Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol/Codeine 500 mg/30 mg, effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg and Codeine Phosphate hemihydrate 30mg.

Excipients with known effect: Each tablet also contains 487 mg of sorbitol and 413 mg of sodium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet

Bevelled, flat, round, white tablet with a scoreline on one face.

Although the tablets have a score line, they are not to be halved as they do not divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PARACETAMOL CODEINE 500 mg / 30 mg, effervescent tablets is indicated in the relief of severe pain in adults. Codeine 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

Adults: The usual dose is one or two tablets every four hours as required. The total daily dose should not exceed 4 g paracetamol and 240 mg of codeine (8 tablets in a day).

Elderly: As for adults, however a reduced dose may be required (see section 4.4)

Paediatric population:
Adolescents 16-18 years old (body weight >35 kg)
The dose should primarily be calculated based on the codeine component and body weight. The recommended dose for codeine 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. Do not take more that 8 tablets in a 24 hour period.

Children aged 12- 15 years:
This combination medicine is not suitable for children aged between 12-15 years. For children aged between12-15 years, other formulations and dose strengths are more appropriate. Alternatively, the medicines can be prescribed separately.

*Children aged less than 12 years:*Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

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

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

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

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

Method of administration:

Oral use.

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

Duration of administration

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.

4.3 Contraindications

- Hypersensitivity to the active substances, or to any of the excipients listed in section 6.1.
- Conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or within 14 days.
- 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 the event of impending childbirth or in case of risk of premature birth (see section 4.6).

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 500 mg / 30 mg, effervescent tablets 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

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 unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (child-pugh>9) acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose 6- phosphate dehydrogenase deficiency, hemolytic anemia, alcohol abuse dehydration and chronic malnutrition (see section 4.2).

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.

The hazards of overdose are greater in those with non- cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with Paracetamol.

Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

Prolonged use except on the doctor's advice may be harmful.

This product should be used only when clearly necessary.

Immediate medical advice should be sought in the event of overdosage, even if the patient feels well, because of the risk of irreversible liver damage.

<u>CYP2D6 metabolism</u>
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%

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).

Patients must be advised not to exceed the recommended dose.

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

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking this product, and to consult their doctor if symptoms persist.

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.
Paracetamol Codeine 500 mg / 30 mg, effervescent tablets 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 depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders.

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 500 mg / 30 mg, effervescent tablets 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.

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 500 mg / 30 mg, effervescent tablets is contraindicated for use in these patients. See section 4.3.

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

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.

The cough suppressant effect of codeine may also be undesirable in other patients with some respiratory conditions.

Important information regarding the excipients in this medicine

Sodium: This medicinal product contains 413mg sodium in each effervescent tablet, equivalent to 20.65%of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product contains 3304 mg of sodium (main component of cooking/table salt) which is equivalent to 165.2% of the WHO recommended maximum daily intake for sodium.

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

Sorbitol: This medicine contains 487mg sorbitol in each effervescent tablet. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The hepatotoxicity of paracetamol may be increased in patients taking substances known to induce liver microsomal enzymes (e.g. barbiturates, tricyclic antidepressants and alcohol). Hepatotoxic substances may increase the possibility of paracetamol accumulation and overdose. This can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances.

Probenecid causes an almost 2-fold reduction clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

- Salicylamide may prolong the elimination t1/2 of Paracetamol
- Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. 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.
- Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

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.

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.
Treatment with paracetamol may interfere with the assay of blood glucose when concentrations are abnormally high.
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
The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.
Concomitant administration of this product and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.
Concomitant administration of codeine and anticholinergics may cause paralytic ileus.
Co-administration with an antimuscarinic drug may cause urinary retention.

Codeine is probably active through the codeine being O-demethylated to morphine via the enzyme CYP2D6. This bioactivation is inhibited by certain medications, e.g. quinidine, terbinafine, certain antidepressants and neuroleptics, etc. These drugs therefore counter the effect of codeine. This interaction has been documented in studies on healthy trial subjects and/or pilot studies on patients.
Direct studies have been performed with quinidine, which is a very strong inhibitor of CYP2D6, and this combination should therefore be avoided.

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. This medicine 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 antiperistalsis antidiarrheal 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, barbiturates, methadone or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression including increased risk of respiratory depression.

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 neuroleptics, antidepressants (e.g. fluoxetine, paroxetine), quinidine, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
On the basis of published literature (Danish National Birth Cohort), paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months.

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.

Use of codeine during pregnancy may lead to withdrawal symptoms in neonates, and use during labour may cause neonatal respiratory depression.

This product is then not recommended during pregnancy.

Breast-feeding:
Codeine must not be used 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.

Fertility
There is no information available concerning the effect of this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if this product causes dizziness or sedation. Codeine may cause visual disturbances.
This medicine 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.

Codeine:

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
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
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 Leukopenia Neutropenia Hemolytic anemia 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 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), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, 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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA website: www.hpra.ie

4.9 Overdose

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.

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

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis, 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: Other analgesics and antipyretics, Anilides.
Paracetamol, combinations excl. psycholeptics
ATC Code: N02BE51

Mechanism of action
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.

Clinical efficacy and safety
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.

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to covert codeine to morphine, thus making codeine ineffective as an analgesic for about 7% of the Caucasian population (see also section 4.4).
The fixed combination of paracetamol and codeine showed to be effective in nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

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.

<u>Paracetamol</u>
Absorption
The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Biotransformation
Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-pbenzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.

Elimination half life is about 2 hours.

Physiopathological Variations
Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects. The capacity for conjugation is not modified.

Codeine
Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 h and the plasma half-life is about 3.5 h. The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine crosses the placenta and is present in the milk of lactating mothers.

Biotransformation and elimination
Codeine is metabolised in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), and other metabolites. After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h.

Due to genetic polymorphism in the liver enzyme CYP2D6 some patients have a deficiency to convert codeine to morphine leading to an inadequate analgesic effect. On the other hand there are patients who are extensive or ultra-rapid metabolisers. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. For further information see also section 4.4.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Sodium Docusate
Sorbitol
Saccharin Sodium
Dimeticone
Sodium Benzoate
Macrogol 6000
Natural grapefruit flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for polypropylene tubes. Use within 2 years of first use.
12 months for foil strips.

6.4 Special precautions for storage

For the foil strips:

This medicinal product does not require any special storage conditions.

For the polypropylene tubes:
Store in the original tubes. Keep the tubes tightly closed.

6.5 Nature and contents of container

Aluminium/polyethylene foils strips of 4, 8, 16, 32 and 100 effervescent tablets.

Polypropylene tubes of 8, 16, 32 and 96 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.
No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

Brillpharma (Ireland) Limited
Inniscarra
Main Street
Rathcoole
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22749/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14th July 2018

10 DATE OF REVISION OF THE TEXT

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