock
Co. Louth
A91 T997
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22871/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th August 2022

10 DATE OF REVISION OF THE TEXT