National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

APC Plus, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Acetylsalicylic Acid 250 mg
Paracetamol 250 mg
Caffeine 30 mg
Alum. Hydroxide Coll. q.s.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APC Plus is a white, double-layer, biplane shaped, beveled-edge tablet, which plain on one side and engraved 'BODE' and breakline on the other side, it has bitter taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

APC PLUS is indicated to relieve headache, muscle and joint pain, and fever in many illnesses such as influenza, pharyngitis, etc.

4.2 Posology and method of administration

Adults : 1 – 2 tablets three times daily.
Or as prescribed by the physician.
APC Plus is recommended to be taken after meals.

For oral administration only

4.3 Contraindications

Hypersensitivity to the active ingredients or any of the other constituents. Peptic ulceration and those with a history of peptic ulceration; haemophilia, concurrent anti-coagulant therapy; children under 16 years and when breast feeding because of possible risk of Reyes Syndrome.

4.4 Special warnings and precautions for use

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease). There is a possible association between Acetylsalicylic Acid (aspirin) and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal.

Caution should be exercised in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not take if you have a stomach ulcer.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Do not take anything else containing paracetamol while taking this medicine.

Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

Limit the use of caffeine containing medications, foods, or beverages while taking this product, because too much caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heartbeat.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic Acid (Aspirin):

Other NSAIDS and corticosteroids: Concurrent use of other NSAIDS or corticosteroids may increase the likelihood of GI side effects.

Diuretics: Antagonism of the diuretic effect.

Anticoagulants: Increased risk of bleeding due to antiplatelet effect.

Metoclopramide: Metoclopramide increases the rate of absorption of aspirin. However, concurrent use need not be avoided.

Phenytoin: The effect of phenytoin may be enhanced by aspirin. However, no special precautions are needed. Valproate: The effect of valproate may be enhanced by aspirin.

Methotrexate: Delayed excretion and increased toxicity of methotrexate.

Paracetamol:

Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone: The speed of absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

Caffeine:

No interaction studies have been performed.

4.6 Pregnancy and lactation

There is clinical and epidemiological evidence of safety of aspirin in pregnancy, but it may prolong labour and contribute to maternal and neonatal bleeding, and so should not be used in late pregnancy.

Aspirin appears in breast milk, and regular high doses may affect neonatal clotting. Not recommended while breast- feeding due to possible risk of Reye's Syndrome as well as neonatal

bleeding due to hypoprothrombinaemia.

Paracetamol is excreted in breast milk but not in a significant amount. Available published data do not contraindicate breast feeding.

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.

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported

4.7 Effect on ability to drive and use machines

None stated.

4.8 Undesirable Effects

Side effects are mild and infrequent, but there is a high incidence of gastro-intestinal irritation with slight asymptomatic blood loss. Increased bleeding time. Aspirin may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions, such as skin reactions (including angioedema and face oedema) in susceptible individuals.

Aspirin may induce gastro-intestinal haemorrhage, occasionally major. It may precipitate gout in susceptible individuals. Possible risk of Reye's Syndrome in children under 16 years.

Adverse effects of paracetamol are rare. Very rare cases of serious skin reactions have been reported. There have been reports of blood dyscrasias including thrombocytopenia purpura and agranulocytosis, but these were not necessarily causality related to paracetamol.

High doses of caffeine can cause tremor and palpitations.

4.9 Overdose

This product contains both paracetamol and aspirin, and as such, any overdose events should be assessed using information available on both active substances.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Adults who have consumed more than 5g of paracetamol, may experience liver damage if they have one of the following risk factors:

- long term treatment with either anti-infectives, anti-epileptics or St John's Wort, or any other drugs that induce liver enzymes
- regular consumption of ethanol in excess of recommended amounts
- likely to be glutathione deplete e.g. eating disorder, cystic fibrosis, HIV infection, starvation, cachexia.

