**SUMMARY PRODUCT CHARACTERISTICS (SPC)**

## 1. NAME OF THE MEDICINAL PRODUCT

Hedex Tablets

## 2. QUALITATIVE AND QUANTITAVE COMPOSITION

Each tablet contains:

Paracetamol ……..200mg

Aspirin ……400mg

Caffeine Anhydrous ……..50mg

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablet

A white caplet free from any foreign particles, chips or cracks engraved HEDEX on both sides.

## .0 CLINICAL PARTICULARS

### .1 Therapeutic Indications

HEDEX Tablets is a mild analgesic and antipyretic formulated to give extra relief from pain. HEDEX Tablets is recommended for the:

- Treatment of most painful and febrile conditions like headaches, including migraine, backache, toothache, rheumatic pain and dysmenorrhea.
- Relief of symptoms of colds, flu and sore throat.

### .2 Posology and Method of Administration Posology

As directed by the physician OR

*Adults (including elderly), and children aged 16 years and over:*

1 – 2 tablets every 3 hours up to 4 times daily.

The dose should not be repeated more frequently than every 4 hours. Do not exceed 8 tablets in 24 hours.
Not recommended for children under 16 years.

**Elderly:**

Should be used with caution in elderly patients who are more prone to adverse events (see Warnings and Precautions)

**Renal Impairment:**

Contraindicated in patients with renal failure (e.g., Glomerular Filtration Rate (GFR) <15 mL/min/1.73m2). Aspirin is known to cause sodium and water retention which may exacerbate hypertension, congestive heart failure and renal impairment (see Contraindications, Warnings and Precautions).

**Hepatic Impairment:**

Contraindicated in patients with hepatic failure (see Contraindications, Warnings and Precautions).

**Method of Administration**

For oral administration

HEDEX Tablets should be taken as a whole.

## .3 Contraindications

This combination is contraindicated in the following conditions:

- Hypersensitivity to Paracetamol, Salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer from bronchospams, rhinitis and urticaria) and Caffeine or 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 16 years and when breast feeding because of possible risk of Reye's Syndrome.
-

## .4 Special warnings and precautions for use

- Do not exceed the stated doses.
- Do not use for pain for more than 5 days or for fever for more than 3 days.
- HEDEX Tablets contains Paracetamol; do not use with any other Paracetamol-containing products. The concomitant use with other products containing Paracetamol 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. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.
- Underlying liver disease increases the risk of Paracetamol-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 Hemolysis or Hemolytic Anemia. 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 paracetamol 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 HEDEX Tablets due to the Caffeine content.
- HEDEX 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 Paracetamol 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 Paracetamol. 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 HEDEX Tablets.
- Care is advised in the administration of Paracetamol 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.

## .5 Interaction with other medicinal products and other forms of interaction

Aspirin, Paracetamol 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, Paracetamol and Caffeine combination medicines should be used with caution when taken in combination with the following drugs as interactions have been reported:
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.
- Flucloxacillin: Caution should be taken when Paracetamol is used concomitantly with Flucloxacillin as concurrent intake has been associated with High Anion Gap Metabolic Acidosis, especially in patients with risks factors (see Section 4.4 Special Warnings and Precautions for Use).

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 (Pranati), 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**

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).

Paracetamol

A large amount of data on pregnant women indicates 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.

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**

Paracetamol

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

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 hypoprothrombinemia.

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

HEDEX 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, gastrointestinal ulceration, vomiting, gastritis, nausea, 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 |
| Metabolism and nutrition disorders | High anion gap metabolic acidosis<br>Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients. | Not known |
| **Caffeine** | | |
| Central Nervous System | Dizziness, 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**
Healthcare professionals are requested to report any suspected adverse reactions to Beta Healthcare International via drugsafety@ke.aspenpharma.com or the National Regulatory Authority reporting systems via national Pharmacovigilance Electronic Reporting Systems' Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org"

