Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solpa-Plus Tablets Paracetamol 500 mg Codeine Phosphate Hemihydrate 12.8 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol and 12.8 mg codeine phosphate hemihydrate.

Excipients with known effect: 5.9 mg lactose monohydrate per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablets).
Red film coated capsule shaped tablets, 15.8 mm x 8.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solpa-Plus Tablets are recommended for the relief of acute moderate pain which requires stronger analgesia than paracetamol or ibuprofen or aspirin alone. For the treatment of: dental pain (including pain after extraction), headache, migraine (with and without aura), dysmenorrhea, backache, pain in bones and joints arising from arthritis and rheumatism, neuralgia, strains and sprains, sciatica.

The product is indicated for use in patients aged 12 years and older.

4.2 Posology and method of administration

Posology
Oral administration only.

Adults:
Two tablets up to 4 times a day. This dose should not be repeated at more than 4 – 6 hours' intervals.

Adolescents 16 to 18 years of age:
Two tablets up to 4 times a day. This dose should not be repeated at more than 6 hours' intervals.
Not more than 4 doses (equivalent to Paracetamol 4g and Codeine phosphate hemihydrate 102.4 mg) should be given in any 24-hour period.

Adolescents 12 to 15 years of age:
One tablet up to 4 times a day. This dose should not be repeated at more than 6 hours' intervals, and not more than 4 doses a day (equivalent to 2g of paracetamol and 51.2 mg of Codeine phosphate hemihydrate) should be given in any 24-hour period to adolescents 12 to 15 year of age.

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:
Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication. 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. The restrictions related to the use of such combinations in patients with renal impairment are primarily a consequence of the paracetamol content of the product (see section 4.4).

Adults:

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

Hepatic Impairment:
Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medication. The restrictions related to the use of such combinations in patients with hepatic impairment are primarily a consequence of the paracetamol content of the product (see section 4.4).

Adults:
The maximum daily dose of paracetamol should not exceed 2g in the following situations unless directed by a 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

Hypersensitivity to the active substances (paracetamol, 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 who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. Underlying liver disease increases the risk of paracetamol-related liver damage. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

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

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 or 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.

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

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:

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

CYP2D6metabolism
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%

Paediatricpopulation

Post-operativeusein 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.

Childrenwithcompromisedrespiratoryfunction

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 should be advised not to take other codeine containing products.

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).

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 related drugs:

Concomitant use of this product 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 whom alternative treatment options are not possible. If a decision is made to prescribe the product 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).

Excipientwarnings:

Patientswithrarehereditaryproblemsofgalactoseintolerance,totallactasedeficiency or glucose-galactosemalabsorptionshouldnottakethismedicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially'sodium-free'.

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 regular 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 due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

Codeine:

Codeine may antagonize 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 Tablets use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate.
The safety of paracetamol-codeine during pregnancy has not been established relative to the possible adverse effects of foetal development.

Breast-feeding
Solpa-Plus Tablets should 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 are no data available regarding the influence of Solpa-Plus 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:

SystemOrganclass	**Undesirableeffect**	**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
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known

Description of selected adverse reactions
High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Codeine:
Undesirable effects depend upon dose and individual patient metabolism.

SystemOrganclass	**Undesirableeffect**	**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

Reportingofsuspected adversereactions
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 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. The pupils may be pin-point in size. Hypotension and tachycardia are possible but unlikely.

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.
Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage.

Risk factors
If the patient

1. is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymesOr
2. regularly consumes ethanol in excess of recommended amountsOr
3. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Anilides, combinations excluding psycholeptics. ATC code: N02B E51.
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.

Codeine:

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

Paracetamol:

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract with maximum plasma concentration being reached 30 minutes after ingestion.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids. Plasma protein binding is variable.

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.

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 and codeine 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

Tablet core

Starch, pre-gelatinised
Povidone K25

Maize starch
Talc

Magnesium stearate
Stearic acid
Microcrystalline cellulose
Croscarmellose sodium

Tablet coating
Lactose monohydrate
Hypromellose
Macrogol 4000
Quinoline yellow (E104)
Erthyrosine (E127)
Titanium dioxide (E171)

6.2 Incompatibilities

None.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC 250 µm / aluminium foil 30 µm blisters in outer cartons, containing 6, 10, 12, 16, 20, 24, 30 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

PA1186/011/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th March 2017
Date of last Renewal: 30th November 2021

10 DATE OF REVISION OF THE TEXT

March 2025