1 NAME OF THE MEDICINAL PRODUCT

Solpadeine Headache Soluble Tablets
SolpaPain 500mg/65mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Caffeine 65 mg

Excipients with known affect:
Sodium Carbonate Anhydrous 134.2 mg per tablet

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet

White bevel-edged scored tablets, one inch in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solpadeine Headache Soluble Tablets are a mild analgesic and antipyretic formulated to give extra pain relief. The soluble tablets are recommended for the treatment of most painful and febrile conditions, for example, headache including migraine, backache, toothache, colds and influenza, sore throat, rheumatic pain and dysmenorrhoea.

4.2 Posology and method of administration

Posology

Adults and adolescents 16 years and over:

Two tablets every 4-6 hours up to four times daily. Do not exceed 4 doses, equivalent to 8 tablets in 24 hours. Do not take more frequently that every 4 hours.

Dose should be reduced in underweight adults (see section 4.4 and 4.9)

Adolescents 12 to 15 years of age:

One tablet every 4-6 hours up to four times daily. Do not exceed 4 tablets in 24 hours. Do not take more frequently that every 4 hours.

Children aged under 12 years:
Not recommended for children under 12 years.

Elderly:
Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing

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).

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

Method of Administration
Solpadeine Headache Soluble Tablets are for oral administration only.

Solpadeine Headache Soluble Tablets should be dissolved in at least half a tumblerful of water.

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 persist 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 paracetamol, caffeine or any of the other constituents listed in section 6.1.

4.4 Special warnings and precautions for use

Paracetamol

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non- cirrhotic 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-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- The elderly, adults and adolescents weighing less than 50kg

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.

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 overdosage 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.

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

This medicinal products contains 854 mg sodium per dose (2 tablets), equivalent to 42.7 % of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 170.8 % of the WHO recommended maximum daily intake for sodium.

Solpadeine Headache Soluble Tablets is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicine contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Cholestyramine should not be administered within one hour of taking 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.

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)

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 (e.g. barbiturates, such as phenobarbitone, tricyclic antidepressants, alcohol, carbamazepine, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes), causing hepatotoxicity, particularly in overdose (see section 4.9).

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 criticized 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.

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

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.
Due to the caffeine content of this product it should not be used if you are pregnant due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

Lactation

Solpadeine Headache Soluble Tablets is preferably not taken during breastfeeding. If use is considered necessary, the drug should be administered right after breastfeeding. Caffeine in breast milk may potentially have a stimulating effect on breast fed infants. Due to the caffeine content of this product it should not be used if you are breast feeding.

Fertility

There are no available data regarding the influence of Solpadeine Headache Soluble Tablets on fertility

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

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

Post marketing data

Paracetamol

System Organ Class	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Very rare
Immune system disorders	Anaphylaxis Allergies (not including angioedema)	Very rare
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	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. Stevens Johnson syndrome/toxic epidermal necrolysis, drug-induced dermatitis, acute generalized	Very rare
Renal and urinary disorders	Sterile pyuria (cloudy urine)	Very rare

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.

*There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Caffeine

System Organ Class	Undesirable effect	Frequency
Central Nervous system	Nervousness Dizziness	Not known

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches,

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. 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. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

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

Symptoms and signs

Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, coma and death.
On initial presentation the patient's symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.
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.

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 and any patient who has ingested around 7.5g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Gastric

lavage or the administration of activated charcoal may be beneficial when performed within one hour of the overdose but can be considered for up to four hours after the overdose. Antidotes such as N-acetylcysteine (NAC) and methionine protect the liver if administered within 12 hours of overdose. Acetylcysteine is considered to reduce the hepatic toxicity of NAPQI (n-acetyl-p-benzo-quinonimine), the highly reactive intermediate metabolite following ingestion of a high dose of paracetamol. N-acetylcysteine (NAC) has been shown to still be effective when infusion is started at up to 12 hours after paracetamol ingestion. When acetylcysteine treatment is begun more than 8 to 10 hours after paracetamol overdose, its efficacy in preventing hepatotoxicity (based on serum indicators) declines progressively with further lengthening of the overdose-treatment interval (the time between paracetamol overdose and start of treatment). However, there is now evidence that it can still be beneficial when given up to 24 hours after overdose. N-acetylcysteine (NAC) may not have beneficial effect 48 hours after overdose

With administration of N-acetylcysteine (NAC) there is a theoretical risk of hepatic encephalopathy. Overdosage of acetylcysteine has been reported to be associated with side effects similar to that of anaphylactoid reactions, but they may be more severe. General supportive measures should be carried out. Such reactions are managed with antihistamines and steroids in the usual way. There is no specific antidote.

Caffeine

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 and signs

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

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.

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 effects 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.

Combination of paracetamol and caffeine:
The combination of paracetamol and caffeine is a well-established analgesic combination.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract with maximum plasma concentrations being reached 10 to 60 minutes after oral administration, depending on the pharmaceutical form.

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

Biotransformation
Paracetamol is metabolized mainly in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalyzed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) 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.

Excretion
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 sulfate conjugates (20-30%). 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 sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects.

Caffeine
Absorption

Caffeine is absorbed readily after oral administration, maximal 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 – 2.2 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 metabolized 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-6formylamino 3-methyluracil (AMFU).

Excretion
65 - 80% of administered caffeine is excreted in the urine as 1- methyluric acid and 1-methylxanthine.

5.3 Preclinical safety data

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

Saccharin sodium

Sodium laurilsulfate

Citric acid anhydrous

Sodium carbonate anhydrous

Povidone

Dimeticone

6.2 Incompatibilities

None known.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PPFP laminate sachets in cardboard carton outers containing 4, 6, 12, 16, 18, 24, 30, 48 or 60 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Omega Pharma Ltd,
Wrafton, Braunton,
Devon,
EX33 2DL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 02855/0079

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