Name of the medicinal product

Avro Paracetamol Tablet

2. Qualitative and quantitative composition

Each tablet contains Paracetamol 500mg.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets.

White, uncoated tablet marked with "P 500" with score line on one side and "AVRO" on the other side.

4. Clinical particulars

4.1 Therapeutic indications
The Tablets is a mild analgesic and antipyretic, and is recommended for the treatment of most painful and febrile conditions, for example, headache including migraine and tension headaches, toothache, backache, rheumatic and muscle pains, dysmenorrhoea, sore throat, and for relieving the fever, aches and pains of colds and flu. Also recommended for the symptomatic relief of pain due to non-serious arthritis.

4.2 Posology and method of administration

Posology:

Unless otherwise directed by the physician:

Adults and children above 12 years: 2 tablets

Children:
Age 6 to under 12 years: 1 tablet
Age 1 to 5 years: ½ tablet

Dosage may be given up to 4 times daily.

Do not exceed the stated dose.

Direction for use:
- The dosing interval should be at least 4 hours.
- Do not use in combination with other paracetamol-containing products.
- The indicated dose should not be exceeded due to risk of serious damage to the liver (see section 4.4 and 4.9).
- The lower frequency of administration is intended for children in the lower limit of the relevant age group.
- Depending on the onset of symptoms (fever and pain) repeated administration is allowed.
- If pain for more than 5 days or fever for more than 3 days exists or get worse, or if any other symptom occur, treatment should be discontinued and a physician should be consulted.
- The ingestion of paracetamol with food and drink does not affect the efficacy of the medicinal product.
- In case of renal insufficiency (renal failure), 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

- In patients with impaired hepatic or Gilberts syndrome, the dose must be reduced or the dosing interval prolonged.
- The daily effective dose should not exceed 60 mg/kg/day (upto maximum 2 g/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

Method of administration:
For oral use only.

The tablet should be swallowed with a large amount of water or, if desired, left to dissolve in plenty of water, which should be stirred well before drinking.

4.3 Contraindications

- Known hypersensitivity to paracetamol or any of the other ingredients.

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.
Multiple daily doses or in the event of overdosage may cause severe damage to the liver; in such cases, immediate medical advice should be sought even if the patient feels well because of the risk of irreversible liver damage (see section 4.9). In young subjects treated with 60 mg/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 severe renal or severe hepatic impairment (child-Pugh> 9), mild to moderate hepatic impairment (incl. Syndrome Gilbert),acute hepatitis, concomitant administration of drugs that affect the liver function, glucose -6-phosphatedehyrogenase deficiency, haemolytic anaemia, alcohol abuse, chronic dehydration and malnutrition.
The hazards of overdose are greater in those with Non-chirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. Alcohol must not be used during treatment period. The daily dose should not exceed 2 grams in such case.
In cases of high fever, signs of a secondary infection, or persistence of the symptoms for more than three days, medical advice should be sought.
After prolonged use (> 3 months) of analgesics intake every day or more often, headaches may occur or worsen. Headaches caused by overuse of analgesics (mean-tested headache) should not be handled by increasing the dose. In those cases, the use of analgesics should be taken after consulting a doctor.
Caution is advised in asthmatic patient sensitive to acetylsalicylic acid, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Paracetamol is extensively metabolized in the liver and can therefore interact with medicinal products with the same metabolic pathway or induce/inhibit the same metabolic pathway. Chronic use of alcohol or medicinal products which induce liver enzymes like rifampicin, barbiturates, some anti-epileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, pirimidone) and St. John's Wort can increase the

hepatotoxicity of paracetamol as a result of an increased and fast formation of toxic metabolites. Caution is therefore necessary with concomitant use of enzyme-inducing drugs.

Probenecide blocks the binding of paracetamol to glucuronic acid reducing paracetamol clearance by a factor of about 2. If probenecide is taken concurrently the paracetamol dose should be reduced.
Paracetamol can increase the plasma concentration of chloramphenicol.
With chronic concomitant use of paracetamol and zidovudine, neutropenia often occurs and is probably due to the reduced metabolism of zidovudine.

Salicylamide may prolong the elimination t1/2 of paracetamol.

Isoniazid reduces the paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver.

Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

Interference with laboratory tests
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests by glucose-oxydase-peroxydase.

4.6 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.

Breastfeeding:
Paracetamol is excreted in breast milk but not in a clinically significant amount. No negative effects on infants have been reported. Paracetamol may be used by breastfeeding women as long as the recommended dosage is not exceeded. In case of long term use caution should be exercised. Fertility: No detrimental effects on fertility upon normal use of paracetamol are known.

4.7 Effects on ability to drive and use machines
Paracetamol 500mg Tablets has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects
Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

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

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

Body System	Undesirable Effects	Frequency
Paracetamol		
Blood and lymphatic system disorders	Thrombocytopaenia	Very rare
Immune System disorders	Anaphylaxis, Cutaneous hypersensitivity reactions, Angiodema, Stevens Johnson Syndrome and toxic epidermal necrolysis	Very rare
	Very rare cases of serious skin reactions have been reported	
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

4.9 Overdose

Paracetamol
Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity. 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 generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic. 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 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. Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include: If the patient;
• Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
• Regularly consumes ethanol in excess of recommended amounts.
• Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Emergency Procedure:

Immediate transfer to hospital. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides

ATC code: N02BE01

Paracetamol is an effective antipyretic and analgesic agent. However, it has no antiinflammatory effect. The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy without a conspicuous peripheral anti-inflammatory activity.

5.2 Pharmacokinetic properties
Absorption
After oral administration paracetamol is rapidly and almost completely absorbed. Peak plasma concentrations are reached after 30 minutes to 2 hours.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. The volume of distribution of paracetamol is approximately 1 L/kg bodyweight. At therapeutic doses protein binding is negligible.

Metabolism
In adults paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~35%) 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 (~3%) and mercaptopuric acid.
In neonates and children <12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation.

Elimination
Elimination of paracetamol is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, predominantly as the glucuronide (60 to 80%) and the sulphate (20 to 30%) conjugates. Less than 5% is eliminated in unchanged form. The elimination half-life is about 2 hours. In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half-life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations. For elderly patients, the capacity for conjugation is not modified.

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Animal studies 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
Maize Starch
Povidone
Methyl hydroxybenzoate
Talc Powder
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The product is presented in blister strip composed of PVC with a printed aluminium foil.

The product is available in packs of 8 x 12 tablets.

6.6 Special precautions for disposal and other handling
Not applicable.

7. Applicant/Manufacturer
Avro Pharma Limited
Daid House Plot 2, Block J, Limca Way,
Isolo Industrial Estate, Oshodi-Apapa Expressway,
Isolo, Lagos State, Nigeria.
Tel: +234(1)2913955
Email: avro@rumon-org.com