# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Codeine Accord 500 mg/30 mg, effervescent Tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500 mg / 30 mg effervescent tablet contains 500 mg paracetamol and 30 mg codeine phosphate hemihydrate.

Excipient(s) with known effect
Each tablet contains 100 mg of sorbitol (E420).
Each tablet contains 419 mg sodium (equivalents to 18.20 mmole).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Effervescent tablet

500 mg / 30 mg
White to off-white, round, flat, bevelled edge tablets, plain on both sides. The diameter of tablet is approximately 26 mm.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Paracetamol/Codeine Accord is indicated in adult patients (18 years of age and older) for relief of severe pain.

Paracetamol/Codeine Accord 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).

### 4.2 Posology and method of administration

Posology
Paracetamol/Codeine Accord should be used at the lowest effective dose for the shortest period of time.

**Adults (18 years and over)**
One to two tablets every 6 hours to a maximum of three doses in any 24 hours. However, in case of more severe pain, this dosage can be increased up to 8 tablets per day (maximum dosage). Do not exceed eight tablets in 24 hours. 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 in adults.

**Pediatric population**
In the paediatric population the dose should primarily be based on the codeine component and body weight. Recommended single codeine dose is 0.5 – 1 mg /kg body weight/dose with a maximum dose of codeine of 60mg, every 6 hours when necessary up to maximum dose of 240 mg daily.

The maximum doses of 15 mg / kg body weight / dose (60 mg / kg body weight / day) of paracetamol and 1 mg / kg body weight / dose (4 mg / kg body weight / day) of codeine must not be exceeded.

This medicine should not be used in adolescents aged 12-18 years who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (see section 4.3)

**Adolescents aged 16 to 18 years (>55 kg)**
One to two tablets every 6 hours to a maximum of three doses in any 24 hours.
Do not exceed 6 tablets in 24 hours.

**Children aged 12 to 15 years (40-55 kg)**
One tablet every 6 hours to a maximum of four doses in any 24 hours.
Do not exceed 4 tablets in 24 hours

**Children aged less than 12 years**:
Paracetamol/Codeine Accord 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).

**Special populations**
Elderly
The initial dosage should be reduced by half to the recommended dosage and should be titrated to the individuals need and overall medical condition.

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. In patients with renal failure (creatinine clearance lower than 10 ml/min), the interval between two doses should be at least 8 hours. See Table below:

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

Hepatic impairment

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

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

Method of administration
Oral administration.
The effervescent tablets should be dissolved in at least half a glass of water (about 100-125 ml water). The resulting solution should be drunk immediately.

*Treatment goals and discontinuation*
Before initiating treatment with Paracetamol/Codeine Accord, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

*Duration of treatment*
Paracetamol/Codeine Accord should be used for the shortest duration necessary to relieve symptoms. If no effective pain relief is achieved while taking the medicine, you should seek the advice of a physician.

**4.3 Contraindications**

Hypersensitive to paracetamol or codeine or to any of the excipients listed in section 6.1..

In patients with acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery.

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 who are are breastfeeding (see section 4.6)

In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.

In patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy.

**4.4 Special warnings and precautions for use**

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

Paracetamol/Codeine Accord should be used after careful risk-benefit assessment in case of:

- Opioid dependence
- Chronic constipation
- Impaired consciousness
- Compromised respiratory function and chronic obstructive airway disease

CY2D6 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 nausea, vomiting, constipation, lack of appetite, somnolence, shallow breathing, small pupils and confusion. 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% |

Risks from concomitant use of opioids and benzodiazepines:
Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression (see Section 4.5).

Risks from concomitant use of opioids and alcohol:
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma, and death. Concomitant use with alcohol is not recommended (see Section 4.5).

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 Accord. Repeated use of Paracetamol/Codeine Accord 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 Accord 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).

Before initiating treatment with Paracetamol/Codeine Accord and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Post-operative use in children
There have been reports in the published literature that codeine given postoperatively 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.

Paracetamol/Codeine Accord should be administered with caution in certain patients, such as those who present impaired cardiac, hepatic or renal function, and in cases of benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, gall bladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

This product should only be used with great care in any patient whose condition may be exacerbated by opioids such as those who are on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders.

Care should also be observed if prolonged therapy is contemplated.

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.

Use with caution in patients with convulsive disorders.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease. In patients with kidney failure (creatinine clearance lower than 10 ml/min): the interval between doses should be increased (minimum 8 hours). See section 4.2

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction (See Section 4.8)

Caution is advised in patients with underlying sensitivity to acetyl salicylic acid and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence (addiction) develop with prolonged use of high doses with withdrawal symptoms, such as restlessness and irritability, after sudden discontinuation of the drug. Cross-tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission). Administration must be discontinued gradually after prolonged treatments.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse.

