Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solpa-Plus with Caffeine Soluble Tablets Paracetamol 500 mg Codeine Phosphate Hemihydrate 12.8 mg Caffeine 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg, Codeine Phosphate Hemihydrate 12.8 mg and Caffeine 30 mg.
Excipients with known effect:
- 24mmol (427mg) sodium per tablet
- 50mg sorbitol per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.
White bevel-edged scored tablets.
The score line is non-functional and not to divide the tablet into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solpa-Plus with Caffeine Soluble Tablets are recommended for the short term relief of acute moderate pain which requires stronger analgesia than single ingredient analgesics alone. For the treatment of: headache, migraine (with and without aura), dental pain (including pain after extraction), dysmenorrhea, muscle ache, neuralgia, backache, pain in bones and joints arising from arthritis and rheumatism, strains and sprains, sciatica.
The product is indicated to use in age of 12 years and older.

4.2 Posology and method of administration

Posology
Oral administration only.
Adults:
Dissolve one to two tablets in at least half a tumbler of water (200 ml) every 4-6 hours up to four times a day if necessary.
Adolescents 16 to 18 years of age:
Dissolve one to two tablets in at least half a tumbler of water (200 ml) every 6 hours up to four times a day if necessary.
Do not exceed 8 tablets (equivalent to paracetamol 4 g, codeine phosphate hemihydrate102.4 mg and caffeine 240 mg) in 24 hours.
Adolescents 12 to 15 years of age:
Dissolve one tablet in at least half a tumbler of water (200 ml) every 6 hours up to four times a day if necessary.
Do not take more than 4 tablets in (equivalent to 2 g paracetamol and 51.2 mg codeine phosphate hemihydrate and caffeine 120 mg) in 24 hours
The tablet will take up to 2 minutes to dissolve.
Elderly patients:
Elderly patients may require a reduced dose.
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 failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.
Adults:

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.
Adults:
The maximum daily dose of paracetamol should not exceed 2g in the following situations unless directed by physician:
- Adults or adolescents weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Method of administration
Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage (see section 4.4 and 4.9).
Minimum dosing interval: 4 hours.
If pain or fever persists for more than 3 days or gets worse, or if any other symptoms occur, treatment should be discontinued and a physician consulted.

4.3 Contraindications

Solpa-Plus with Caffeine Soluble Tablets are contraindicated in patients with hypersensitivity to the active substances (paracetamol, caffeine, codeine, opioid analgesics) or to any of the excipients listed in section 6.1.
The product is contraindicated in:
- Women who are breastfeeding (see section 4.6)
- Respiratory depression, chronic constipation
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- 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).

4.4 Special warnings and precautions for use

Paracetamol:

Patients should be advised not to take other paracetamol containing products concurrently.

Paracetamol should be administered only with particular caution under the following circumstances:

- Hepatocellular insufficiency
- Chronic alcoholism
- Renal failure (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
- The elderly, adults and adolescents weighing less than 50kg

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

Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid since mild bronchospasms are reported in association with paracetamol (cross reaction).

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.

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

Hepatotoxicity at therapeutic dose of paracetamol
Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 Kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9).
Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

Codeine

Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped.

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

CYP2D6 metabolism
Codeine is metabolised by the liver enzyme CYP2D6 into morphine. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may
include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	**Prevalence %**
African/Ethiopian	29
African American	3.4 to 6.5
Asian	1.2 to 2
Caucasian	3.6% to 6.5
Greek	6.0
Hungarian	1.9
Northern European	1-2

Paediatric population
Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life- threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

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

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.
Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Risk from concomitant use of sedative medicines such as benzodiazepines or relateddrugs:

Concomitant use of Solpa-Plus Tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Solpa-Plus Tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Patients should be advised not to take other codeine containing products.

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

Caffeine

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product (see section 4.9: Overdose, caffeine).

Excipient warnings:
This medicinal product contains 427 mg sodium per tablet equivalent to 21% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The maximum daily dose of this product is equivalent to 171% of the WHO recommended maximum daily intake for sodium. Solpa-Plus Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicine contains 50mg sorbitol in each tablet.

Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol:

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Paracetamol is metabolized in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or induce this route; causing hepatoxicity, particularly in overdose (see section 4.9).
The rate of paracetamol absorption may be reduced by cholestyramine. Cholestyramine should not be administered within one hour of taking paracetamol.

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

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics but its validity has been criticised and evidence of a clinically relevant interaction appears to lack. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

Metoclopramide increases the rate of absorption of paracetamol and raises its maximum plasma levels. As the total amount of paracetamol absorbed was unchanged, this interaction is not likely to be clinically significant, although a more rapid onset of action may be advantageous.

Domperidone may speed up the absorption of paracetamol from the gut, this effect can be useful in migraine.

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).

Caffeine:

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

Codeine:

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

Codeine potentiates the central depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

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

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Solpa-Plus with Caffeine Soluble Tablets use should be avoided unless advised by a physician during pregnancy. This includes maternal use during labour because of the potential of codeine to induce respiratory depression in the neonate.
In pregnancy a total daily consumption above 200 mg caffeine per day could possibly increase the risk of spontaneous abortion and low birth weight.

The safety of paracetamol-caffeine and codeine use during pregnancy has not been established relative to the possible adverse effects of foetal development.

Breast-feeding
Solpa-Plus with Caffeine Soluble Tablets 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.

