# SUMMARY PRODUCT CHARACTERISTICS (SPC)

## 1. NAME OF THE MEDICINAL PRODUCT

Cafenol Tablets

**Strength:**

Aspirin 375mg and Caffeine Anhydrous 25mg per tablet

**Pharmaceutical Form**

Tablet

## 2. QUALITATIVE AND QUANTITAVE COMPOSITION

**Qualitative Declaration**

Aspirin BP, Caffeine Anhydrous BP

**Quantitative Declaration**

Each tablet contains: Aspirin 375mg

Caffeine Anhydrous 25mg

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablet

A white, circular tablet with a break line on one side and '***Cafenol***' embossment on the other side. Free from foreign matter

## 4.0 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications.

Cafenol Tablets is used for the relief of headaches, toothaches, rheumatic pains, menstrual pains and other feverish conditions.

### 4.2 Posology and Method of Administration

**Posology**

*Adults:*

1 - 2 tablets every 3 to 4 hours up to a maximum of 8 tablets daily.

Do not exceed 8 tablets in 24 hours.

Not recommended for children under 12 years.

**Method of Administration**

For oral administration

Cafenol Tablets should be taken as a whole.

### 4.3 Contraindications

This combination is contraindicated in the following conditions:

- Hypersensitivity to Salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer from bronhospams, rhinitis and urticaria) and Caffeine or to any other ingredients used.
- Peptic ulceration and those with a history of peptic ulceration;
- History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- History of Hemophilia, Hypothrombinemia or other clotting disorders
- Renal failure (GFR < 15mL/min/1.73m$^2$).

- Hepatic failure.
- Third trimester of pregnancy
- Children under 12 years and when breast feeding because of possible risk of Reye's Syndrome.

**4.4 Special Warnings and Precautions for Use**

**Special Warnings**

- Do not exceed the stated doses.
- Cafenol Tablets contains Aspirin & Caffeine; do not use with any other medicine-containing products. Then because it may lead to an overdose.
- Do not take if you have a stomach ulcer.
- Do not take more medicine than the label tells you to. Aspirin & Caffeine overdose may cause liver failure which may require liver transplant or lead to death.
- Underlying liver disease increases the risk of Aspirin & Caffeine -related liver damage. The overall benefit-risk should be considered in patients diagnosed with hepatic or renal impairment before use.
- There is a possible association between Aspirin and Reye's syndrome when given to children, especially during or immediately after a viral illness. 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, particularly during or immediately after Chickenpox, Influenza, or other viral infections, unless prescribed by a physician or specifically indicated (e.g. Kawasaki's disease).
- In patients with Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency, Aspirin may induce Haemolysis or Haemolytic Anaemia. Factors that may increase the risk of Haemolysis are high dosage, fever, or acute infections.
- 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.
- Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. These effects generally have more serious consequences in the elderly (see Section 4.5 Interactions).
- Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol or have Sepsis.
- In patients with glutathione depleted states, the use of Aspirin & Caffeine may increase the risk of Metabolic Acidosis.

**Precautions**

- Serious hypersensitivity reactions or anaphylaxis can occur, bronchospasm may be precipitated in patients suffering from or with a previous history of asthma, allergic disease or nasal polyps. Aspirin should be used with caution in patients with uncontrolled hypertension (in whom target blood pressure has not been achieved), impaired renal or hepatic function, or in patients who are dehydrated or suffering from diabetes mellitus. The overall benefit-risk should be considered in patients diagnosed with hepatic or renal impairment before use. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
- Pregnant women and lactating mothers should consult their physician or pharmacist before taking Cafenol Tablets due to the Caffeine content.

- Cafenol Tablets should be used with caution in elderly patients who are more prone to adverse events.
- The concomitant use of Aspirin with other systemic NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive undesirable effects (see Section 4.5 Interactions).
- Caution is advised if Aspirin & Caffeine is administered concomitantly with Flucloxacillin due to increased risk of High Anion Gap Metabolic Acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of Glutathione Deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of Aspirin & Caffeine. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.
- Aspirin can reduce uric acid excretions and therefore should be used with care in patients with gout or a history of gout.
- Caution to be taken when giving patients with impaired kidney or liver function when taking Cafenol Tablets.
- Care is advised in the administration of Aspirin & Caffeine to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
- Excess intake of Caffeine (coffee, tea and some canned drinks) should be avoided while taking this product.
- If symptoms persist consult your doctor.
- Keep out of reach of children.

