

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solpadeine capsules

Paracetamol 500mg, Codeine Phosphate Hemihydrate 8mg, Caffeine 30mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains paracetamol 500 mg, codeine phosphate hemihydrate 8 mg and caffeine 30 mg. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Gelatin capsules with a red, opaque cap and a white, opaque body plain on both halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine-containing products are indicated in patients older than 12 years of age for the short-term treatment of acute, moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen alone.

Solpadeine is indicated in the management of symptoms of headache, including migraine, toothache, backache, common cold, influenza, menstrual pain, musculoskeletal pain.

4.2 Posology and method of administration

Posology

Adults

1-2 capsules up to four times daily as required to a 8 capsules in 24 hours.

The dose should not be repeated more frequently than every 4 hours.

Adolescents aged 16 to 18 years of age

1-2 capsules every 6 hours. Do not exceed 4 doses, equivalent to 8 capsules.

Adolescents aged 12 years to 18 years:

This medicine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and/or cold (see section 4.4).

Adolescents aged 12 to 15 years of age

1 capsule every 6 hours. Do not exceed 4 doses, equivalent to 4 capsules.

Paediatric population

Children aged less than 12 years:

This medicine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough and/or cold (see section 4.3).

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 patients

Experience has indicated that normal adult dose of paracetamol is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

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:

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

Do not exceed the stated dose.

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.

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:

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

The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Hepatic Impairment

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. The daily dose of paracetamol should not exceed 2g/day unless directed by a physician. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Method of administration

For oral administration only.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1;
- Acute asthma;
- 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 children below the age of 12 years for the symptomatic treatment of cough and/or cold due to an increased risk of developing serious and life-threatening adverse reactions;
- In patients with chronic constipation.

4.4 Special warnings and precautions for use

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking paracetamol or codeine. Underlying liver disease increases the risk of paracetamol-related liver damage.

The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Care should be observed in administering the product to any patients whose condition may be exacerbated by opioids, particularly the elderly, who are especially sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs and those with prostate hypertrophy.

Excessive intake of caffeine (e.g. tea, coffee and some canned drinks) should be avoided while taking this product. Patients with inflammatory or obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Neo-codion contains codeine whose regular or prolonged use may produce psychological and physical dependence. This product should be used with caution in patients with current or past history of substance abuse or dependence (including drug or alcohol) or mental illness (e.g., major depression). Abuse or misuse may result in overdose and/or death (see Section 4.9).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of 'medication overuse headache' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 ($GFR \leq 50 \text{ ml/min}$)
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Concomitant treatment with medicinal products affecting hepatic function
- Hepatic impairment
- Gilbert's Syndrome (familial non-haemolytic jaundice)

Patients taking, or who have taken, monoamine oxidase inhibitors (MAOIs) within the preceding two weeks (see section 4.5) should not take this product.

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

Concomitant use of Solpadeine and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant use with these sedative medicines should be under medical supervision and reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Solpadeine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The 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)

Do not take with other paracetamol or codeine containing medicines.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

Codeine, as with other opioids should be used with caution in patients with hypotension, hypothyroidism, head injury or raised intracranial pressure.

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%

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 morphinotoxicity.

This product should be used only when clearly necessary. Prolonged use without medical supervision may be harmful. Do not take for more than 3 days without consulting a doctor. Do not exceed the stated dose.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

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.

If symptoms persist, consult your doctor.

Keep this medicine out of the sight and reach of children.

Do not take with other paracetamol or codeine containing medicines. Contains Carmoisine (E122). May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The rate of paracetamol absorption may be increased by metoclopramide or domperidone may be reduced by cholestyramine. Colestyramine should not be administered within one hour of taking paracetamol.

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 use of drugs which induce hepatic microsomal enzymes, such as anticonvulsants and oral contraceptive steroids, may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentrations of the drug and a faster elimination rate.

Drugs which induce hepatic microsomal enzymes, such as alcohol and barbiturates, may increase the hepatotoxicity of paracetamol, particularly after overdose.

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

Paracetamol may affect the half-life of chloramphenicol. Evidence of a clinically relevant interaction appears to be lacking. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

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 risks factors (see section 4.4).

Codeine

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOIs) and result in serotonin syndrome. Whilst evidence is limited for the interaction with codeine, it is recommended that the product should not be taken concurrently or within two weeks of stopping treatment with a MAOI. The effect of CNS depressants (including alcohol) may be potentiated by codeine.

Codeine may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility. 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.

Quinidine can inhibit the analgesic effect of codeine.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Sedative medicines such as benzodiazepines or related drugs

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).

Caffeine

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilisers. Caffeine may enhance the tachycardia effect of some decongestants.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate. Regular use of codeine during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate.

The safety of paracetamol-caffeine-codeine during pregnancy has not been established relative to the possible adverse effects on foetal development and should be avoided. In pregnancy a total daily consumption above 200 mg caffeine per day could possibly increase the risk of spontaneous abortion and low birth weight.