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

Common features exist for both active substances when taken in overdose, but these can be tabulated as follows:

Paracetamol	Aspirin	Caffeine
Within the first 24 hours: Pallor Nausea Vomiting Anorexia Abdominal pain After 12-48 hours: Liver damage Abnormalities of glucose metabolism and metabolic acidosis Severe poisoning: Hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. With or without severe liver damage: Acute renal failure with acute tubular necrosis strongly suggested by loin pain haematuria and proteinuria. Cardiac arrhythmias Pancreatitis	Common: Vomiting, Dehydration, Tinnitus Vertigo, Deafness, Sweating Warm extremities with bounding pulses Increased respiratory rate Hyperventilation Acid base disturbance Mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) in adults and children aged over 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis can increase salicylate transfer across the blood brain barrier. Uncommon: Haematemesis Hyperpyrexia Hypoglycaemia Hypokalaemia Thrombocytopenia Increased INR/PTR Intravascular coagulation Renal failure Non-cardiac pulmonary oedema Confusion, disorientation, coma and convulsions are more common in children than adults.	Other symptoms of overdosage, associated with the caffeine component, include: CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions Cardiac: tachycardia, cardiac arrhythmia Gastric: Abdominal or stomach pains Other: diuresis, facial flushing

Management

Paracetamol:

Immediate treatment is essential in the management of overdose due to the paracetamol content of the product.

There may be few or no initial symptoms, and these can 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 concentrations 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.

Management of patients who present with serious hepatic dysfunction, or are under 10 years or over 70, beyond 24h from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

Salicylates:

Treatment with activated charcoal should be considered if salicylate plasma concentration is greater than 250mg/kg.

Plasma salicylate concentrations should be measured although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Elimination of aspirin is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Metabolic acidosis should be corrected with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features.

Patients under 10 years or over 70 years of age may be at an increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine:

Treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by intravenous administration of diazepam.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics; Salicylic acid and derivatives
ATC code: N02B E51

Aspirin:

Mechanisms of action/effect

Salicylates inhibit the activity of the enzyme cyco-oxygenase to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although many of the therapeutic effects may result from inhibition of prostaglandin synthesis (and consequent reduction of prostaglandin activity) in various tissues, other actions may also contribute significantly to the therapeutic effects.

Analgesic

Produces analgesia through a peripheral action by blocking pain impulse generation and via a central action, possibly in the hypothalamus.

Anti-inflammatory (Non-steroidal)

Exact mechanisms have not been determined. Salicylates may act peripherally in inflamed tissue probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other mediators of the inflammatory response.

Antipyretic

May produce antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasolidation resulting in increased cutaneous blood flow, sweating and heat loss.

Paracetamol

Mechanism of action/effect

Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic – paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involved inhibition of prostaglandin synthesis in the hypothalamus.

Caffeine

Mechanisms of action/effect

Central nervous system stimulant – caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

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 enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine

5.2 Pharmacokinetics properties

Aspirin

Absorption and fate

Absorption is generally rapid and complete following oral administration. It is largely hydrolysed in the gastrointestinal tract, liver and blood to salicylate, which is further metabolised primarily in the liver.

Paracetamol

Absorption and fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed-function oxidases in the liver, and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Caffeine

Absorption and fate

Caffeine is completely and rapidly absorbed after oral administration with peak concentrations occurring between 5 and 90 minutes after dose in fasted subjects. There is no evidence of presystemic metabolism. Elimination is almost entirely by hepatic metabolism in adults.

In adults, marked individual variability in the rate of elimination occurs. The mean plasma elimination half-life is 4.9 hours with a range of 1.9 - 12.2 hours. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methylacrylic acid and 5-acethylamine-6-formylamine-3-methyluracil (AFMU).

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aerosil 200-V, Avicel PH-101, Dried Aluminium hydroxide Gel, Gelatin, Magnesium stearate, Methyl hydroxybenzoate, Maize starch, Sodium starch glycolate, Propyl hydroxybenzoate, Talc.

6.2 Incompatibilities

None known.

6.3 Shelflife

36 months.

6.4 Special precaution for storage

Store below 30°C

6.5 Special precautions for disposal

Not applicable.

6.6 Nature and content of container

10 caplets are packed into PVC 250 µm / aluminium foil 20 µm + heat seal coating 6-8 gsm blister. 2 blisters are packed in a folding box of duplex carton 250 gsm.

7. MARKETING AUTHORIZATION HOLDER

Orange Drug Ltd.
66/68 Town Planning Way Ilupeju, Lagos