ZAIKI AFTER 5 POWDER

(Acetylsalicylic Acid 450mg, Acetaminophen 275mg, Caffeine 50mg)

Summary of Product Characteristics:

1. Name of the medicinal product

ZAIKI AFTER 5

2. Qualitative and quantitative composition

Each tablet contains Acetylsalicylic Acid 450mg, Acetaminophen 275mg, Caffeine 50mg

3. Pharmaceutical form

Powder

White, fine powder

4. Clinical particulars

4.1. Therapeutic indications

For the treatment of headache, menstrual pain, influenza, toothache, cold, fever, rheumatic pain and muscular pain

4.2. Posology and method of administration

Oral administration only.

Adult: Take 1 sachet 3 times daily with water

Do not exceed the stated dose or frequency of dosing Adults (including the elderly) and not to be used for children below 12 years of age

4.3. Contraindications:

- Patients with severe hepatic failure

- Patients who are hypersensitive to the active ingredients or any of the other constituents

- Patients with history of hemophilia and thrombocytopenia

- Patients who are treated with anticoagulants such as warfarin

- Patients with allergic disease (asthma), stomach ulcer, have or often experience bleeding under the skin (consult a physician)

4.4. Special warnings and precautions for use:

Contains Acetylsalicylic Acid. Do not use with any other Acetylsalicylic Acid-containing products. The concomitant use with other products containing Acetylsalicylic acid may lead to an overdose. Aspirin is unsafe in disease conditions such as blood-clotting disorders (such as hemophilia, Vitamin K deficiency, low platelet count), kidney diseases, liver diseases, stomach problems (such as heartburn, ulcers, stomach pain) aspirin-sensitive asthma (a history of worsening breathing with runny/stuffy nose after taking aspirin or other NSAIDs).

Caution is advised if Acetylsalicylic acid 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 Acetylsalicylic Acid. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Aspirin containing medications such as this may cause stomach bleeding, and daily use of alcohol and tobacco, especially when combined with this product, may increase your risk for this side effect. Limit alcoholic beverages, and stop smoking

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Reviews on long-term observational data reported increased cardiovascular, gastrointestinal, and renal adverse events during therapy with paracetamol, especially in the high dose range.

Contains caffeine and is possibly unsafe when used for a long time or in doses over 400mg daily. Caffeine can cause insomnia, nervousness, restlessness, nausea, increased heart rate, and other side effects. Larger doses might cause headache, anxiety, and chest pain, irregular heartbeat and even death. The patient should limit the use of caffeine containing products when taking this drug, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heartbeat.

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

Hepatotoxic substances may increase the possibility of Acetylsalicylic Acid accumulation and overdose. The risk of hepatotoxicity of Acetylsalicylic Acid may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

Probenecid causes an almost two-fold reduction in clearance of Acetylsalicylic Acid by inhibiting its conjugation with glucuronic acid. A reduction of the Acetylsalicylic Acid dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination half-life of Acetylsalicylic Acid.

The absorption of Acetylsalicylic Acid may be increased by metoclopramide and decreased by cholestyramine. Oral contraceptives may increase the rate of clearance of Acetylsalicylic Acid. Concomitant use of Acetylsalicylic Acid (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of Acetylsalicylic Acid with increased risk of bleeding; occasional doses have no significant effect.

Isoniazid reduces Acetylsalicylic Acid clearance by 20%, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver. The clinical relevance is unknown.

Acetylsalicylic Acid decreases the bioavailability of lamotrigine with possible reduction of its effect due to possible induction of its metabolism in the liver.

Co-administration of Acetylsalicylic Acid with zidovudine may result in neutopenia or hepatotoxicity. However, these effects have not been consistently reported. The chronic / multiple dose Acetylsalicylic Acid use in patients on zidovudine therapy should be avoided, however, if chronic Acetylsalicylic Acid and zidovudine are to be given concurrently white blood count and liver function tests should be monitored particularly in malnourished patients.

Acetylsalicylic Acid may increase the elimination half-life of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining Acetylsalicylic Acid with chloramphenicol injection treatment. Interference with laboratory tests: Acetylsalicylic Acid may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase

Flucloxacillin: Caution should be taken when Acetylsalicylic Acid is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors.