## 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 |
|---|---|---|
| Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.<br>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:<br>•long term treatment with either anti-infectives, anti-epileptics or St John's Wort, or any other drugs that induce liver enzymes<br>•regular consumption of ethanol in excess of recommended amounts<br>•likely to be glutathione deplete e.g. eating disorder, cystic fibrosis, HIV | Common:<br>Vomiting, Dehydration, Tinnitus<br>Vertigo, Deafness, Sweating<br>Warm extremities with bounding pulses Increased respiratory rate<br>Hyperventilation<br>Acid base disturbance<br>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.<br>In children aged 4 years or less, a dominant metabolic acidosis with law arterial pH (raised hydrogen ion concentration) is common.<br>Acidosis can increase salicylate transfer across the blood brain barrier.<br>Uncommon:<br>Haematemesis<br>Hyperpyrexia<br>Hypoglycaemia<br>Hypokalaemia<br>Thrombocytopenia<br>Increased INR/PTR | *Other symptoms of overdosage, associated with the caffeine component, include:*<br>*CNS stimulation; agitation, anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions*<br>*Cardiac: tachycardia, cardiac arrhythmia*<br>*Gastric: Abdominal or stomach pains, vomiting*<br>*Other: diuresis, facial flushing*<br>For clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be |

| | | |
|---|---|---|
| infection, starvation, cachexia<br>Symptoms of paracetamol overdosage after 12-48 hours are:<br>•Liver damage<br>•Abnormalities of glucose metabolism and metabolic acidosis<br>•Severe poisoning: Hepatic failure may progress to Encephalopathy, Haemorrhage, Hypoglycaemia, cerebral oedema, and death.<br>•With or without severe liver damage: Acute renal failure with acute tubular necrosis strongly suggested by loin pain, haematuria and proteinuria. | Intravascular coagulation<br>Renal failure<br>Non-cardiac pulmonary oedema<br>Confusion, disorientation, coma and convulsions are more common in children than adults. | associated with serious paracetamol-related liver toxicity. |

**Management**

Paracetamol

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

If overdose is confirmed or suspected, seek immediate advice from your Poison Centre and refer patients to nearest Emergency Medical Centre for management and expert treatment. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage. Where a Poison Information Centre is not available, refer patients to the nearest Emergency Medical Centre for management and expert treatment.
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

Give activated charcoal if an adult presents within one hour of ingestion of more than 120 mg/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:** Acetylsalicylic Acid, combinations excl. psycholeptics

**ATC code:** N02BA51

**Mechanism of Action**

Paracetamol

Paracetamol appears to exert its effects through two mechanisms: the inhibition of cyclooxygenase and actions of its metabolite N-arachidonoylphenolamine (AM404).
Supporting the first mechanism, pharmacologically and in its side effects, Paracetamol is close to classical nonsteroidal anti-inflammatory drugs (NSAIDs) that act by inhibiting COX-1 and COX-2 enzymes and especially similar to selective COX-2 inhibitors.
Paracetamol inhibits prostaglandin synthesis by reducing the active form of COX-1 and COX-2 enzymes. This occurs only when the concentration of arachidonic acid and peroxides is low. Under these conditions, COX-2 is the predominant form of cyclooxygenase, which explains the apparent COX-2 selectivity of Paracetamol. Under the conditions of inflammation, the concentration of peroxides is high, which counteracts the reducing effect of Paracetamol. Accordingly, the anti-inflammatory action of Paracetamol is slight.
The anti-inflammatory action of Paracetamol (via COX inhibition) has also been found to primarily target the central nervous system and not peripheral areas of the body, explaining the lack of side effects associated with conventional NSAIDs such as gastric bleeding.
The second mechanism centers on the Paracetamol metabolite AM404. This metabolite has been detected in the brains of animals and cerebrospinal fluid of humans taking Paracetamol.
It is formed in the brain from another Paracetamol metabolite 4-aminophenol by action of fatty acid amide hydrolase. AM404 is a weak agonist of cannabinoid receptors CB1 and CB2, an inhibitor of endocannabinoid transporter, and a potent activator of TRPV1 receptor.
This and other research indicates that cannabinoid system and TRPV1 may play an important role in the analgesic effect of Paracetamol.
Aspirin

Acetylsalicylic acid (ASA) blocks prostaglandin synthesis. It is non-selective for COX-1 and COX-2 enzymes. Inhibition of COX-1 results in the inhibition of platelet aggregation for about 7-10 days (average platelet lifespan). The acetyl group of acetylsalicylic acid binds with a serine residue of the cyclooxygenase-1 (COX-1) enzyme, leading to irreversible

inhibition. This prevents the production of pain-causing prostaglandins. This process also stops the conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent inducer of platelet aggregation Label.
Platelet aggregation can result in clots and harmful venous and arterial thromboembolism, leading to conditions such as pulmonary embolism and stroke.
It is important to note that there is 60% homology between the protein structures of COX-1 and COX-2. ASA binds to serine 516 residue on the active site of COX-2 in the same fashion as its binding to the serine 530 residue located on the active site of COX-1.
The active site of COX-2 is, however, slightly larger than the active site of COX-1, so that arachidonic acid (which later becomes prostaglandins) manages to bypass the aspirin molecule inactivating COX-2.
ASA, therefore, exerts more action on the COX-1 receptor rather than on the COX-2 receptor 14. A higher dose of acetylsalicylic acid is required for COX-2 inhibition.
Caffeine

