Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Codeine phosphate hemihydrate Accord 500 mg/30 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3 PHARMACEUTICAL FORM

Tablet.
White, oval (17 mm x 8.5 mm) biconvex tablet marked 'LK' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Paracetamol/Codeine phosphate hemihydrate Accord is indicated in patients from 12 years of age and older 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

Paracetamol/Codeine phosphate hemihydrate Accord should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day. Maximum daily dose of codeine should not exceed 240 mg.

Adults (18 years and over):
One-two tablets at intervals of not less than 6 hours to a maximum of four doses in any 24 hours.
Do not exceed eight tablets in 24 hours.

Elderly:
The initial dosage should be reduced to half the recommended dosage and should be titrated to the individuals need and overall medical condition.

Paediatric Population
Adolescents aged 16 to 18 years:
The dose should primarily be based on the codeine component and body weight. Recommended single codeine dose is 0.5 - 1 mg codeine/kg, every 6 hours, maximum 4 times daily.
The Paracetamol/Codeine phosphate hemihydrate Accord dose should be adjusted so that the paracetamol component does not exceed 15 mg/kg/dose (up to 60 mg/kg/day).
One to two tablets every 6 hours to a maximum of four doses in any 24 hours. Do not exceed 8 tablets in 24 hours. Maximum daily dose of codeine should not exceed 240 mg.

Adolescents aged 12 to 15 years:
The dose should primarily be based on the codeine component and body weight. Recommended single codeine dose is 0.5 - 1 mg codeine/kg, every 6 hours, maximum 4 times daily.
The Paracetamol/Codeine phosphate hemihydrate Accord dose should be adjusted so that the paracetamol component does not exceed 15 mg/kg/dose (up to 60 mg/kg/day).
One tablet every 6 hours to a maximum of four doses in any 24 hours. Do not exceed 4 tablets in 24 hours. Maximum daily dose of codeine should not exceed 120 mg.

Children aged less than 12 years:

Paracetamol/Codeine phosphate hemihydrate 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).

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. 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 2 g/day.

The maximum daily dose of paracetamol should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in the following situations:

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

Method of administration
For Oral administration

Treatment goals and discontinuation
Before initiating treatment with Paracetamol/Codeine phosphate hemihydrate 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
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.

Paracetamol/Codeine phosphate hemihydrate 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

- 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 the event of impending childbirth or in case of risk of premature birth (see section 4.6).
- In women during breastfeeding (see section 4.6).
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- In patients hypersensitive to paracetamol or codeine, or hypersensitivity to any of the other 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 patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy.
- In association with sodium oxybate.

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 phosphate hemihydrate 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

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% to 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 phosphate hemihydrate Accord. Repeated use of Paracetamol/Codeine phosphate hemihydrate 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 phosphate hemihydrate 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 phosphate hemihydrate 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 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 ultrarapid 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 phosphate hemihydrate Accord should be administered with caution in certain patients, such as those with impaired cardiac, hepatic or renal function, hypotension, benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, 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 drugs, those with prostatic hypertrophy or 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 aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Severe-cutaneous adverse reactions (SCARs): Very rare cases of serious skin reactions such as Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately Paracetamol/Codeine phosphate hemihydrate Accord treatment and seek medical advice.

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.

Monitoring after prolonged use should include blood count, liver function and renal function.
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 phosphate hemihydrate 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.

Important information about some of the ingredients of Paracetamol/Codeine phosphate hemihydrate Accord
This medicinal product 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

Paracetamol

Pharmacokinetic interactions:
Paracetamol may increase the elimination half-life of *chloramphenicol*. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by *metoclopramide* or *domperidone* and absorption reduced by *colestyramine*.

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

Co-administration of *flucloxacillin* with paracetamol may lead to metabolic acidosis, due to pyroglutamic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

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.

Treatment with paracetamol may interfere with the assay of blood uric acid by the phosphotungstic acid method.

Pharmacodynamic interactions:
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.

Codeine

Pharmacokinetic interactions:
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 rifampicin, barbiturates, several antiepileptics, St John's wort) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Pharmacodynamic interactions:
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).

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

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

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 phosphate hemihydrate Accord with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol/Codeine phosphate hemihydrate Accord should not be used in pregnancy. Codeine can cause respiratory depression and withdrawal syndrome in newborns.

A large amount of data on the use of paracetamol in pregnancy indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Breast-feeding

Paracetamol/Codeine phosphate hemihydrate 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 are no known effects of paracetamol/codeine on fertility in human.

4.7 Effects on ability to drive and use machines

Paracetamol/Codeine phosphate hemihydrate 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

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).

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

Related to Paracetamol

MedDRA system organ class	Subject incidence	Adverse reaction
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, neutropenia, Leukopenia
	Not known	Agranulocytosis, haemolytic anaemia, in particular in patients with underlying glucose 6-phosphate-dehydrogenase deficiency
Immune system disorders	Not known	Hypersensitivity such as anaphylactic shock, angioedema
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm
Skin and subcutaneous disorders	Very rare	Erythema, urticaria, rash
	Not known	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption
Hepatobiliary disorders	Not known	Cytolytic hepatitis, which may lead to acute hepatic failure
Metabolism and nutrition disorders	Not known	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.

Related to Codeine

MedDRA system organ class	**Subject incidence**	**Adverse reaction**
Immune system disorders	Not known	Hypersensitivity
Psychiatric disorders	Not known	Confusional state, dysphoria, euphoria. Long term use also entails the risk of drug dependence.
Nervous system disorders	Not known	Seizure, headache, somnolence, dizziness, sedation
Eye disorders	Not known	Miosis, visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients.
Ear and labyrinth disorders	Not known	Tinnitus
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression
Gastrointestinal Disorders	Not known	Constipation, vomiting, nausea, dry mouth
Skin and subcutaneous tissue disorders	Not known	Pruritus
Renal and urinary disorders	Not known	Urinary retention
Hepatobiliary disorders	Not known	Sphincter of Oddi dysfunction
General disorders and administration site conditions	Not known	Fatigue
Vascular disorders	Not known	Hypotension

Description of selected adverse reactions
Drug dependence
Repeated use of [product name] 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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Paracetamol

Symptoms
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, 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.

Codeine

The effects in overdosage 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 four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics
ATC code: N02AJ06

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 tablets (i.e. a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 15.96μg/ml and 212.4ng/ml respectively. The mean times to maximum plasma concentrations were 0.88 hours for paracetamol 1.05 hours for codeine phosphate.

The mean AUC for the 9 hours following administration was 49.05μg.ml^{-1}.h for paracetamol and 885.0 ng.ml^{-1}.h for codeine.

The bioavailabilities of paracetamol and codeine phosphate 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous (E551)
Croscarmellose sodium (E468)
Copovidone
Cellulose microcrystalline (E460)
Talc (E553b)
Magnesium stearate (E570)
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC//Alu/Paper blisters containing 10, 16, 20, 30, 50, 90 or 100 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

PA2315/255/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th June 2023

10 DATE OF REVISION OF THE TEXT

March 2026