SUMMARY PRODUCT CHARACTERISTICS (SPC):

1. NAME OF THE MEDICINAL PRODUCT

Trade Name: PERFAMOL
Generic Name: Effervescent Paracetamol Tablets BP 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Effervescent Tablet contains:
Paracetamol BP: 500 mg
For full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Effervescent Tablets for Oral Use
A white coloured flat beveled edge round effervescent tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of mild to moderate pain and/or fever.

4.2 Method of administration

NOT TO BE SWALLOWED DIRECTLY
Posology and method of administration

Children below 12 years of age:
Not recommended

Adolescents of 12 to 15 years and weighing 41 to 50 kg : One 500mg tablet, every 4 - 6 hours.
(Maximum of 4 doses in 24 hours)

Adults and children 16 years and older: One or two 500mg tablets, every 4 - 6 hours (Maximum of 4 doses in 24 hours)

Maximum single dose is 1g (2 effervescent tablets) Or As directed by physician.
Paracetamol 500 mg Effervescent Tablets are for oral administration. The tablets should be placed in a full tumbler of water and allowed to dissolve completely before swallowing.
Frequency of administration: The specific dose interval depends on the symptoms and the maximum daily dose. Systematic administration enables to avoid pain or fever oscillation.
Depending on the reoccurrence of symptoms (fever and/or pain), repeated administration is allowed. It should, however, preferably never fall below 6 hours and in no case fall below 4 hours. In adolescents administration should be regularly spaced, including night time, preferably at 6 hour intervals, otherwise at intervals of a minimum of 4 hours. If the pain persists for more than 5 days

or the fever lasts for more than 3 days, or gets worse or other symptoms appear, you should stop the treatment and consult a doctor.
Renal Insufficiency:
In case of renal insufficiency the dose should be reduced;;

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

Impaired liver function:
In patients with impaired hepatic function 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 2g/day) in the following situations :
• adults weighing less than 50 kg
• mild to moderate hepatic insufficiency, Gilberts'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 adolescents 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 hepatic 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, hemolytic anemia, alcohol abuse dehydration and chronic malnutrition.

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 2 grams 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.

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

Paracetamol Effervescent Tablet is considered high in sodium. Paracetamol Effervescent Tablet should be taken into account for those on a low salt diet.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, 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
• Cholestyramine: reduces absorption of Paracetamol
• Concomitant use of Paracetamol (4 g 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. 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.
• 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 its metabolism in the liver.
Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

4.6 PREGNANCY:
Pregnancy:

Epidemiological data on the oral administration of therapeutic doses of Paracetamol indicate no adverse effects on pregnancy or on the health of the fetus/newborn child. Prospective data on overdose during pregnancy showed no increased risk of malformations. Reproduction studies investigating oral administration did not indicate any signs of malformation or fetotoxicity.
Paracetamol is considered to be safe in normal therapeutic doses for short-term use as a minor analgesic/antipyretic in pregnancy.

Lactation:
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 Effect
The frequency using the following convention: very common (> 1/10); common (>1/100 to < 1/10); uncommon (>1/1000 to <1/100); rare (>1/10000 to < 1/1000); very rare (< 1/10000), including isolated reports; not known: frequency cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequency: Rare (>1/10000 – <1/1000)
System: Blood and lymphatic system disorders
Symptoms: Platelet disorders, stem cell disorders.
System: Immune system disorders
Symptoms: Allergies (excluding angioedema).
System: Psychiatric disorders
Symptoms: Depression NOS, confusion, hallucinations.

System: Nervous system disorders
Symptoms: Tremor NOS, headache NOS.
System: Eye disorders
Symptoms: Abnormal vision.
System: Cardiac disorders
Symptoms: Oedema.
System: Gastrointestinal disorders
Symptoms: Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
System: Hepato-biliary disorders
Symptoms: Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
System: Skin and subcutaneous tissue disorders

Symptoms: Pruritus, rash, sweating, purpura, angioedema, urticaria
System: General disorders and administration site conditions
Symptoms: Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
System: Injury, poisoning and procedural complications
Symptoms: Overdose and poisoning
Frequency: Very Rare (< 10 000)
System: Hepato-biliary disorders
Symptoms: hepatotoxicity
System: General disorders and administration site conditions
Symptoms: hypersensitivity reaction (requiring discontinuation of treatment)
System: Blood and lymphatic system disorders
Symptoms: thrombocytopenia
leukopenia
neutropenia
hemolytic anemia
agranulocytosis

System: Metabolism and nutrition disorders
Symptoms: Hypoglycaemia
System: Renal and urinary disorders
Symptoms: Sterile pyuria (cloudy urine) and renal side effects
System: Skin and subcutaneous disorders
Symptoms: Serious skin reactions have been reported.
Not known: Edema of the larynx, anaphylactic shock, anaemia, bronchospasm*, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.
* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

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 national pharmacovigilance reporting system.

4.9 Overdosage
There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal.
Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors

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

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. 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.

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. The effectiveness of the antidote declines sharply after this time. 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.

High doses of sodium bicarbonate may be expected to induce gastrointestinal symptoms including belching and nausea. In addition, high doses of sodium bicarbonate may cause hypernatraemia; electrolytes should be monitored and patients managed accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: other analgesics and antipyretics, anilides
ATC code: N02BE01
Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of acetylsalicylic acid. The antipyretic effect is probably achieved through action on the hypothalamic heat-regulation centre, whereby heat dissipation is increased. Central action is probably related to the inhibition of prostaglandin synthesis in the hypothalamus.
The latency period for the analgesic effect is approx. ½ hour. The peak effect is achieved within 1-2 hours and lasts for 4-5 hours. The course of the antipyretic effect is somewhat slower. Thus the latency period is approx. ½-1 hour, maximum reduction in fever is recorded after 2-3 hours and the effect lasts for about 8 hours.

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 sulphuric 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 cystein 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.
Physiopathological Variations
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, sub chronic 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 sub toxic 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

1. Anhydrous Citric Acid – BP
2. Sodium Bicarbonate – BP
3. Povidone K-30 – BP
4. Sodium Saccharin – BP
5. Purified Water – BP
6. Anhydrous Sodium Carbonate – BP
7. Simethicone Emulsion 100% – USP
8. Polysorbate 80 – BP
9. Aspartame – BP
10. Dry Strawberry Flavour – IH

6.2 Incompatibilities

Not known

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Store below 30°C in dry place. Protect from light.
Keep medicine out of reach of children.

6.5 Nature and contents of container:

Primary Packing : 4 tablets are packed in Alu-Strip.
Secondary Packing : Such 4 Strips of 4 Tablets to be packed in a carton along with pack insert

6.6 Special Precaution for Disposal and other handling:
None

7.0 Marketing Authorization Holder
Company name: Signature Healthcare Limited
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8. Marketing Authorization Numbers:
H2022/CTD9686/20073

9. Date of First Authorization/Renewal of the Authorization: --
09/8/2023

10: Date of Revision of the Text: ---
09/8/2023