Caffeine Phenylpropanolamine increases caffeine plasma concentrations four-fold. There is a risk of additive CNS adverse events. Isolated reports describe the development of acute psychosis when caffeine was given with phenylpropanolamine.

Fluvoxamine, a potent inhibitor of CYP 1 A2, markedly reduces the clearance of caffeine. Concomitant administration may lead to caffeine intoxication.

Ciprofloxacin reduces caffeine metabolism, leading to two-fold increases in caffeine plasma concentrations. Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers. Caffeine may enhance the tachycardic effect of phenylpropanolamine and other sympathomimetic drugs. Caffeine can increase blood pressure and counters the hypotensive action of Beta blockers such as atenolol, metoprolol, oxprenolol and propranolol. This medicine should not be used at the same time as beta blockers.

Disulfiram decreases caffeine clearance by up to 50%.

Treatment with caffeine should be discontinued at least 5 days before myocardial imaging. Coffee, tea and chocolate consumption should be avoided in the 24 hours preceding the test. Use with caution.

Enoxacin: increase of caffeine plasmatic concentrations due to a decrease of its hepatic metabolism, which can lead to excitement or hallucinations. Concomitant use is therefore not recommended.

Mexiletine: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with mexiletine. To be taken into account.

Norfloxacin: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with norfloxacin. To be taken into account.

Stiripentol: possible increase of caffeine plasmatic concentration with risk of overdose, due to its hepatic metabolism inhibition. Use with caution.

Caffeine exerts a competitive inhibition of the metabolism of clozapine. Therefore, clozapine and caffeine must not be used concurrently.

Caffeine can increase the elimination of lithium from the body. Concomitant use is therefore not recommended.

Monoamine oxidase inhibitors may increase the stimulant effects of caffeine.

Methoxsalen reduces clearance of caffeine and may increase the effects of caffeine.

Phenytoin doubles caffeine clearance, although caffeine does not affect the metabolism of phenytoin.

Pipemidic acid reduces caffeine clearance, enhancing the effects of caffeine.

Theophylline and caffeine share the same metabolic pathway, leading to decreased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided.

Levothyroxine, like caffeine can increase blood pressure, and therefore these two active ingredients should not be used concurrently. Ephedrine and caffeine interact to produce significant cardiovascular effects. Therefore, caffeine should be avoided when ephedrine is being taken

4.6 Fertility, pregnancy and lactation

Pregnancy: A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to Acetylsalicylic Acid in utero show inconclusive results. If clinically needed, Acetylsalicylic Acid 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. Acetylsalicylic Acid-caffeine is not

recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Breast-feeding: Acetylsalicylic Acid is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding. Caffeine in breast milk may have a stimulating effect on breast-fed infants. Irritability and poor sleeping pattern in the infant have been reported.

Not recommended for use during breastfeeding.

Fertility: There is insufficient information available on the effects of Acetylsalicylic Acid and Caffeine on human fertility.

4.7 Effects on ability to drive and use machines

Zaiki After 5 Powder has no or negligible influence on the ability to drive and use machines 4.8 Undesirable effects Adverse events from historical clinical trial data are both infrequent and from minimal patient exposure.

Accordingly, adverse events reported from extensive post-marketing experience at therapeutic/labelled dose are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, 1/1000, 1/10,000, very rare (<1/10,000 including isolated reports) and not known (cannot be estimated from available data)

Frequency	System	Symptoms
Common >1/100, <1/10	Psychiatric disorders:	Insomnia, restlessness, anxiety
	Gastrointestinal disorders	
Rare >1/10000 - < 1/1000	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders.
	Psychiatric disorders	Depression NOS, confusion, hallucinations
	Nervous system disorders	Tremor NOS
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting
	Hepato-biliary disorders	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria