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

In patients who have had a cholecystectomy, codeine may induce acute biliary or pancreatic abdominal pain, which usually occurs with abnormal laboratory results, suggesting a spasm of the sphincter of Oddi. Paracetamol/Codeine Accord is contraindicated for use in these patients. Section 4.3.

If the patient has a productive cough, codeine may impede expectoration.

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.

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.

Elderly patients may be more sensitive to the effects of this medicinal product, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age-related kidney impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.

Elderly patients:
The initial dosage should be reduced to half the recommended dosage; this may be later increased based on patient tolerance and needs. See section 4.2.

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 and 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.

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.

Excipients with known effect

This medicinal product contains 419 mg sodium per dose, equivalent to 21% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 2g of the WHO recommended maximum daily intake for sodium. Paracetamol/Codeine Accord is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.
This medicine 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.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Paracetamol**
Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance.

The rate of absorption of paracetamol may be increased by metoclopramide or domperidone. The absorption of paracetamol is reduced by cholestyramine. Cholestyramine should not be given within one hour if maximum analgesic effect is to be obtained

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine,), rifampicin and alcohol.

Paracetamol may increase the risk of bleeding in patients taking warfarin, antivitamin K and other coumarins. These patients should be monitored for appropriate coagulation and bleeding complications.

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).

Treatment with paracetamol may interfere with the assay of blood uric acid by the phosphotungstic acid method. Treatment with paracetamol may interfere with the assay of blood glucose when concentrations are abnormally high.

**Benzodiazepines and Opioids:**
The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma, and death, because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Section 4.4).

**Alcohol and Opioids:**
The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see Section 4.4).

**Codeine**

Mono Amine Oxidase Inhibitors (MAOI's)
Concomitant administration of MAOI can potentiate the central nervous effects and other side effects of unpredictable severity. Codeine should not be used in patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy. See section 4.3.

Tricyclic antidepressants
A codeine-induced respiratory depression can be potentiated by tricyclic antidepressants.

Antiperistaltic antidiarrhoeal drugs
Concomitant use of codeine with antiperistaltic antidiarrhoeal drugs can increase the risk of severe constipation and CNS depression.

Inadvisable combinations with codeine
Morphine agonists-antagonists (buprenorphine, nalbuphine, pentazocine): Reduced analgesic effect due to competitive receptor blockade, with a risk of withdrawal syndrome.

Naltrexone:
Risk of reduced analgesic effect. The doses of the morphine derivative should be increased if necessary

Combinations to be taken into account:
Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety agents, benzodiazepines, barbituates, methadone or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression including increased risk of respiratory depression.

Concomitant use of Paracetamol/Codeine Accord with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

CYP2D6 inhibitors
Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers
Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

**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.

*Codeine*
There are limited data on the use of codeine during pregnancy in human. Opiates pass the placenta. Codeine can cause respiratory depression and withdrawal syndrome in newborns.
Administration of codeine just before delivery can cause respiratory depression in the neonate and delayed gastric emptying and a risk of pneumonia in the mother during delivery.
Codeine should not be used during the late stages of delivery and during delivery of a premature neonate.

Breastfeeding
Paracetamol/Codeine Accord is contraindicated during breastfeeding (see Section 4.3).
Codeine and paracetamol are excreted in breast milk.
Codeine is partially metabolized by cytochrome P450 2D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breast-fed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses.

Fertility
There a no known effects of paracetamol/codeine on fertility in human

**4.7 Effects on ability to drive and use machines**

Paracetamol/Codeine Accord may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairing the mental and/or physical ability required for the performance of potentially dangerous tasks, such as driving vehicles or using machines.

**4.8 Undesirable effects**

Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.
The frequency using the following convention: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥1/1000 to < 1/100); Rare (≥1/10000 to < 1/1000); Very rare (< 1/10000), including isolated reports; Not known: frequency cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Codiene:

| **System Organ Class** | **Very common (≥ 1/10)** | **Not known (frequency cannot be estimated from the available data)** |
|---|---|---|
| Immune system disorders | | Hypersensitivity |
| Nervous system disorders | Dizziness, Sedation, Headache | Confusion, Seizure, somnolence<br>Eye |
| Eye disorders | | Miosis, visuomotorcoordination and visual acuity may be adversely affected in a dose-dependentmanner at higher doses or in particularly sensitive patients. |
| Psychiatric disorders | Dysphoria, Euphoria | Confusional state, Long term use also entails the risk of drug dependence. |
| Ear and labyrinth disorders | | Tinnitus |
| Respiratory, thoracic and mediastinal disorders | Shortness of breath | Respiratory depression |
| Gastrointestinal disorders | Nausea, Vomiting, Constipation, Abdominal pain | Dry mouth |
| Skin and subcutaneous tissue disorders | Pruritus, Rash, Urticaria | |
| Renal and urinary disorders | | Urinary retention |
| Hepatobiliary disorders | | Sphincter of Oddi dysfunction |
| General disorders and Administration site conditions | | Fatigue |
| Vascular disorders | | Hypotension |