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

Aspirin and Caffeine combination medicines should not be used together with other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including Aspirin and Cyclo-Oxygenase-2 specific inhibitors as these may increase the risk of adverse effects.

Aspirin and Caffeine combination medicines should be used with caution when taken in combination with the following drugs as interactions have been reported:

*Aspirin*

- Other NSAIDS and Corticosteroids: Do not use in combination with other NSAIDs as these may increase the risk of adverse effects.
- Thrombolytics: There is an increased risk of bleeding. Particularly, treatment with Aspirin should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended. (see Section 4.4 Special Warnings and Precautions for USE).
- Uricosurics (e.g. Probenecid, Sulfinpyrazone): Aspirin may reduce the activity of Uricosurics (e.g. Probenecid, Sulfinpyrazone) due to inhibition of tubular resorption, leading to high plasma levels of Aspirin.
- Loop diuretics (e.g. Furosemide), diuretics and antihypertensive agents: Aspirin may reduce the activity of loop diuretics (e.g., Furosemide) due to competition and inhibition of urinary prostaglandins. NSAIDs can cause acute kidney failure, especially in dehydrated patients. If a diuretic is administered simultaneously with aspirin, it is necessary to ensure adequate hydration of the patient and to monitor the kidney function and blood pressure, particularly when starting diuretic treatment.
- Like other NSAIDs, concomitant use of Aspirin with diuretics or antihypertensive agents (e.g., beta-blockers, Angiotensin Converting Enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity.

Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

- Anticoagulants: Aspirin may enhance the effects of oral anticoagulants, such as Heparin and Coumarins, and of platelet aggregation inhibitors, such as Ticlopidine, Clopidogrel, and Cilostazol, as there is an increased risk of bleeding. Clinical and laboratory monitoring of the bleeding time and prothrombin time should be performed.
- Metoclopramide: Metoclopramide increases the rate of absorption of Aspirin. However, concurrent use need not be avoided.
- Phenytoin: Aspirin increases phenytoin serum levels; serum phenytoin should be well monitored.
- Valproate: Aspirin inhibits valproate metabolism and hence could increase its toxicity; valproate levels should be well monitored.
- Methotrexate ≤ 15 mg/week: The toxicity of Methotrexate may be enhanced by concomitant use of Aspirin. In case of concomitant use with Aspirin, renal function should be monitored.
- Sulphonylureas: Aspirin increases the hypoglycaemic effect of sulphonylureas, thus some downward readjustment of the dosage of the antidiabetic may be appropriate if large doses of Salicylates are used. Increased blood glucose controls are recommended.
- Alcohol: Co-administration of alcohol and aspirin increases the risk of gastrointestinal haemorrhage.
- Antacids: Antacids may increase the excretion of aspirin by alkalinization of the urine.
- Selective Serotonin Re-Uptake Inhibitors (SSRIs): Concurrent use of Aspirin and SSRIs can increase the risk of gastrointestinal bleeding.

*Caffeine*

- Ephedrine: Stimulant drugs speed up the nervous system. Caffeine and ephedrine are both stimulant drugs. Taking Caffeine along with Ephedrine might cause too much stimulation and sometimes serious side effects and heart problems. Do not take Caffeine-Containing products and Ephedrine at the same time.
- Adenosine (Adenocard) and Dipyridamole (Persantine): Caffeine might block the effects of adenosine (Adenocard) and dipyridamole (Persantine). Adenosine (Adenocard) and Dipyridamole (Persantine) are often used by doctors to do a test on the heart. This test is called a cardiac stress test. Stop consuming caffeine-containing products at least 24 hours before a cardiac stress test.
- Antibiotics (Quinolone antibiotics): The body breaks down caffeine to get rid of it. Some antibiotics might decrease how quickly the body breaks down caffeine. Taking these antibiotics along with caffeine can increase the risk of side effects including jitteriness, headache, increased heart rate, and other side effects.
- Some antibiotics that decrease how quickly the body breaks down caffeine include ciprofloxacin (Cipro), enoxacin (Penetrex), norfloxacin (Chibroxin, Noroxin), sparfloxacin (Zagam), trovafloxacin (Trovan), and grepafloxacin (Raxar).
- Cimetidine (Tagamet): The body breaks down caffeine to get rid of it. Cimetidine (Tagamet) can decrease how quickly your body breaks down caffeine. Taking Cimetidine (Tagamet) along with Caffeine might increase the chance of Caffeine side effects including jitteriness, headache, fast heartbeat, and others.
- Estrogens: The body breaks down Caffeine to get rid of it. Estrogens can decrease how quickly the body breaks down Caffeine. Taking Caffeine along with Estrogens might cause jitteriness, headache, fast heartbeat,

and other side effects. Some Estrogen pills include conjugated equine estrogens (Premarin), Ethinyl Estradiol, Estradiol, and others.

