SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol & Codeine Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	mg/tablet
Paracetamol Cryst EP	300.0
Paracetamol DC EP	200.0
Codeine Phosphate Fine Cryst EP	8.0
Excipients with known effect	
Sodium metabisulphite (E223)	0.08

3. Pharmaceutical form

Capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine is indicated in patients older than 12 years of age.
For the short term treatment of acute moderate pain which is not considered to be relieved by other analgesics (e.g. paracetamol, ibuprofen or aspirin) alone, such as: headache, migraine, period pain, dental pain, neuralgia, rheumatic and muscular pain and backache.

4.2 Posology and method of administration

For oral administration

Adults
One to two capsules, if necessary, three or four times daily at intervals of not less than four hours, up to maximum of eight capsules in 24 hours.

Children aged 16 to 18 years
One or two capsules every 6 hours when necessary up to a maximum of eight capsules in 24 hours.

Children aged 12 to 15 years

One capsule every 6 hours when necessary up to a maximum of four capsules in 24 hours.

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).

Elderly
In the elderly, the rate and extent of paracetamol absorption is normal, but plasma half-life is longer, and paracetamol clearance is lower than in young adults. Elderly patients may require a reduced dose or frequency of dosing.

Treatment goals and discontinuation
Before initiating treatment with Paracetamol & Codeine Capsules, treatment duration and treatment goals, should be agreed together with the patient, in accordance with pain management guidelines.

Duration of treatment
Do not take for more than 3 days continuously without medical review. 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.

4.3 Contraindications

Hypersensitivity to any of the ingredients. Severe liver disease.

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.

In patients with respiratory depression, chronic constipation or raised intracranial pressure.

4.4 Special warnings and precautions for use

Should be taken with caution by patients with impaired kidney or liver function. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not take more medicine than the label tells you to.
If you do not get better, talk to your doctor.
Do not give to children under 12 years.
Contains paracetamol.
Do not take anything else containing paracetamol while taking this medicine.
Keep all medicines out of the reach of children.

The label will state:
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Front of pack

- Can cause addiction
- Contains opioids
- For three days use only

Back of pack

- List of indications as agreed in 4.1 of the SPC
- If you need to take this medicine continuously for more than 3 days you must speak to your doctor or pharmacist for advice
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. If you take this medicine for headaches for more than 3 days it can make them worse

The leaflet (or combined label/leaflet) will state:
Talk to a 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.

'Headlines' section (to be prominently displayed)

- This medicine can only be used for.....(indications**)**
- You should only take this product for a maximum of 3 days at a time. If you need to take it for longer than 3 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 3 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 3 days it can make them worse

"What this medicine is for" section

- Succinct description of the indications from 4.1 of the SPC

"Before you take this medicine" section

- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 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 3 days it can make them worse

"How to take this medicine" section

- Do not take for more than 3 days. Paracetamol & Codeine Capsules should be used for 3 days only to relieve symptoms. If no effective pain relief is achieved while taking the medicine, you should seek the advice of a healthcare professional.
- This medicine contains codeine and can cause addiction if you take it continuously for more than 3 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

"Possible side effects" section

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly

via the Yellow Card Scheme at: www.mhra.go.uk/yellowcard, or search for MHRA Yellow Card in Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

"How do I know if I am addicted?" section
If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to you doctor:

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

Codeine

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 Paracetamol & Codeine Capsules. Repeated use of Paracetamol & Codeine Capsules 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 Paracetamol & Codeine Capsules 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.

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.

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.

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.

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%

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.

Codeine should be used with caution in patients with:

- head injuries
- prostatic hypertrophy
- hypotension
- hypothyroidism
- Addison's disease
- myasthenia gravis
- inflammatory or obstructive bowel disorders or acute abdominal conditions
- history of cholecystectomy as it may cause acute pancreatitis in some patients.

Codeine should be used with caution in patients with conditions which may be exacerbated by opioids, including the elderly, who may be sensitive to their respiratory depressant effects.

As with other opioids, codeine should be used with caution in patients taking benzodiazepines or other central nervous system (CNS) depressants, including alcohol and in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping MAOIs (see section 4.5).

Paracetamol
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 the underlying cause of HAGMA in patients with multiple risk factors.