Paracetamol:

| System Organ Class | Very common (≥1/10) | Rare (≥1/10,000 to <1/1000) | Very Rare (< 1/10000) | Not known (frequency cannot be estimated from the available data) |
|---|---|---|---|---|
| Blood and lymphatic system disorders | | Platelet disorders, stem cell disorders, Blood dyscrasias | Thrombocytopenia<br>Leukopenia<br>Neutropenia<br>Hemolytic anemia<br>Agranulocytosis | Anaemia |
| Immune system disorders | | hypersensitivity including skin rash(excluding angioedema) | | anaphylactic shock,angioedema |
| Nervous system disorders | | Tremor NOS, headache NOS | | Vertigo |
| Eye disorders | | Abnormal vision | | |

| | | | | |
|---|---|---|---|---|
| Psychiatric disorders | | Depression NOS, confusion, hallucinations | | |
| Respiratory, thoracic and mediastinal disorders | | | | Edema of the larynx<br>Bronchospams (more likely in asthmatics sensitive to aspirin or other NSAIDs) |
| Gastrointestinal disorders | | Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting | | Gastrointestinal effects |
| Skin and subcutaneous tissue disorders | | Sweating, purpura, angioedema | Very rare cases of seriousskin reactions have been reported. Erythema, urticaria, rash | Toxic epidermal necrolysis (TEN),<br>Stevens-Johnson syndrome (SJS),<br>acute generalised exanthematous pustulosis,<br>fixed drug eruption |
| Renal and urinary disorders | | | Sterile pyuria (cloudy urine) and renal side effects | |
| Cardiac disorders | | Oedema | | |
| Hepato-biliary disorders | | Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice. | Hepatotoxicity | Cytolytic hepatitis, which may lead to acute hepatic failure |
| General disorders and administration site conditions | | Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS. | Hypersensitivity reaction (requiring discontinuation of treatment) | |
| Injury, poisoning and procedural complications | | Overdose and poisoning | | |
| Metabolism and Nutrition disorders | | | Hypoglycaemia | Pyroglutamicacidosis, in patients with pre-disposing factors for glutathione depletion,<br>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.

Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

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

*Drug dependence*
Repeated use of Paracetamol/Codeine Accord 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 reaction
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**

***Codeine:***
The effects of Codeine over-dosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

***Symptoms***
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, rash, pruritis, ataxia, pulmonary edema (more rare) are possible.

The ingestion of very high doses can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

***Management***
Respiratory assistance: This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

***Paracetamol:***
Paracetamol overdose can result in liver damage which may be fatal.

***Symptoms***
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, disseminated intravascular coagulation, 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

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

***Emergency Procedure***
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. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics, codeine and paracetamol
ATC Code: N02 AJ06

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits 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 such as paracetamol, has been shown to be effective in acute nociceptive pain.

### 5.2 Pharmacokinetic properties

Following oral administration of two effervescent tablets (i.e. a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 20.4μg/ml and 218.8ng/ml respectively. The mean times to maximum plasma concentrations were 0.34 hours for paracetamol 0.42 hours for codeine.
The mean AUC for the ten hours following administration was 50.0μg.ml-1.h for paracetamol and 450.0ng.ml-1.h for codeine.

The bioavailabilities of paracetamol and codeine when given as the combination are similar to those when they are given separately.

### 5.3 Preclinical safety data

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

Paracetamol and codeine were not found to be genotoxic in conventional genotoxicity assays.
There are no additional relevant non-clinical data on paracetamol and codeine that add to the information provided in other sections of this SmPC

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Citric acid (E 330)
Sorbitol (E420)
Sodium hydrogen carbonate (E 500 (II))
Povidone (E 1201)
Simeticone
Sodium carbonate (E 500 (I))
Saccharin sodium (E 954)
Polyethylene glycol (E 1521)

*500 mg / 30 mg Strength*
Lemon Flavor (contains Maize maltodextrin, Acacia gum (gum arabic, E414), Natural flavouring substances, Flavouring preparations, Flavouring substances, Alpha-tocopherol (E307))

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store below 25°C.
Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

Surlyn strip (plain 4ply paper based laminated strip foil 50gsm outer side paper/12gsm PE extrusion / 9 µ Aluminium / 23 gsm surlyn inner side) packs { Surlyn is a copolymer of ethylene and methacrylic acid used as packaging material}: containing : 4, 8, 10, 12, 14, 16, 20, 24, , 28, 30, 32, 36, 40, 50, 60, 90 and 100 tablets
For France: 4, 8, 10, 12, 14, 16, 20, 24 tablets

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

**7 MARKETING AUTHORISATION HOLDER**

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

**8 MARKETING AUTHORISATION NUMBER**

PA2315/266/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14th June 2024

**10 DATE OF REVISION OF THE TEXT**

April 2026