- Lithium: The body naturally gets rid of Lithium. Caffeine can increase how quickly your body gets rid of lithium. If you take products that contain Caffeine and you take Lithium, stop taking Caffeine products slowly. Stopping Caffeine too quickly can increase the side effects of Lithium.
- Medications for Depression (MAOIs): Caffeine can stimulate the body. Some medications used for depression can also stimulate the body. Taking caffeine along with some medications for Depression might cause serious side effects including fast heartbeat, high blood pressure, nervousness, and others. Some of these medications used for Depression include Phenelzine (Nardil), Tranylcypromine (Parnate), and others.
- Anticoagulant / Antiplatelet drugs: Caffeine might slow blood clotting. Taking Caffeine along with medications that also slow clotting might increase the chances of bruising and bleeding. Some medications that slow blood clotting include Aspirin, Clopidogrel (Plavix), Diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), Naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), Enoxaparin (Lovenox), Heparin, Warfarin (Coumadin), and others.
- Alcohol: The body breaks down caffeine to get rid of it. Alcohol can decrease how quickly the body breaks down caffeine. Taking caffeine along with alcohol might cause too much caffeine in the bloodstream and caffeine side effects including jitteriness, headache, and fast heartbeat.
- Birth control pills (Contraceptive drugs): The body breaks down caffeine to get rid of it. Birth control pills can decrease how quickly the body breaks down caffeine. Taking caffeine along with birth control pills can cause jitteriness, headache, fast heartbeat, and other side effects. Some birth control pills include ethinyl estradiol and levonorgestrel (Triphasil), ethinyl estradiol and norethindrone.
- Antidiabetes drugs: Caffeine might increase blood sugar. Diabetes medications are used to lower blood sugar. Taking some medications for diabetes along with caffeine might decrease the effectiveness of diabetes medications. Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others.

## 4.6 Fertility, Pregnancy and Lactation

**Fertility**

*Aspirin*

There is some evidence that medicinal products that inhibit Cyclo-Oxygenase/Prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation.

This is reversible on withdrawal of treatment. However, no accurate data are available on when the reversibility of fertility effects occur after the treatment is suspended.

Caution should be exercised when used by women who are planning on becoming pregnant.

**Pregnancy**

Not recommended for use during pregnancy. This medicine is contraindicated during the third trimester of pregnancy (see Section 4.3 Contraindications).

*Aspirin*

Aspirin should be avoided in the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus in the view of the treating physician.

Aspirin is contraindicated during the third trimester of pregnancy as there is a risk of premature closure of the Foetal Ductus Arteriosus with possible persistent Pulmonary Hypertension (see Section 4.3 Contraindications) and a risk of foetal renal impairment with subsequent oligohydramnios.

The onset of labour may be delayed, and its duration increased with an increased risk of bleeding tendency in both the mother and child. If the expected benefit to the mother is greater than the possible risk to the foetus, the lowest effective dose and the shortest duration of treatment should be considered.

*Caffeine*

Caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

**Lactation**

*Aspirin*

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*

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**

Cafenol Tablets does not affect the ability to drive and use machines.

**4.8 Adverse Effects**

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse reactions from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labeled dose and considered attributable are tabulated below by MedDRA System Organ Class. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is not known but likely to be rare or very rare (<1/1000).

Adverse events are more likely to occur with increasing dose and duration of use.

