1. Name of product

Emzor Para 1000 Tablet

Paracetamol 1000mg Tablet

2. Qualitative and quantitative composition

Each Tablet contains 1000mg of Paracetamol.

Excipients: Sodium content approximately 438mg/tablet.

For a full list of excipients see section 6.1.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

This presentation is reserved for use in adults and in adolescents aged 16 years and above.

Maximum daily dose:

• The maximum daily dose of Paracetamol must not exceed 4000mg.

• Maximum single dose is 1000mg (1 Tablet).

Paracetamol 1000mg Tablet 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 Paracetamol 1000mg Tablet should not be given more frequently than every 6 hours, and not more than 4 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	500mg every 6 hours
<10 ml/min	500mg every 8 hours

Paracetamol 1000mg Tablet 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 60mg/kg/day (up to maximum 2000mg/day) in the following situations:

• Adults weighing less than 50 kg

• Mild to moderate hepatic insufficiency, Gilbel1's syndrome (familial nonhaemolytic jaundice)

• Dehydration

• Chronic malnutrition

• Chronic alcoholism Intake of paracetamol with food and drink does not affect the efficacy of the medical 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 2000mg 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."

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.

Paracetamol 1000mg Tablet should not be administered in children and adolescents below 16 years of age and under 50 kg body weight.

This medicinal product contains 438mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

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 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The metabolisation 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.

• Cholestyramine reduces absorption of Paracetamol and therefore should not be administered within an hour following Paracetamol administration.

• Concomitant use of Paracetamol (4000mg 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.

Interference with laboratory tests:

Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by 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.

Animal studies do not indicate reproductive toxicity (see section 5.3).

Lactation:

Paracetamol/ metabolites are excreted in human milk, but at therapeutic doses of Paracetamol 1000mg Tablet no effects on the breastfed newborns/infants are anticipated.

Paracetamol 1000mg Tablet can be used during breast-feeding.

Fertility:

There are no or limited amount of date from the influence of Paracetamol 1000mg Tablet on fertility.

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

The frequency using the following convention should be: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
glucose-oxidase-peroxidase.

Frequency	System	Symptoms
Rare (≥1/10000 - <1/1000)	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic, anaemia, pancytopenia
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea,vomiting.
	Hepato-biliary disorders	Abnormal Hepatic function, hepatic failure, hepatic necrosis jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria
	General disorders and administration site	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.

	conditions	
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (<10,000)	Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Hepato-biliary disorders	Hepatotoxicity
	General disorders and administration site conditions	Hypersensitivity reaction (requiring discontinuation of treatment)
	Metabolism and nutrition disorders	Hypoglycaemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

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.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.

• Overdose, 10g or more of Paracetamol in adults or 150mg/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.

Emergency Procedure:

• Immediate transfer to hospital.

• Blood sampling to determine initial paracetamol plasma concentration.

• IV (or oral if possible) administration of the antidote N-acetylcysteine as soon as possible or within 8 hours of the overdose.

• Activated charcoal may be used if the dose of Paracetamol ingested exceeds 12g or 150mg/kg and should be undertaken if within 1 hour of the overdose.

• Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose.

• Symptomatic treatment should be implemented.

• Haemodialysis or haemoperfusion is possible in cases of severe poisoning.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics; anilides

ATC code: N02BEO1

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 metabolised mainly in the liver following two major metabolic pathways: glucoronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed 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 10ml/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 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 (E330)

Sodium Bicarbonate (E500)

Sucralose (E955)

Sucrose monopalmitate (Sucroester 15) (E 473)

Sodium Benzoate (E211)

Grapefruit flavour

Kollidon 30 (Povidone K30) (E1201)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

For Blister Pack:

Store below 25ºC. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Paracetamol 1000mg Tablet are packed in Blisters.

The packaging is opaque and child resistant**.**

Blister pack:

Box containing 1 or 2 or 4 or 5 or 10 or 12 or 20 or 25 nylon/aluminium/PVC/lacquer blisters (2 tablets per blister) and a patient leaflet.

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 authorization holder

Emzor Pharmaceutical Industries Limited.

Sagamu/Benin Expressway, Makun, Sagamu Local Govt, Ogun state.

8. Marketing authorization number(s)

N/A

9. Date of first authorization/renewal of authorization

N/A

10. Date of revision of text

N/A