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

Fertility
There are no data available regarding the influence of Solpa-Plus with Caffeine Soluble Tablets on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Paracetamol

System Organ class	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune system disorders	Anaphylaxis	Very rare
	Allergies (not including angioedema)	Rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare
Skin and subcutaneous tissue disorders	Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema.	Very rare
	Very rare cases of serious skin reactions have been reported.	Very rare
Renal and urinary disorders	Sterile pyuria (cloudy urine)	Very rare

Caffeine

System Organ class		Undesirable effect	Frequency
Nervous disorders	system	Nervousness Dizziness	Not Known

Codeine
Undesirable effects depend upon dose and individual patient metabolism.

System Organ class	Undesirable effect	Frequency
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine at higher doses	Not known
Nervous system disorders	Dizziness, worsening of headache with prolonged use, drowsiness	Not known
Gastrointestinal disorders	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy	Not known
Skin and subcutaneous tissue disorders	Pruritus, sweating	Not known
Renal and urinary disorders	Difficulty with micturition	Not known
System Organ class	Undesirable effect	Frequency
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine at higher doses	Not known
Nervous system disorders	Dizziness, worsening of headache with prolonged use, drowsiness	Not known
Gastrointestinal disorders	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy	Not known

Skin and subcutaneous tissue disorders	Pruritus, sweating	Not known
Renal and urinary disorders	Difficulty with micturition	Not known

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

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

Codeine:
The effects in overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.
Symptoms
An overdose of codeine is characterized, in the first phase, by nausea and vomiting.
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large.
Management
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg 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:
There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases.
Symptoms
Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain, or patients may be asymptomatic.
Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue. Cardiac arrhythmias and pancreatitis have been reported.
Risk factors
If the patient
a) is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes
Or
b) regularly consumes ethanol in excess of recommended amounts
Or
c) is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
Management
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.
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 >150mg/kg paracetamol has been taken within 1 hour.
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.
Symptomatic treatment should be implemented.

Caffeine:

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity. In pregnancy a total daily consumption above 200 mg caffeine per day could possibly increase the risk of spontaneous abortion and low birth weight.

Symptoms and signs

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

Management

Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Anilides, combinations excluding psycholeptics.
ATC code: N02AJ06
Mechanism of action

Paracetamol:

Analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Caffeine:

Central nervous system stimulant: caffeine stimulates all levels of the CNS, although its cortical affects are milder and shorter than those of amphetamines. Caffeine possesses a weak diuretic action.

Analgesia adjunct: caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhancing pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

Caffeine enhances and prolongs the analgesic activity of paracetamol up to 3 hours.

Codeine:

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has a low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract with maximum plasma concentration being reached 30 minutes after ingestion (with solid forms observation of peak plasma up to 60 mins and soluble form in 30 mins.

The soluble form of Solpa-Plus with Caffeine Soluble Tablets is first detected in plasma at 15 mins

Distribution

Paracetamol is relatively uniformly distributed throughout most bodily fluids and exhibits variable protein binding.

Biotransformation

Paracetamol is mainly metabolised in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinone imine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Less than 5% is excreted as unmodified paracetamol; the elimination half-life varies from 1 to 4 hours. Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulphate conjugates (20-30%). Less than 5% is eliminated in unchanged form. Elimination half-life is about 2 hours.
In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with renal failure (GFR≤50ml/min), to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.

Caffeine:

Absorption

Caffeine is rapidly absorbed from the gastrointestinal tract after oral administration. Maximum plasma concentrations are achieved within one hour and the plasma half-life is about 4.9 hours, but there are large inter-individual and intra-individual differences ranging between 1.9-12.2 hours.

Distribution

Caffeine administered orally is practically fully bioavailable and distributes into all body fluids. The mean plasma protein binding of caffeine is 35%. Maximum plasma concentrations are reached after 30-40 minutes.

Biotransformation

Caffeine is almost completely metabolised in the liver by oxidation, demethylation and acetylation, and is excreted in the urine. The major metabolites are 1-methylxantine, 7-methylxantine, 1,7-dimethylxantine (paraxantine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6-formylamino 3-methyluracil (AMFU).

Elimination

Caffeine and its metabolites are primarily eliminated by the kidneys.

Codeine:

Absorption

Codeine is well absorbed from the gastrointestinal tract following oral administration with peak plasma concentration being reached in approximately 1 hour after ingestion.

Distribution

It is widely distributed throughout most body fluids and exhibits low plasma protein binding with a plasma half-life of approximately 2.5 to 3 hours.

Biotransformation

Codeine is metabolised in the liver by the hepatic enzyme Cytochrome P450 2D6 (CYP2D6) to form morphine, and Cytochrome (CYP3A4) to form norcodeine, which are further metabolized by conjugation with glucuronic acid.

Elimination

Codeine and its metabolites are excreted almost entirely in the urine (approximately 90%).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Sodium saccharin
Sodium bicarbonate
Sodium lauryl sulfate
Citric acid
Sodium carbonate anhydrous
Povidone K-25
Dimeticone 350

6.2 Incompatibilities

None.

6.3 Shelf life

4 Years (48 Months)

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Paper/LDPE/aluminium/LDPE laminate strips packed into cardboard cartons containing 8, 10, 12, 16, 20, 24 or 32 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/011/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th March 2017
Date of last renewal: 8th March 2021

10 DATE OF REVISION OF THE TEXT

November 2022