| MedDRA SOC | Adverse Reaction | Frequency |
|---|---|---|
| **Aspirin** | | |
| Blood and lymphatic system disorders | Prolonged bleeding time, thrombocytopenia, ecchymosis. | Not known |

| | | |
|---|---|---|
| Immune system disorders | Hypersensitivity reactions (e.g. anaphylaxis, angioedema, bronchospasm, urticaria, skin reactions and rhinitis). | Not known |
| Respiratory, thoracic and mediastinal disorders | Aspirin-exacerbated respiratory disease | Very rare |
| Metabolism and Nutrition disorders | Sodium and fluid retention. | Not known |
| Ear and labyrinth disorders | Temporary hearing loss, tinnitus. | Not known |
| Gastrointestinal disorders | Gastrointestinal haemorrhage,<br>gastrointestinal ulceration,<br>vomiting,<br>gastritis,<br>nausea,<br>and dyspepsia. | Not known |
| Hepatobiliary disorders | Reye's syndrome *(see Warnings and Precautions).*<br>Elevation in aminotransferase levels. | Not known |
| Renal and urinary disorders | Renal dysfunction, increased blood uric acid levels. | Not known |
| **Paracetamol** | | |
| Blood and lymphatic system disorders | Thrombocytopenia. | Very rare |
| Immune system disorders | Anaphylaxis<br>Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, Stevens– Johnson syndrome and Toxic Epidermal Necrolysis. | Very rare |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm in patients sensitive to aspirin and other NSAIDs. | Very rare |
| Hepatobiliary disorders | Hepatic dysfunction. | Very rare |
| **Caffeine** | | |
| Central Nervous System | Dizziness,<br>headache. | Not known |
| Cardiac disorders | Palpitation. | Not known |
| Psychiatric disorders | Insomnia, restlessness, anxiety and irritability, nervousness. | Not known |
| Gastrointestinal disorders | Gastrointestinal disturbances. | Not known |
| *When the recommended aspirin-paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects.* | | |

**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.

## 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 is 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, agitation, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions. Cardiac Symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include vomiting, abdominal or stomach pains. Other symptoms of overdosage, associated with the caffeine component, include diuresis and facial flushing. For clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious -related liver toxicity.

**Management**

*Aspirin*

Give activated charcoal if an adult presents within one hour of ingestion of more than 120 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

**Pharmacotherapeutic group:** Acetylsalicylic Acid, combinations excl. psycholeptics

**ATC code:** N02BA51

**Mechanism of Action**

*Aspirin*

- Salicylate inhibits the activity of the enzyme cyclo-oxygenase to decrease the formation of precursors of prostaglandins and thromboxane 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.

**Caffeine**

- 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 cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a 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.

**Pharmacodynamic Effects**

*Aspirin*

- 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 centre to produce peripheral vasolidation resulting in increased cutaneous blood flow, sweating and heat loss.

*Caffeine*

- Central Nervous System Stimulant:

Caffeine stimulates the central nervous system (CNS), heightening alertness and sometimes causing restlessness and agitation. It relaxes smooth muscle, stimulates the contraction of cardiac muscle and enhances athletic performance.

- Analgesia Adjunct:

Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain.

It is believed that Caffeine helps to relieve headache by providing a 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 Pharmacokinetic Properties

**Aspirin**

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

**Caffeine**

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 pre-systemic 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 metabolized 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

*Aspirin*

- Acute toxicity

Salicylate toxicity is a problem that may develop with both acute and chronic salicylate exposure. Multiple organ systems may be affected by salicylate toxicity, including the central nervous system, the pulmonary system, and the

gastrointestinal system. Severe bleeding may occur. In the majority of cases, patients suffering from salicylate toxicity are volume-depleted at the time of presentation for medical attention. Fluid resuscitation should occur immediately and volume status should be monitored closely. Disruptions in acid-base balance are frequent in ASA toxicity.
The acute toxicity of acetylsalicylic in animals has been widely studied. The signs of poisoning in rats from lethal doses are mild to severe gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and some toxic effects on other organs and tissues. Mortality has been observed following convulsions or cardiovascular shock. An important differentiating property between various animal species is the ability to vomit toxic doses. Humans, cats and dogs have this ability, but rodents or rabbits do not.

- Chronic toxicity and carcinogenesis

Chronic ASA toxicity is frequently accompanied by atypical clinical presentations that may be similar to diabetic ketoacidosis, delirium, cerebrovascular accident (CVA), myocardial infarction (MI) or cardiac failure. Plasma salicylate concentrations should be measured if salicylate intoxication is suspected, even if there no documentation available to suggest ASA was ingested. In older age, nephrotoxicity from salicylates increases, and the risk of upper gastrointestinal hemorrhage is increased, with higher rates of mortality. It is also important to note that ASA toxicity may occur even with close to normal serum concentrations. Prevention of chronic ASA includes the administration of smallest possible doses, avoidance of concurrent use of salicylate drugs, and therapeutic drug monitoring. Renal function should be regularly monitored and screening for gastrointestinal bleeding should be done at regular intervals.
Chronic toxicity studies were performed in rodents. ASA was administered at doses measured to be 2 to 20 times the maximum tolerated clinical dose to mice for up to one year. Negative dose-related effects were seen. These include decreased mean survival time, decreased number of births and progeny reaching an appropriate age for weaning. No evidence of carcinogenesis was found in 1-year studies. At daily doses of 0.24 g/kg/day given for 100 days to albino rats, ASA led to signs to excessive thirst, aciduria, diuresis, drowsiness, hyperreflexia, piloerection, changes in respiration, tachycardia, followed by soft stools, epistaxis, sialorrhea, dacryorrhea and mortality during hypothermic coma in the second study month.