Glutathione deficiency can also increase the risk of hepatotoxicity with paracetamol use, even at therapeutic doses. Caution is advised for patients at risk of glutathione depletion (see section 4.9).

Hepatotoxicity at therapeutic dose
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 (adults <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 section 4.9).

Dosage adjustment of paracetamol should be considered where there are risk factors for glutathione deficiency or hepatotoxicity and for those of low weight (for adults weighing less than 50kg).

Information about some of the ingredients in this medicine
This medicine contains sodium metabisulphite (E223) which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Codeine may antagonise the gastrointestinal effects of metoclopramide and domperidone.

Concomitant use of codeine with central nervous system depressants (e.g. alcohol, hypnotics, sedatives including benzodiazepines, tricyclic antidepressants, antipsychotics including phenothiazines, general anaesthetics and centrally acting muscle relaxants) may cause additive CNS depression and respiratory depression and hypotensive effects.

The concomitant use of Paracetamol & Codeine Capsules with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur. Therefore, the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

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

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.

Alcohol and drugs which induce hepatic microsomal enzymes e.g. antiepileptic drugs, may increase the hepatotoxicity of paracetamol, particularly after overdose.

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).

4.6 Fertility, pregnancy and lactation

The safety of this medicine during pregnancy has not been established and in view of the possible association of codeine with respiratory depression and heart malformations, use during this period should be avoided.

Codeine should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites 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.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

A large amount of data on pregnant women indicates paracetamol is neither malformative, nor feto/neonatally toxic. 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.

4.7 Effects on ability to drive and use machines

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

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 a '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

Codeine
The most common side effects are nausea, vomiting, constipation, dry mouth, sweating, skin rashes and other allergic reactions. Dizziness, drowsiness and pruritus may occur with frequency not known.

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.

Gastrointestinal disorders
Frequency "Not known" (cannot be estimated from the available data):

- Pancreatitis.

Hepatobiliary disorders
Frequency "Not known" (cannot be estimated from the available data):

- Sphincter of Oddi dysfunction.

Paracetamol
Very rare cases of serious skin reactions have been reported.

Very rarely there have been reports of blood dyscrasias including thrombocytopaenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Hepatobiliary disorders
Frequency "Not known" (cannot be estimated from the available data):

- Hepatic dysfunction

Metabolism and nutrition disorders
Frequency "Not known" (cannot be estimated from the available data):

- High anion gap metabolic acidosis.

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.

Drug dependence
Repeated use of Paracetamol & Codeine Capsules 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).

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
Liver damage is possible in patients who have taken more than recommended doses of paracetamol.

Ingestion of paracetamol at therapeutic doses 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 depleted e.g. diet (malnutrition, fasting, dietary restrictions, eating disorders and starvation), catabolic states (sepsis), cachexia and chronic illness (cystic fibrosis, liver disease, HIV, and muscular dystrophy).

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 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
Immediate treatment is essential in the management of paracetamol overdosage. 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) but results should not delay initiation of treatment beyond 8 hours after ingestion, as 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.

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

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 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 4 hours after ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is an analgesic with antipyretic activity.

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, 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 2 hours after ingestion. Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucoronide and sulphate conjugates with about 10% as glutathione conjugates. Less than 5 % is excreted as unchanged paracetamol. The elimination half life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by 0- and N-demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half life has been reported to be between 3 and 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

Sodium metabisulphite

Magnesium stearate

Sodium starch glycolate

Sodium lauryl sulphate

Erythrosine (El27)

Indigo carmine (E132)

Gelatine

Water

6.2 Incompatibilities

None Known

6.3 Shelf life

18 Months

6.4. Special precautions for storage

None

6.5 Nature and contents of container

A child resistant push through pack of opaque 250 micron PVC/40gsm PVdC blisters heat sealed to 35gsm Glassine paper/9micron soft temper aluminium foil.

Pack sizes: 8/12/16/24/32.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

The Boots Company PLC
1 Thane Road West
Nottingham NG2 3AA

8. MARKETING AUTHORISATION NUMBER

PL 00014/0325

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/03/2009

10 DATE OF REVISION OF THE TEXT

27/03/2026