SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Codamol Tablets BP 8/500mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Paracetamol BP 500mg,
Codeine Phosphate BP 8mg.

3 PHARMACEUTICAL FORM

Compressed tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

POM:

For the treatment of most febrile conditions such as headache, toothache, colds, influenza, dysmenorrhoea, arthritic and rheumatic pain.

P:

For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone. For headache, toothache, dysmenorrhoea, arthritic and rheumatic pain.

4.2 Posology and method of administration

This preparation is intended for oral administration.

Treatment goals and discontinuation

Before initiating treatment with Co-codamol, treatment duration and treatment goals, should be agreed together with the patient, in accordance with pain management guidelines.

Duration of treatment

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. The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

Adults:

One or two tablets not more frequently than every 4- 6 hours, up to a maximum of 8 tablets in any 24 hour period.

Elderly:

Same as for adults, however a reduced dose may be required (see section 4.4).

Paediatric population:

P

Children aged 16-18 years: One or 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).

POM

Co-codamol is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cold (see section 4.4).

Children aged 16-18 years: One or 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: Co-codamol is contraindicated in children below the age of 12 years for the symptomatic treatment of cold (see sections 4.3).

4.3 Contraindications

Known hypersensitivity to Paracetamol, Codeine or other opioid analgesics.

Respiratory depression and obstructive airways disease.

Bronchial asthma attack or heart failure secondary to chronic lung disease.

Diarrhoea associated with pseudomembranous colitis. Diarrhoea caused by poisoning until the toxic material has been eliminated from the gastrointestinal tract.

Not to be used in infants.

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

POM: In children below the age of 12 years for the symptomatic treatment of cold due to an increased risk of developing serious and life-threatening adverse reactions.

4.4 Special warnings and precautions for use

Caution is advised in the administration of both Paracetamol and Codeine to patients with impaired kidney or liver function. The hazard of overdose with Paracetamol is greater in those with non-cirrhotic liver disease.

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.

Codeine should be given with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenal insufficiency, prostatic hypertrophy, shock, inflammatory or obstructive bowel disorders, acute abdominal conditions, recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of cardiac arrhythmias or convulsions and in patients with a history of drug abuse or emotional instability.

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 Co-Codamol. Repeated use of Co-codamol 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 Co-codamol 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).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.

For patients who experience signs and symptoms of OUD, and/or exhibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use.

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.

Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain, and rarely, colonic obstruction.

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/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.

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 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%

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.

For product in packs of 32 tablets or fewer (P status), the label and leaflet will state:

The label will state:

On front of pack (to be prominently displayed) –

- Can cause addiction.
- For three days use only.

On back of pack (to be prominently displayed not boxed) -

- For the short term treatment of acute, moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers. For headache, toothache, period pains, arthritic and rheumatic pain.

- If you need to take this medicine for more than three days you must see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

Headlines section (to be prominently displayed)

- This medicine can only be used for the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.

Section 1 – What the medicine is for

- For the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone. For headache, toothache, period pains, arthritic and rheumatic pain. When other painkillers have not worked. Wait at least 4 hours after you last took other painkillers before taking this medicine.

Section 2 – Before taking

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take a painkiller for headaches for more than three days it can make them worse.
- Under 'Pregnancy and Breastfeeding':

Do not take codeine while you are breast feeding. Codeine and morphine pass into breast milk.

Section 3 – Dosage

- Do not take for more than three days. If the pain does not improve after 3 days, talk to your doctor for advice.
- This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk

to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

- Talk to your doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Section 4 – Side effects

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 at: www.mhra.gov.uk/yellowcard.

How do I know if I am addicted?

If you take this medicine according to the instructions on the pack it is unlikely that you will become addicted to this medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

For product in packs of more than 32 tablets (POM status):

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

The label and leaflet will state:

Patient Information Leaflet (in '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.
- In Section 3 'How to take Co-codamol tablets': Talk to your doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

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

For product in any pack sizes:

Do not take more medicine than the label tells you to.

Talk to your doctor at once if you take too much of this medicine even if you feel well.

Do not take anything else containing paracetamol while taking this medicine. Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of Paracetamol with increased risk of bleeding; occasional doses have no significant effect.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, primidone or rifampicin.

Excretion of paracetamol may be reduced and plasma concentrations increased when given with probenecid.

Hepatotoxicity at therapeutic doses of paracetamol has been reported in patients receiving isoniazid.

The depressant effects of Codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines. The concomitant use of Co-Codamol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

The hypotensive actions of diuretics and antihypertensive agents may be potentiated when used concurrently with opioid analgesics. Concurrent use of hydroxyzine with Codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

Concurrent use of Codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

The respiratory depressant effects caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

CNS depression or excitation may occur if Codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them. Quinidine can inhibit the analgesic effect of Codeine.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Interference with laboratory tests: Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying, and with hepatobiliary imaging using technetium Tc99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increases biliary tract pressure.

4.6 Fertility, pregnancy and lactation

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. 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 crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible association with respiratory and cardiac malformations has been reported. Regular use during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate. Use during pregnancy should be avoided if possible.

