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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT
Toptabs Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Ingredients:

Aspirin BP	350mg/tablet
Caffeine	30mg/tablet

For excipients see section 6.1

3. PHARMACEUTICAL FORM
Tablet for oral administration.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains and aches and pains.

For the symptomatic treatment of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and symptoms of cold.

4.2 Posology and method of administration
Adults, the elderly and young persons aged 12 years and over:

2 tablets every 4 hours to a maximum of 12 tablets in 24 hours.

Do not exceed 12 tablets in 24 hours.

Do not give to children aged under 12 years, unless specifically indicted (e.g. Kawasaki's disease).

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 12 years and when breast feeding because of possible risk of Reyes Syndrome.

4.4 Special warnings and precautions for use
Caution should be exercised in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration.

Do not take if you have a stomach ulcer.

Do not exceed the stated dose.

If symptoms persist for more than 3 days consult your doctor.

There is a possible association between 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. For this reason aspirin should not be given to children under 12 years unless specifically indicated (e.g. Kawasaki's disease).

4.5 Interaction with other medicinal products and other forms of interaction
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.

Warfarin: Low-dose aspirin (75 to 325 mg daily) increases the risk of bleeding when given with warfarin. High doses of aspirin (4 g daily or more) can also increase prothrombin times in patients taking warfarin. Avoid high-dose aspirin. If low-dose aspirin is indicated, monitor for signs of bleeding. Consider giving gastroprotection (e.g. a proton pump inhibitor) to at-risk patients.

Sulfinpyrazone: The uricosuric effects of aspirin and sulfinpyrazone are mutually antagonistic. Concurrent use for uricosuria should be avoided. Doses of aspirin as low as 700 mg can cause an appreciable fall in uric acid excretion but the effects of a small dose are probably of little practical importance. Sulfinpyrazone can cause gastric bleeding and inhibit platelet aggregation which may be additive with aspirin. (Severity – moderate).

Blood pressure lowering treatments (ACE inhibitors): High-dose aspirin can reduce the antihypertensive efficacy of ACE inhibitors. Low-dose aspirin (100 mg daily or less) appears to have little effect. It is unclear if aspirin attenuates the benefits of ACE inhibitors in heart failure: the likelihood of an interaction possibly depends on disease state and its severity. (Severity – moderate).

Antacids: The serum salicylate concentrations of patients taking aspirin have been reduced to subtherapeutic levels by aluminium and magnesium hydroxide. Care should be taken to monitor serum salicylate levels if any antacid is started or stopped in patients where the control of salicylate levels is critical. Occasional doses of aspirin for analgesia and aspirin given in doses that produce low salicylate levels do not appear to be affected. (Severity – moderate).

Cilostazol: Concurrent use of multiple antiplatelets would be expected to increase the risk of bleeding. Aspirin very slightly increases the exposure to cilostazol with no clinically relevant effect on bleeding times. Be aware of the increased risk of bleeding. Cilostazol is contraindicated with two or more antiplatelets or anticoagulants (UK). (Severity – moderate).

Mifepristone: Theoretically aspirin and NSAIDs might reduce the efficacy of mifepristone. However, evidence from two studies with naproxen and diclofenac suggests no reduction in mifepristone efficacy. No action needed. (Severity – moderate but theoretical).

Probenecid: The uricosuric effects of aspirin and probenecid are mutually antagonistic. Low dose, enteric-coated aspirin appears not to interact. Regular dosing with substantial amounts of salicylates should be avoided, but small very occasional analgesic doses probably do not matter. Serum salicylate levels of 5 to 10 mg/100 mL are necessary before this interaction occurs. (Severity – moderate).

Venlafaxine/SSRIs: The bleeding risk associated with antiplatelet drugs such as aspirin might be further increased by the concurrent use of an SNRI/SSRI. Advise patients to report bleeding. Consider gastroprotection (such as a proton pump inhibitor) in those at high risk of gastrointestinal bleeding (e.g. history of gastrointestinal bleeding, the elderly). (Severity – severe).

Sympathomimetics: Caffeine acts synergistically towards the hypertensive and tachycardic effects of sympathomimetics.

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.

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

4.7 Effects on ability to drive and use machines

None known

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 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.

High doses of caffeine can cause tremor and palpitations.

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.

4.9 Overdose

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 dose less than 100mg/kg are unlikely to cause serious poisoning.

Aspirin

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of four years old. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are more common in children than adults.

Caffeine

Common features include CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions.

Cardiac Symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include abdominal or stomach pains.

Other symptoms of overdosage, associated with the caffeine component, include diuresis and facial flushing.

Management

Aspirin

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration 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 is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intraveneous 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 have 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

ASPIRIN

Mechanisms of action/effect
Salicylates inhibit the activity of the enzyme cyclo-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 (Nonsteriodal)
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 centre to produce peripheral vasodilation resulting in increased cutaneous blood flow, sweating and heat loss.

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 enhancing 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 Pharmacokinetic 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.

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. The major metabolites are 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6 formylamino 3-methyluracil (AMFU).

5.3 Preclinical safety data
None stated.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize Starch
Colloidal Silicon Dioxide
Microcryatalline Cellulose
Isopropyl Alcohol

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30^{o}C.

6.5 Nature and contents of container
Cartons containing ALU/PVC Blister Packs.

Pack Size: 2 x 24, 2 x 50.

6.6 Special precautions for disposal and other handling
Not applicable

7. Applicant/Manufacturer
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