Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Codeine Phosphate Hemihydrate/Caffeine Accord 500 mg/8 mg/30 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 500 mg paracetamol, 8 mg codeine phosphate hemihydrate and 30 mg caffeine.

Excipients with known effect
Each effervescent tablet contains 100 mg of sorbitol and 419 mg (18.22 mmol) of sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.
White to off-white, round (26 mm in diameter), bevelled edged effervescent tablet.

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 relieved by paracetamol or ibuprofen alone.

4.2 Posology and method of administration

Posology

Adults(>55 Kg)
1 or 2 tablets each administration, depending on the extent of pain, taken 1 to 3 times daily, at intervals of at least 6 hours. The minimum interval time between doses shouldn't be reduced. However, in case of more severe pain, this dosage can be increased up to 8 tablets per day (maximum dosage). The maximum total daily dose of paracetamol should not exceed 4 g per day; the maximum total daily dose of codeine should not exceed 240 mg.

Adolescents aged 16 to 18 years of age
One to two tablets every 6 hours. Do not exceed 4 doses, equivalent to 6 tablets.

Adolescents aged 12 to 15 years of age
1 tablet every 6 hours. Do not exceed 4 doses, equivalent to 4 tablets.

This medicine should not be used adolescents aged 12-18 years who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome

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/cares 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.
Tablets should be dissolved in at least half a glass of water. The resulting solution should be drunk immediately.

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.
- treatment with MAO inhibitors or within two weeks after their continuation
- In respiratory depression head injuries and raised intra cranial pressure

4.4 Special warnings and precautions for use

Hepatic/renal impairment
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.

Elderly patients
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.

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

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction). 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 ≤50ml/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 this medicineand 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 this medicineconcomitantly 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 morphine toxicity.

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.

Do not take with other paracetamol or codeine containing medicines.

Excipients with known effect

This medicinal product contains 419 mg sodium per effervescent tablet, equivalent to 21% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicinal product contains 100 mg sorbitol in each effervescent tablet. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal products.

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 and 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 led 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 tachycardiac effect of some decongestants.

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol
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
There are limited data on the use of codeine during pregnancy in human. Opiates pass the placenta. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

Caffeine
There is evidence that the prolonged intake of high amounts of caffeine may lead to spontaneous abortion or premature birth in pregnant women. Non-clinical studies have shown reproductive toxicity at very high doses (see section 5.3).

This medicine should only be used when strictly necessary.

Breastfeeding

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 events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post marketing data and are considered to be very rare.

Paracetamol

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Very rare	Thrombocytopaenia Agranulocytosis
Immune system disorder	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. The frequency of these reactions is not known.

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 disorder	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 disorder	Not known	Pruritis, 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Paracetamol

Symptoms and Signs
Paracetamol overdose may cause liver failure. Ingestion of more than 140 mg paracetamol per kg bodyweight (9 g paracetamol in a 60 kg individual), can cause severe liver damage. 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, coma and death. 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.

Treatment
Immediate medical attention (in-hospital, if possible) is required in the event of overdose, even if there are no significant early symptoms. There may be no early symptoms following a life-threatening overdose.

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. Activated charcoal should be considered if the dose of paracetamol ingested exceeds 12 g or 150 mg/kg, whichever is the smaller, and the procedure can be undertaken within 1 hour of the overdose. 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

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 and Signs

An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

Treatment
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. Give naloxone if coma or respiratory depression is present. Observe for at least four hours after ingestion or eight hours for a sustained release formulation.

Caffeine

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

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

Sodium hydrogen carbonate

High doses of Sodium hydrogen carbonate would be expected to induce gastrointestinal symptoms including belching and nausea. In addition, high doses of Sodium hydrogen carbonate may cause hypernatraemia, electrolytes should be monitored and patients managed accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Analgesics, Opioids in combination with non-opioid analgesics.*,
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 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 l-methyluric acid l-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

Citric acid (E330)
Sorbitol (E420)
Sodium hydrogen carbonate (E 500 (II))
Povidone (E 1201)
Simeticone
Sodium Carbonate, anhydrous (E 500 (I))
Saccharin sodium (E 954)
Macrogol(E 1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Paper/PE/Alu/ Surlyn (co-polymer of Ethylene/Methacrylic acid/Zinc material) strip
Pack sizes 4, 8, 10, 12, 16, 20, 24, 32, 40, 60, or 80 effervescent tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd,
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Euro Business Park,
Little Island,
Cork T45 K857,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/267/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th April 2024

10 DATE OF REVISION OF THE TEXT