Breast-feeding

This medicine 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.

Paracetamol and caffeine are excreted in breast milk but not in a clinically significant amount.

Although significant caffeine toxicity has not been observed in breastfed infants, caffeine may have a stimulating effect on the infant.

Fertility

There are no data available regarding the influence of paracetamol, codeine and caffeine on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Paracetamol

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Very rare	Thrombocytopaenia Agranulocytosis
Immune system disorders	Very rare	Anaphylaxis

	Very rare	Allergies (not including angioedema)
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Very rare	Hepatic dysfunction
Skin and subcutaneous tissue disorders	Very rare	Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema.
	Very rare	Very rare cases of serious skin reactions have been reported: toxic epidermal necrolysis (TEN), drug-induced dermatitis, Stevens-Johnson syndrome

		(SJS), acute generalized exanthematous. pustulosis (AGEP)
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine)

Caffeine

System Organ Class	Frequency	Undesirable Effect
Nervous system disorders	Not known	Dizziness, headache, tremor
Psychiatric disorders	Not known	Nervousness, irritability

When the recommended paracetamol-caffeine-codeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Codeine

Adverse reactions identified during post-marketing use are listed below by organ system class.

System Organ Class	Frequency	Undesirable Effect
Psychiatric disorders	Not known	Drug dependency can occur after prolonged use of codeine at high doses
	Rare	Hallucinations, nightmares and restlessness
Nervous system disorders	Not known	Dizziness, worsening of headache with prolonged use, drowsiness
Eye disorders	Not known	Blurred or double vision
Cardiac disorders	Not known	Palpitations
Vascular disorders	Not known	Facial flushing, postural hypotension
Gastrointestinal disorders	Not known	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy
	Rare	Stomach cramps
Skin and subcutaneous tissue disorders	Not known	Pruritus, sweating
	Not known	Allergic reactions (itch, skin rash, facial oedema)
Renal and urinary disorders	Not known	Difficulty with micturition (dysuria, increased frequency, decrease in amount)

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Paracetamol

Paracetamol overdose can result in liver damage which may be fatal. Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include:

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

On initial presentation, the patient's symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Acute renal failure with acute tubular necrosis may also develop. Cardiac arrhythmias and pancreatitis have also been reported.

Liver damage (as demonstrated by a rise in plasma transaminase levels) may be apparent between 8 and 36 hours following overdose. Biochemical evidence of maximal damage, however, may not be attained until 72-96 hours after ingestion of the overdose.

Symptoms of paracetamol overdose in the first 24 hours may include pallor, nausea, vomiting, anorexia, and abdominal pain. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. On initial presentation, the patient's symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Liver damage results when excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. Symptomatic treatment should be implemented.

Intravenous N-acetylcysteine (NAC) is effective when initiated within 8 hours of the overdose. Efficacy declines progressively after this time, but NAC may provide some benefit up to and possibly beyond 24 hours. Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour. There is little evidence that undertaking gastric lavage will be of benefit to a patient in whom paracetamol is known to have been the only substance ingested.

Codeine

The effects of codeine overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Effects of overdose due to codeine would be subsumed by serious liver toxicity caused by paracetamol overdose. Immediate medical management is required in the event of overdosage, even if symptoms of overdose are not present.

Symptoms

An overdose of codeine is characterized, in the first phase, by nausea and vomiting. 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.

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 350 mg of codeine or a child more than 5mg/kg of codeine. Naloxone should be administered if coma or respiratory depression is present. The patient should be monitored for at least four hours after ingestion or eight hours for a sustained release formulation.

Caffeine

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Symptoms

An overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

Management

No specific antidote is available, but supportive measures such as beta adrenoreceptor antagonists to reverse the cardiotoxic effects may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics, codeine and paracetamol, ATC code: N02AJ06

Paracetamol is an analgesic and antipyretic.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has a 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. Caffeine is a potent stimulator of the CNS.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract. It is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost completely renal, in the form of conjugated metabolites.

Caffeine is absorbed readily after oral administration, maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65-80% of administered caffeine is excreted in the urine as 1-methyluric acid 1- methylxanthine.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86% is excreted in the urine in 24 hours; 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine and 10-20% is free or conjugated norcodeine.

5.3 Preclinical safety data

Codeine and caffeine, individually and in combination, have a well-established safety profile. There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Magnesium stearate

Capsule Shell

Titanium dioxide (E171)
Erythrosine (E127) Patent
blue (E131) Quinoline
yellow (E104) Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/aluminium foil blister strip in a cardboard carton, containing 6, 12, 24, 32, 36, 48, 60, 72 or 96.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

MA1005/00401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 September
2006

Date of latest renewal: 19 September 2011

10. DATE OF REVISION OF THE TEXT

August 2022