SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Toptabs

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 350 mg Aspirin and 50 mg Caffeine.

Excipient with known effect: Each tablet contains 115 mg of Lactose.

3 PHARMACEUTICAL FORM

Tablet.
White bi-convex tablets with logo on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The product may be recommended as an analgesic and antipyretic for:

a) The symptomatic relief of influenza, feverishness, chills and colds, including feverish colds.
b) The relief of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains, rheumatic pain and muscular aches and pains.

4.2 Posology and method of administration

Posology

Adults and children aged 16 years and over:

1 or 2 tablets with a drink of water and preferably after a little food. The dose can be repeated every 4 to 6 hours, up to a maximum of 8 tablets in any 24 hour period.
If symptoms persist consult your doctor.

Elderly
Use with particular caution in elderly patients who are more prone to adverse events.

Pediatric population (under 16 years)
Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

Product should be discontinued if pain gets worse or lasts more than 10 days (or lasts more than 3 days for fever).

Do not exceed the stated dose.

Method of administration
Oral administration.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- A history of hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, urticaria, nasal polyps) in response to aspirin or non-steroidal anti-inflammatory drugs.
- Patients with severe hepatic or renal failure. Aspirin is known to cause sodium and water retention which may exacerbate hypertension, congestive heart failure and renal impairment.
- Aspirin is contraindicated in patients with active peptic ulceration or a history of peptic ulceration. History of gastrointestinal bleeding or perforation after treatment with aspirin or other NSAIDS.
- It should not be used if suffering from haemophilia, hypothrombinaemia or other clotting disorders, or gout.
- Doses > 100 mg/day during the third trimester of pregnancy.

4.4 Special Warnings and Special Precautions for Use

- Aspirin should be used with caution in patients with hypertension, mild to moderate renal or hepatic impairment, or in patients who are dehydrated.

- Aspirin decreases platelet adhesiveness and increases bleeding time. Haematological and haemorrhagic effects can occur, and may be severe. Patients should report any unusual bleeding symptoms to their physician. Due to its inhibitory effect on platelet aggregation aspirin may cause increased bleeding during and after surgery.
- Aspirin may precipitate acute haemolytic anaemia in patients with G6PDH deficiency.
- Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.
- If you suffer from asthma, allergic disease, kidney or liver problems consult your doctor before taking this product.

Paediatric population:
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 16 years of age, unless specifically indicated (e.g. for Kawasaki's disease).

Warnings for the label:
If you do not get better talk to your doctor.
Contains aspirin.
Do not give to children under 16 years of age unless your doctor tells you to.

Warnings for the leaflet:
Aspirin can cause Reye’s syndrome when it is given to children. This is a very rare disease but it can be fatal. Do not give aspirin to children under 16 of age unless your doctor tells you to.

Important information regarding excipients in this medicine:

Lactose: Toptabs contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactase malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Other non-steroidal anti-inflammatory drugs (NSAIDs): Do not use in combination with other non-steroidal anti-inflammatory drugs (NSAIDs) as these may increase the risk of adverse effects.

- Ibuprofen: Ibuprofen may inhibit the anti-platelet effect of low dose aspirin. Patients on low dose aspirin should be instructed to consult their doctor or pharmacist before taking ibuprofen.
- Alcohol: Co-administration of alcohol and aspirin increases the risk of gastrointestinal haemorrhage.
- Angiotensin-converting enzyme inhibitors (ACE inhibitors): Aspirin can diminish the effects of ACE inhibitors.
- Antacids: Antacids (carbonates and alkali hydroxides) may increase the excretion of aspirin by alkalinisation of the urine.
- Anticoagulants (oral): Aspirin may enhance the effects of oral anticoagulants such as heparin and coumarins.
- Anticonvulsants: Aspirin may enhance the activity of phenytoin and valproate.
- Beta-blockers: Aspirin can reduce antihypertensive effect of beta-blockers.
- Carbonic anhydrase inhibitors: There is an increased risk of salicylate toxicity when high dose aspirin is co-administered with carbonic anhydrase inhibitors (such as acetazolamide).
- Corticosteroids: The risk of gastrointestinal ulceration and bleeding may be increased when aspirin and corticosteroids are co-administered. Plasma salicylate concentrations may be reduced by concurrent use of corticosteroids, and salicylate toxicity may occur following withdrawal of the corticosteroids.
- Diuretics: There is a risk of a reduced diuretic effect especially in patients with existing renal or cardiovascular disease.
- Hypogylcaemic agents (oral): Aspirin may enhance the effects of oral hypoglycaemic agents of the sulphonylurea type.Methotrexate: The toxicity of methotrexate may be enhanced by concomitant use of aspirin.
- Selective Serotonin Re-Uptake Inhibitors (SSRIs): Concurrent use of aspirin and SSRIs can increase the risk of gastrointestinal bleeding.
- Uricosuric agents: Aspirin diminishes the action of uricosurics such as probenecid and sulfinpyrazone.
- Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of aspirin should be avoided during pregnancy, particularly during the third trimester. If aspirin is administered during pregnancy, the dose should be the lowest possible and the duration of treatment as short as possible.