Use of opioid analgesia during labour may cause respiratory depression in the neonate, especially the premature neonate. These agents should not be given during the delivery of a premature baby.

Co-Codamol is contraindicated in women during breastfeeding (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.

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.

4.7 Effects on ability to drive and use machines

Codeine may cause drowsiness, if affected patients should be advised not to drive or 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

- 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.

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

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).

Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. Anaphylactic shock and angioedema may occur but frequency is unknown.

Metabolism and nutrition disorders: high anion gap metabolic acidosis (frequency unknown). 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 a few reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily causally related to Paracetamol.

The most frequent undesirable effects of Codeine are constipation and drowsiness. Less frequent effects are nausea, vomiting, sweating, facial flushing, dry mouth, blurred or double vision, dizziness, orthostatic hypotension, malaise, tiredness, light-headedness, confusion, headache, anorexia, vertigo, bradycardia, palpitations,

respiratory depression, dyspnoea, allergic reactions (itch, skin rash, facial oedema) and difficulties in micturition (urinary retention, dysuria, increased frequency, decrease in amount). Side effects which occur rarely include convulsions, hallucinations, nightmares, uncontrolled muscle movements, muscular rigidity, mental depression and stomach cramps. There have been very rare occurrences of pancreatitis and sphincter of Oddi dysfunction with unknown frequency.

The euphoric activity of Codeine may lead to its abuse and dependence.

Drug dependence

Repeated use of Co-Codamol 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).

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

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

Very rare cases of serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption have been reported.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Symptoms

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, gastrointestinal bleeding, coma 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.

Liver damage is possible in adults who have taken 10G or more of Paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of Paracetamol are ingested), become irreversibly bound to liver tissue.

Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has any of the following risk factors:

- is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes, or

- regularly consumes ethanol in excess of recommended amounts, or
- is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Management

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 serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Codeine

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

Symptoms

Symptoms of Codeine overdosage include cold clammy skin, confusion, convulsions, dizziness, drowsiness, nervousness or restlessness, miosis, bradycardia, dyspnoea, unconsciousness, circulatory failure and deepening coma. The pupils may be pinpoint in size; Nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely. 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.

Death may occur from respiratory failure.

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.

Intensive support therapy may be required to correct respiratory failure and shock due to the effects of Codeine. In addition the specific narcotic antagonist, naloxone hydrochloride, may be used to rapidly counteract the severe respiratory depression and coma. Naloxone has a short half-life so large and repeated doses may be required in a seriously poisoned patient. A dose of

0.4 - 2mg is given intravenously or intramuscularly to adults, this is repeated at intervals of 2 - 3 minutes if necessary. Up to a total of 10mg of naloxone may be given. In children doses of naloxone of 5 - 10mcg/Kg bodyweight may be given intravenously or intramuscularly. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

Codeine is not dialysable.

General supportive measures must be available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol has analgesic and antipyretic actions.

Codeine Phosphate is an analgesic of the opioid class. Opioid analgesic bind with stereospecific receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to it. It has been hypothesised that alterations in release of various neurotransmitters from afferent nerves sensitive to painful stimuli may be partially responsible for the analgesic effect.

Codeine 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.

The drugs are additive and some workers suggest there may be synergy between the constituents.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma levels occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged.

The elimination half life of Paracetamol varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic doses.

Codeine Phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by O- and N-demethylation in the liver to morphine, and norcodeine and other metabolites. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

Codeine is not extensively bound to plasma proteins. The plasma half life varies from about 3 to 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

Each tablet contains:	Maize Starch BP	77.000mg
	Povidone BP	10.000mg
	Colloidal Silica BP	3.200mg
	Magnesium Stearate BP	1.500mg
	Potassium Sorbate BP	0.700mg

6.2 Incompatibilities

This product is designed for oral administration.

Admixture with other medicines prior to ingestion is not intended or desirable.

6.3 Shelf life

The shelf life of the product is 36 months when stored in the unopened container and taking the precautions described below.

In the case of tubs, provided the pack is re-sealed after each use there should be no reduction in shelf life.

Re-packing into any other pack may affect the shelf life and appropriate pharmaceutical judgement should be exercised.

6.4 Special precautions for storage

Store in a well-closed container. Store in a dry place at a temperature not exceeding 25°C, protected from light.

6.5 Nature and contents of container

A HDPE or polypropylene tub fitted with a plastic cap, child resistant and/or tamper-evident as appropriate, containing 16, 25, 32, 50, 100, 500 or 1000 tablets.

Child Resistant Blister pack strips, 0.25mm PVC/35 gsm Glassine (Pergamin) paper/ 0.009mm Aluminium enclosed in a cardboard carton, containing 10, 12, 16, 20, 24, 30, 32, 50, and 100 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Palla Pharma (UK) Holding Limited

10 Norwich Street,

London,

EC4A 1BD

8 MARKETING AUTHORISATION NUMBER(S)

PL 52635/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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