	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (< 10, 000)	Hepato-biliary disorders	Hepatotoxicity, hepatic dysfunction
	Blood and lymphatic system disorders	Thrombocytopenia, leukopenia neutropenia hemolytic anemia agranulocytosis
	Immune system disorders	Anaphylaxis, Cutaneous hypersensitivity reactions, Angioedema, Stevens Johnson Syndrome and toxic epidermal necrolysis
	Metabolism and nutrition disorders	Hypoglycaemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects
	Respiratory, thorasic and mediastinal disorder	Bronchospasm inpatients sensitive to aspirin and other NSAIDs
	Skin and subcutaneous disorders	Serious skin reactions have been reported

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 HPRA Pharmacovigilance website: www.hpra.ie

4.9 Overdose

Acetylsalicylic acid overdose

Acetylsalicylic acid overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

There is a risk of poisoning with Acetylsalicylic Acid particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases. Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of Acetylsalicylic Acid in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults who have taken more than the recommended amounts of Acetylsalicylic Acid. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of Acetylsalicylic Acid are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from Acetylsalicylic Acid toxicity. Risk Factors include: If the patient; - Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. - Regularly consumes ethanol in excess of recommended amounts - Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Blood sampling to determine initial Acetylsalicylic Acid plasma concentration. In the case of a single acute overdose, Acetylsalicylic Acid plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if >150mg/kg Acetylsalicylic Acid has been taken within 1 hour.

Treatment of overdose:

The patient must be transferred to hospital and the Poison Control Center contacted immediately. When the patient is suspected of ingesting more than 120 mg/kg salicylate within the last hour, repeated doses of activated charcoal are to be given orally. Plasma concentrations should be measured in patients having ingested more than 120 mg/kg salicylate, although the severity of the poisoning cannot be determined from these alone. Clinical and biochemical features must equally be taken into account. In plasma concentrations exceeding 500 micrograms/ml (350 micrograms/ml in children under 5 years of age) the intravenous administration of sodium bicarbonate is effective in removing salicylate from the plasma. Forced diuresis should not be used alone since it does not enhance salicylate excretion and may cause pulmonary oedema. Heamodialysis or haemoperfusion are the methods of choice in cases where the plasma salicylate concentration is more than 700 micrograms/ml, or lower in children and elderly people, or if there is a severe metabolic acidosis.

Paracetamol overdose

Overdose (>10 g in total in the adult or >150 mg/kg in one intake) can provoke a hepatic cytolysis which can lead to complete and irreversible necrosis (hepatic failure, metabolic acidosis, renal failure) and eventually to coma and possibly death or may require liver transplant. Less often renal tubular necrosis may develop. Early signs of overdose (very commonly nausea, vomiting, anorexia, pallor, lethargy and sweating) generally settle within first 24 hours.

Abdominal pain may be the first indication of liver damage, which is not usually apparent for the first 24 to 48 hours, and may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Patients are considered at high risk when receiving enzyme-inducing medicinal products, such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or with a history of alcohol abuse, or suffering from malnutrition.

Treatment of overdose: Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. If overdose is confirmed or suspected, seek immediate advice from your Poison Centre and refer patient 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. When the patient is suspected of ingesting more than 150 mg/kg paracetamol within the last hour, repeated doses of activated charcoal are to be given orally. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote. Antidotes N-acetylcysteine should be administered intravenously or orally as soon as possible after ingestion. It is most effective during the first 8 hours after taking the overdose. The effect of the antidote then diminishes progressively after that. Nevertheless it has been shown that treatment up to and beyond 24 hours after ingestion remains beneficial. Methionine is most effective within the first 10 hours after ingestion of paracetamol overdose. Hepatic damage is more frequent and severe if treatment with methionine if started more than 10 hours after ingestion. Oral absorption might be reduced by vomiting or activated charcoal.

Caffeine Overdose

Caffeine Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions). It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious Acetylsalicylic Acid-related liver toxicity. 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

Zaiki After 5 powder is an extensively used mild analgesic.

Mechanism of action

Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory properties, primarily due to the inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid by irreversible acetylation of cyclooxygenase (COX) enzymes.

Paracetamol has analgesic and antipyretic properties, but unlike acetylsalicylic acid does not inhibit platelet aggregation.

The addition of caffeine augments the antinociceptive effects of acetylsalicylic acid and paracetamol.