Aspirin increases the risk of peripartum hemorrhage. Aspirin may also delay the onset and increase the duration of labor. With high doses, there may be premature closure of the ductus arteriosus.

Aspirin – caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion and low birth weight associated with total caffeine consumption above 200 mg per day.

Low doses (up to and including 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of above 100 mg/day and up to 500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:
From the 20th week of pregnancy onward, Toptabs use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Toptabs should not be given unless clearly necessary. If Toptabs is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Toptabs for several days from gestational week 20 onward. Toptabs should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses higher than 100 mg/day is contraindicated during the third trimester of pregnancy (see sections 4.3). Doses up to and including 100 mg/day may only be used under strict obstetric monitoring.

Breast-feeding

Aspirin is secreted into breast milk in low concentration and should, therefore, be avoided during lactation, as there is a risk of Reye's syndrome and the fact that high doses could potentially impair platelet function.

Caffeine in breast milk may potentially have a stimulating effect on breast fed infants but significantly toxicity has not been observed.

4.7 Effects on ability to drive and use machines

No effect on driving.

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by MedDRA System Organ Class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data).

Aspirin

Tabulated list of adverse reactions

Body System	**Undesirable effect**
Gastrointestinal disorders	Nausea, vomiting, dyspepsia. Gastrointestinal ulceration, gastrointestinal haemorrhage and gastritis.
Renal and urinary disorders	Renal dysfunction, increased blood uric acid levels.
Hepatobiliary disorders	Elevation in aminotransferase levels.
Blood and lymphatic system disorders	Prolonged bleeding time. Thrombocytopenia. Ecchymosis
Metabolism and Nutrition disorders	Sodium and fluid retention.
Immune system disorders	Hypersensitivity reactions e.g. rhinitis,

	angioedema, urticaria, bronchospasm, skin reactions and anaphylaxis.
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs
Ear and labyrinth disorders	Tinnitus, temporary hearing loss.

Caffeine

Tabulated list of adverse reactions

Body System	**Undesirable effect**
Central nervous system	Nervousness and dizziness.
When the recommended aspirin-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.	

Reporting of suspected adverse reactions

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Aspirin

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 of salicylate poisoning 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 4 years. In children aged 4 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 of salicylate poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

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

Management

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 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 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Caffeine

Symptoms

Common features include GI disturbance, epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, "rambling" flow of thought and speech, psychomotor agitation, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions) or periods of inexhaustibility.

Management
No specific antidote is available, but supportive measures such as beta adrenoceptor antagonists to reverse the cardiotoxic effects may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aspirin:
Aspirin has analgesic, anti-pyretic and anti-inflammatory actions which are thought to be related to the effect on the biosynthesis of prostaglandins.
It also inhibits platelet aggregation.

Caffeine:
It acts on the central nervous system and produces a condition of wakefulness and increased mental activity.
Caffeine is a mild stimulant.

The actions of both Aspirin and Caffeine are well documented in various literatures including the Martindale.

5.2 Pharmacokinetic properties

Aspirin:

Aspirin is rapidly absorbed from the upper gastrointestinal tract after oral administration and is rapidly distributed throughout the whole body. It is hydrolysed to its active primary metabolite salicylic acid and completely excreted in the urine, principally as glucuronic acid and glycine conjugates of salicylic acid, but also as salicylic acid itself.
Salicylates are extensively bound to plasma proteins. Maximum plasma concentrations are reached after 10-40 minutes (acetylsalicylic acid) and 0.3 - 2 hours (total salicylate) depending on dosage form. The elimination half life of acetylsalicylic acid is dose-dependent, typically two hours after a single dose of 0.5 g aspirin, 4 hours after 1 gram and 20 hours after 5 grams. Following administration of acetylsalicylic acid, salicylic acid can be detected in breast milk, cerebral spinal fluid and synovial fluid. The substance crosses the placenta.

Caffeine:
It is absorbed readily after oral administration but absorption from the gastro-intestinal tract may be erratic. There is little evidence of accumulation in any particular tissue. Caffeine passes readily into the central nervous system and into saliva. Concentrations have also been detected in breast milk. It is metabolised almost completely and is excreted in the urine as 1-methyluric acid, 1- methylxanthine and other metabolites with only about 1% unchanged.

The actions of both Aspirin and Caffeine are well documented in various literatures including the Martindale and publications by Goodman & Gillman.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to a prescriber which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch

6.2 Incompatibilities

None stated

6.3 Shelf life

5 years for blister packs and glass bottle containers.
3 years for paper strips.

6.4 Special precautions for storage

Toptabs should be stored in a dry place below 25 °C.

6.5 Nature and contents of container

Blister pack specification:
250 micron UPVC coated with 40 gsm PVDC
20 micron Aluminium Foil coated with H66 Universal Lacquer
Paper strip specification:
20 gsm paper coated with 40 gsm PVDC

Pack Sizes:
Blister pack: 24, 30 and 48
Paper strip: 50
Glass bottles: 100

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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