Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solpa-Extra 500 mg/65 mg Soluble Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Caffeine 65 mg.
Excipients with known effect:
- 24 mmol (427 mg) sodium per tablet
- 50 mg sorbitol per tablet
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet.
White bevel-edged scored tablets, 25 mm in diameter.
The score line is not intended for breaking the tablet into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solpa-Extra 500 mg/65 mg Soluble Tablets are used for the treatment of mild to moderate pain, for example: headache including migraine (with and without aura), backache, toothache, muscle ache, neuralgia, joint pain, dysmenorrhea, sore throat, and for the relief of fever, aches and pains of colds and influenza.
This product is indicated to be used in adults and adolescents 12 years and over.

4.2 Posology and method of administration

Posology
Oral administration only.

Adults (including the elderly) and adolescents16 years and over:
Dissolve one to two tablets in at least half a tumbler of water every 4-6 hours.

Do not exceed 4 doses, equivalent to 8 tablets (4000/520mg/24h).

Elderly:
It is recommended that frail or immobile patients should reduce the dose or frequency of dosing.

Do not exceed 8 (4000/520mg) tablets in 24 hours.

Adolescents 12-15 years of age:
Dissolve one tablet in at least half a tumbler of water every 4-6 hours.
Do not exceed 4 doses, equivalent to 4 tablets (2000/260mg/24h).
The tablet will take up to 2 minutes to dissolve.

Children aged less than 12 years:
Not suitable for children under 12 years of age.

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 paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (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:
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 2000 mg in the following situations unless directed by a physician:

- Adults or adolescents weighing less than 50kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

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 paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Method ofadministration
Do not exceed the recommended daily dosage or the specified number of doses because of 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 physician consulted.

4.3 Contraindications

Hypersensitivity to the active substances (paracetamol, caffeine) or any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Paracetamol:
Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
The hazard of overdose is greater in those with alcoholic liver disease.
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-phosphatedehydrogenase 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).

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

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).

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).

Solpa-Extra 500mg/65mg Soluble Tablets should not be taken immediately before bedtime.

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. To be taken into consideration by patients on a controlled sodium diet.

Solpa-Extra 500mg/65mg Soluble Tablets contains sorbitol (E420). 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 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 hepatotoxicity, 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 since 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 be lacking. 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.

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

4.6 Fertility, pregnancy and lactation

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

Caffeine
Solpa-Extra 500mg/65mg Soluble Tablets is not recommended during pregnancy unless advised by a physician.
In pregnancy a total daily consumption above 200 mg caffeine per day could possibly increase the risk of spontaneous abortion and low birth weight.

Breast-feeding
Solpa-Extra 500mg/65mg Soluble Tablets is preferably not taken during breastfeeding. If use is considered necessary the drug should be administered right after breastfeeding. Caffeine may have a stimulating effect on the breastfed infants, but significant caffeine toxicity has not been observed in breastfed infants.
Fertility
There are no available data regarding the influence of Solpa-Extra 500mg/65mg Soluble Tablets on fertility.

4.7 Effects on ability to drive and use machines

Solpa-Extra 500 mg/65 mg Soluble Tablets has no or negligible influence on the ability to drive and use machines.

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
	Neutropenia	Unknown
	Leukopenia	Unknown
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 cases of serious skin reactions have been reported.	Very rare
	Toxic epidermal necrolysis (TEN), drug-induced dermatitis, Stevens-Johnson syndrome (SJS). Acute generalised exanthematous pustulosis (AGEP)	Very rare
Renal and urinary disorders	Sterile pyuria (cloudy urine)	Very rare

Caffeine:

System Organ class	**Undesirable effect**	**Frequency**
Nervous system disorder	Nervousness Dizziness	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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.

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.
In severe poisoning, 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, haemorrhage, hypoglycaemia, cerebral oedema 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. Abnormalities of glucose metabolism and metabolic acidosis may occur. On initial presentation the patient's symptoms may not reflect the severity of overdose or the risk of organ damage. However, 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. 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 toxicity.

Symptoms
An overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardia arrhythmia, stimulation of nervous system (insomnia, restlessness, excitement, agitation, nervousness, tremors and convulsions).

Management
Patients should receive general supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Paracetamol:
Paracetamol is an 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.
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.

5.2 Pharmacokinetic properties

Paracetamol:
Absorption
Paracetamol in its soluble form 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). The soluble form of Solpa-Extra 500mg/65mg 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-formylamino3-methyluracil (AMFU).

Elimination
Caffeine and its metabolites are primarily eliminated by the kidneys.

5.3 Preclinical safety data

Paracetamol and caffeine, individually and in combination, have a well-established safety profile.

There are no preclinical 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

Sodium hydrogen carbonate
Sorbitol (E420)
Saccharin sodium
Sodium laurilsulfate
Citric acid anhydrous
Sodium carbonate anhydrous
Povidone K25
Dimeticone 315/385

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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/PE/aluminium/PE laminate strips in cardboard carton outers containing 4, 6, 12, 16, 18, 24, 30, 48 or 60 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

PA1186/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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