Pharmacodynamic Effects

Analgesic: Acetylsalicylic Acid may act predominantly by inhibiting a 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 sensitize pain receptors to mechanical or chemical stimulation.

Antipyretic: Acetylsalicylic Acid produces antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. 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.

5.2 Pharmacokinetic properties

Acetylsalicylic Acid

Absorption:
Acetylsalicylic acid is completely absorbed from the gastrointestinal (GI) tract after oral administration. Approximately 70% of an acetylsalicylic acid dose reaches the circulation unchanged; the remaining 30% is hydrolyzed to salicylic acid during absorption by esterases in the GI tract, liver or plasma. The salicylate peak plasma concentration is reached in 1-2 hours with single doses. Food reduces the speed but not the extent of absorption.

Distribution:
Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS). The highest concentrations are found in the plasma, liver, renal cortex, heart, and

lungs. Acetylsalicylic acid and salicylic acid bind partially to serum proteins and mainly to albumin. The protein binding of salicylate is concentration-dependent, i.e., nonlinear. At low Health Products Regulatory Authority 08 July 2024 CRN00F9J4 Page 12 of 14 concentrations (< 100 micrograms/milliliter (mcg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 (mcg/mL)), only about 40-70% is bound. Salicylic acid crosses the placenta and is excreted in breast milk.

Metabolism:
Acetylsalicylic acid is hydrolyzed in the plasma to salicylic acid (with a half-life of 15-20 minutes) such that plasma levels of acetylsalicylic acid are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid by conjugation with glycine, salicyl phenolic glucuronide and salicyl acyl glucuronide by conjugation with glucuronic acid, and a number of minor metabolites. Following a single 1 g dose of acetylsalicylic acid, the average half-life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. The half-life of salicylate varies with dosage. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

Elimination:
Salicylic acid and its metabolites are excreted through the kidneys. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises from 5 up to 8, greater fraction of the administered dose is eliminated as free salicylic acid and the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, and 10 percent phenolic and 5 percent acyl glucuronides of salicylic acid.

Paracetamol

Absorption:
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion.

Distribution:
Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism:
It is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. A minor hydroxylated metabolite which is usually produced in very small amounts by

mixed- function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdose and cause liver damage.

Elimination:
Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours.

Caffeine

Absorption:
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.

Distribution:
Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Metabolism:
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).

Elimination:
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.

5.3 Preclinical safety data

Acetylsalicylic acid

Preclinical studies in animals using acetylsalicylic do not show organ toxicity except for effects on gastrointestinal mucosa and, at high dosages, renal damage. Acetylsalicylic acid is neither mutagenic nor carcinogenic. Salicylates have been found to have teratogenic effects at maternally toxic doses in a number of animal species (e.g. cardiac and skeletal malformations, midline defects). There have been reports of implantation disturbance, embryotoxic and fetotoxic effects, and disturbance of learning capacity in the offspring after prenatal exposure.

Paracetamol

Preclinical data reveal no special hazard for humans at therapeutically relevant doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and

carcinogenicity. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available. Overdose may lead to serious hepatotoxicity.

Caffeine

Caffeine was shown to be devoid of mutagenic and oncogenic risk. In animal studies in different species (rat, mice, rabbit), very high doses of caffeine were associated with an increase in birth defects.

6 Pharmaceutical Particulars

6.1. List of excipients

Maize starch, Povidone, Saccharine, Talc, Orange Essence, Strawberry Essence

6.2. Incompatibilities

None.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30°C

Keep medicine out of reach of children

6.5. Nature and contents of container

ZAIKI AFTER 5 is packaged in powder form in an Alu-Alu foil sachet then packed into outer cardboard cartons, containing 100 sachets each.

6.6. Special precautions for disposal and other handling

Not applicable

7. Marketing Authorisation Holder

Orange Drugs Limited.

66/68, Town Planning Way Illupeju, Lagos, Nigeria

8. Marketing Authorisation Number(s)

YET TO BE RECEIVED

9. Date of first Authorisation/Renewal of the Authorization

YET TO BE RECEIVED