Caffeine acts by blocking the binding of adenosine to the adenosine A1 receptor123. Adenosine is a modulator of CNS neurotransmission and its modulation of dopamine transmission through A2A receptors has been implicated in the effects of caffeine. Caffeine has a three-dimensional structure similar to that of adenosine, which allows it to bind and block its receptors. The most prominent mechanism of action of caffeine is that it reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine.

**Pharmacodynamic Effects**

Paracetamol

- 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 hypothalmus.
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

Paracetamol

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.

Aspirin

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

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

Paracetamol

LD50 = 338 mg/kg (oral, mouse); LD50 = 1944 mg/kg (oral, rat)

- Overdose and liver toxicity

Acetaminophen overdose may be manifested by renal tubular necrosis, hypoglycemic coma, and thrombocytopenia. Sometimes, liver necrosis can occur as well as liver failure. Death and the requirement of a liver transplant may also
occur. Metabolism by the CYP2E1 pathway releases a toxic acetaminophen metabolite known as N-acetyl-p- benzoquinoneimine(NAPQI). The toxic effects caused by this drug are attributed to NAPQI, not acetaminophen alone.

- Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to study the carcinogenic risk of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice consumed a diet containing acetaminophen up to 6,000 ppm.

Female rats showed evidence of carcinogenic activity demonstrated by a higher incidence of mononuclear cell leukemia at doses 0.8 times the maximum human daily dose (MHDD). No evidence of carcinogenesis in male rats (0.7 times) or mice (1.2 to 1.4 times the MHDD) was noted. The clinical relevance of this finding in humans is unknown.

- Mutagenesis

Acetaminophen was not found to be mutagenic in the bacterial reverse mutation assay (Ames test). Despite this finding, acetaminophen tested positive in the in vitro mouse lymphoma assay as well as the in vitro chromosomal aberration assay using human lymphocytes. In published studies, acetaminophen has been reported to be clastogenic (disrupting chromosomes) when given a high dose of 1,500 mg/kg/day to the rat model (3.6 times the MHDD). No clastogenicity was observed at a dose of 750 mg/kg/day (1.8 times the MHDD), indicating that this drug has a threshold before it may cause mutagenesis. The clinical relevance of this finding in humans is unknown.

- Impairment of Fertility

In studies conducted by the National Toxicology Program, fertility assessments have been performed in Swiss mice in a continuous breeding study. No effects on fertility were seen.

- Use in pregnancy and nursing

The FDA label for acetaminophen considers it a pregnancy category C drug, meaning this drug has demonstrated adverse effects in animal studies. No human clinical studies in pregnancy have been done to this date for intravenous acetaminophen. Use acetaminophen only when necessary during pregnancy. Epidemiological data on oral acetaminophen use in pregnant women demonstrate no increase in the risk of major congenital malformations. While prospective clinical studies examining the results of nursing with acetaminophen use have not been conducted, acetaminophen is found secreted in human milk at low concentrations after oral administration. Data from more than 15 nursing mothers taking acetaminophen was obtained, and the calculated daily dose of acetaminophen that reaches the infant is about 1 to 2% of the maternal dose. Caution should be observed when acetaminophen is taken by a nursing woman.

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

- Avicel PH – 200 (Microcrystalline Cellulose)
- Pregelatinised Starch (Sepistab ST – 200)
- Acdisol NF 18 (Croscarmelose Sodium)
- Stearic Acid (Micronized)
- Aerosil 130V

## 6.2 Incompatibilities

None

## 6.3 Shelf life

60 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

HEDEX Tablets is blister-packed in Alu/PVC Foil in 10 x 10 tablets and 10 x 2 tablets. They are packed in chipboard dispenser cartons together with paper literature inserts.

## 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 AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

BETA HEALTHCARE INTERNATIONAL LTD

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

P.O. BOX 42569-00100 Nairobi, Kenya

Telephone: +254-20-2652042/89

E-Mail: **regulatory@ke.aspenpharma.com**

## 8. MARKETING AUTHORIZATION NUMBER

14

## 9. DATE OF FIRST REGISTRATION

August 2002

## 10. DATE OF REVISION OF THE TEXT

June 2026