- Use in pregnancy and lactation

While teratogenic effects were observed in animals nearly lethal doses, no evidence suggests that this drug is teratogenic in humans. It is advisable, however, to avoid ASA use the first and second trimester of pregnancy, unless it is clearly required. If acetylsalicylic acid containing drugs are ingested by a patient attempting to conceive, or during the first and second trimester of pregnancy, the lowest possible dose at the shortest possible duration should be taken. This drug is contraindicated in the 3rd trimester of pregnancy.

*Caffeine*

The oral LD50 of caffeine in rats is 192 mg/kg. An acute fatal overdose of caffeine in humans is about 10–14 grams (equivalent to 150–200 mg/kg of body weight).

- Caffeine overdose

In the case of caffeine overdose, seizures may occur, as caffeine is a central nervous system stimulant. It should be used with extreme caution in those with epilepsy or other seizure disorders. Symptoms of overdose may include nausea, vomiting, diarrhea, and gastrointestinal upset. Intoxication with caffeine is included in the World Health Organization's International Classification of Diseases (ICD-10). Agitation, anxiety, restlessness, insomnia, tachycardia, tremors, tachycardia, psychomotor agitation, and, in some cases, death can occur, depending on the amount of caffeine consumed. Overdose is more likely to occur in individuals who do not consume caffeine regularly but consume energy drinks.

- Overdose management

For a mild caffeine overdose, offer symptomatic treatment. In the case of a severe overdose, intubation for airway protection from changes in mental status or vomiting may be needed. Activated charcoal and hemodialysis can prevent further complications of an overdose and prevent absorption and metabolism. Benzodiazepine drugs can be administered to prevent or treat seizures. IV fluids and vasopressors may be necessary to combat hypotension associated with caffeine overdose. In addition, magnesium and beta blocking drugs can be used to treat arrhythmias that may occur, with defibrillation and resuscitation if the arrhythmias are lethal. Follow local ACLS protocols.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Maize Starch

### 6.2 Incompatibilities

None

### 6.3 Shelf life

36 Months

### 6.4 Special precautions for storage

Store in a cool dry place below $30^0$C. Protect from light.

### 6.5 Nature and contents of container

Cafenol Tablets are packed in PVC Aluminium blister pack of 8x20 Tablets and contained in cardboard dispenser carton with paper literature insert.

Pack sizes: 160’s

### 6.6 Special precautions for disposal and other handling

Do not throw away any medicines you no longer use.

Ask your pharmacist or medical facility how to properly dispose of any medicine you no longer use. These measures will help protect the environment.

## 7. MARKETING AUTHPROZATION HOLDER AND MANUFACTURING SITE ADDRESSES

**Marketing Authorization Holder**

Name: **ARTEMIS LIFE SCIENCES NIGERIA LIMITED**

Address: **2EB, Aswan Market Osolo Way, Lagos**

Country: **Nigeria**

**Manufacturing Site(s)**

Name: **BETA HEALTHCARE INTERNATIONAL LTD**

Address: **Plot No. Nairobi/Block59/135, Mogadishu Road, Industrial Area, Nairobi**

**P.O. BOX 42569-00100 Nairobi, Kenya**

Country: **KENYA**

Telephone: **+254-20-2652042/89**

E-Mail: info@ke.aspenpharma.com

## 8. MARKETING AUTHORIZATION NUMBER

NAFDAC REG. No. 04 - 0023

## 9. DATE OF FIRST REGISTRATION

Date of First Registration: **31-July-2018**

Date of Renewal of Registration: **27-July-2024**

## 10. DATE OF REVISION OF THE TEXT

September 2024

## 11. DOSIMETRY (IF APPLICABLE)

Not Applicable

## 12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable