1. NAME OF THE MEDICINAL PRODUCT

Solpadeine One 1000 mg Soluble Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Soluble tablet contains 1000mg of Paracetamol.

Excipient(s) with known effect: Sodium content approximately 435.25 mg /tablet
Sorbitol 100 mg/tablet.

For a full list of excipient see section 6.1

3 PHARMACEUTICAL FORM

Soluble Tablet

White to off white, round, flat faced, bevelled edged tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For adults and adolescents only:

Treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Posology

This presentation is reserved for use in adults and in adolescents over 50kg of body weight aged 16 years and above.

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight (= b.w.) to a maximum of 60 mg/kg b.w. for total daily dose.

Adults and adolescents (aged 16 years and above) > 50 kg of body weight
Take one tablet (1000 mg) every four to six hours, upto a maximum of 3 tablets (3000 mg) in 24 hours.

Maximum daily dose:

- The maximum daily dose of Paracetamol must not exceed 3000 mg.
- Maximum single dose is 1000 mg (1 soluble tablet).

Solpadeine One 1000 mg Soluble Tablets are for oral administration. The tablets should be placed in a full tumbler of water immediately before use and allowed to dissolve completely before swallowing.

Frequency of administration:

Doses of Solpadeine One 1000 mg Soluble Tablets should not be given more frequently than every 6 hours, and not more than 3 doses should be given in any 24 hour period.

Renal insufficiency:
In case of renal insufficiency the dose should be reduced:

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

Paracetamol 1000 mg Tablets are not suitable for patients with renal and hepatic insufficiency when reduced dose is required. More appropriate pharmaceutical forms are available in the market for use.

Hepatic insufficiency:
In patients with impaired hepatic or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 60 mg/kg/day (upto maximum 2000 mg /day) in the following situations:

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

Intake of paracetamol with food and drink does not affect the efficacy of the medicinal product.

4.3 Contraindications

- Hypersensitivity to Paracetamol, or any of the excipients.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (***Child-Pugh >9***), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse and chronic malnutrition (see section 4.2).

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2000 mg in such case. Alcohol should not be used during the treatment with Paracetamol.

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

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.

Abrupt discontinuation of long-term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

Solpadeine One Tablets should not be administered in children and adolescents below 16 years of age and under 50 kg body weight.

This medicinal product contains 435.25 mg sodium per dose, equivalent to 21.76 % of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 65.28 % of the WHO recommended maximum daily intake for sodium.

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

This medicine contains 100 mg sorbitol in each tablet.

Do not exceed the stated dose.

If symptoms persist consult a doctor.

Treatment with an antidote is advised if an overdose is suspected.

4.5 Interactions with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The metabolization of paracetamol is increased in patients taking enzyme-inducing drugs such as rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing drugs and alcohol.

- Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.
- Salicylamide may prolong the elimination t1/2 of Paracetamol.
- Metoclopramide and domperidone accelerate absorption of Paracetamol. However, concurrent use need not be avoided.
- Cholestyramine reduces absorption of Paracetamol and therefore should not be administered within an hour following Paracetamol administration.
- Concomitant use of Paracetamol (4000 mg per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.
- Isoniazid : Reduction of paracetamol clearance, with possible potentiation of its action and/ or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of liver metabolism.
- Chloramphenicol: Increased plasma concentration of chloramphenicol

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).

Interference with laboratory tests:
Paracetamol may affect uric acid tests by wolframato phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children

exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding**:**
Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are known in association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding

4.7 Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class and frequency.

The following convention has been utilised for the classification of the undesirable effects: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data.

Body System	**Undesirable effect**	**Frequency**
Immune system disorders	Allergies (excluding angioedema)	Rare
	Anaphylactic shock Hypersensitivity reaction (requiring discontinuation of treatment), Cutaneous hypersensitivity reactions including, among others, skin rashes and angiodema.	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Very rare

	edema of the larynx	Unknown
Skin and subcutaneous tissue disorders	Erythema multiforme	Unknown
	Pruritus rash sweating purpura urticaria	Rare
Blood and lymphatic system disorders	Leukopenia Pancytopenia Hemolytic anemia	Rare
	Thrombocytopenia Agranulocytosis	Very Rare
Psychiatric disorders	Depression NOS confusion hallucinations	Rare
Nervous system disorders	Tremor NOS headache NOS	Rare
Eye disorders	Abnormal vision	Rare
Cardiac disorders	Oedema	Rare
Gastrointestinal disorders	Haemorrhage NOS abdominal pain NOS diarrhoea NOS nausea vomiting	Rare
Hepatobiliary disorders	Hepatic failure hepatic necrosis jaundice	Rare
	Hepatotoxicity Hepatic dysfunction	Very rare

General disorders and administration site conditions	Dizziness (excluding vertigo) malaise pyrexia sedation drug interaction NOS	Rare
Injury, poisoning and procedural complications	Overdose and poisoning	Rare
Metabolism and nutrition disorders	Hypoglycaemia	very rare
	High anion gap metabolic acidosis	Not known
Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects (Severe renal impairment, Haematuria, Anuria, Tubulointerstitial nephritis)	very rare

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

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.

Reporting of suspected adverse reactions

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

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism and in patients with chronic malnutrition. Overdose of Paracetamol is potentially fatal in all populations.Ingestion of 5g 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 of paracetamol overdosage 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, and death. 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.

Overdose, 10g or more of Paracetamol in adults or 150 mg/kg of body weight, causes 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.

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. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however, the maximum protective effect is obtained up to 8 hours post ingestion.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *other analgesics and antipyretics; anilides*

ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Elimination half life is about 2 hours.

Special patient groups

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

Elderly Subjects. The capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal studies investigating the acute, subchronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At subtoxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.
Paracetamol crosses the placental barrier. Animal studies and clinical experience to date have not indicated any teratogenic potential.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Citric acid
Sorbitol E420
Sodium Carbonate, Anhydrous
Sodium Bicarbonate
Povidone K 25 (E1201)
Simeticone
Saccharin Sodium
Macrogol 6000
Powdarome Lemon Premium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

For Polypropylene tube:

Do not use the product after 1 month from the date of first opening.

6.4 Special precautions for storage

Store below 25°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from moisture and light.

6.5 Nature and contents of container

Solpadeine One 1000 mg Soluble Tablets are packed in Surlyn Strip pack and Polypropylene tubes.

Surlyn Strip pack:
Paper/PE/Alu/Surlyn strips

Each strip has 4 or 10 tablets. The strips are packed in a carton having 4 tablets (4x1), 8 tablets (4x2), 12 tablets (4x3), 20 tablets (4x5), 40 tablets (4x10), or 10 tablets (1 x 10) and packed with a patient information leaflet.

Polypropylene Tubes:
White opaque plain polypropylene tube and white opaque tamper evident polyethylene caps with inbuilt desiccant. Each tube contains 10 or 12 tablets.
Pack size: 36 (3 x 12) tablets per carton, 10 (1 x 10) tablets per carton and 20 (2 x 10) tablets per carton. Each carton has a patient leaflet for each polypropylene tube.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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Middlesex,

United Kingdom

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