SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caffetin SC tablets 250 mg/210 mg/50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Paracetamol 250 mg,
Propyphenazone 210 mg,
Caffeine 50 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Tablets

Caffetin SC tablets are white, round, flat tablets with facet, with bisection line on one side, and trademark of the manufacturer Alkaloid () impressed on the other side of the tablet.
Tablets can be divided into two equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caffetin SC is used for the relief of mild to moderate pain of different etiology: headache, migraine, toothache, arthralgia, myalgia and dismenorrhea.
Caffetin SC is also used in complex therapy as an antipyretic for the treatment of fever in infectious and inflammatory diseases (viral respiratory infections, flu, etc.).

4.2 Posology and method of administration

Posology
Adults*:* 1-2 tablets, 1-3 times a day. Maximum single dose: 2 tablets. Maximum daily dose: 6 tablets.
Adolescents 12 to 18 years of age: ½ - 1 tablet, 1-3 times a day.
Caffetin SC should not be used for more than 3 days as an antipyretic and more than 5 days as a pain reliever.
Treatment duration may only be prolonged following consultation with a physician. The recommended dose must not be exceeded. In case of taking more than the recommended dose, patients should seek medical assistance even if they feel well. Paracetamol overdose

can cause liver failure.
Special populations
Patients with renal impairment
The interval between 2 doses of Caffetin SC in patients with moderate renal impairment (creatinine clearance <10 ml/min) should be at least 8 hours.

Method of administration
Caffetin SC tablets are used orally, 1-2 hours after a meal, with plenty of water.

4.3 Contraindications

Hypersensitivity to the drug components; severe kidney and/or liver failure; glucose-6-phosphate dehydrogenase deficiency; bone marrow hematopoiesis suppression (leukopenia, anemia, including hemolytic anemia); acute hematoporphyria; complete or partial syndrome (or history) of bronchial asthma, recurrent sinonasal polyposis and nonsteroidal anti-inflammatory drugs intolerance; conditions accompanied by respiratory depression; intracranial hypertension; acute myocardial infarction; cardiac ischemia; arrhythmias; arterial hypertension; acute gastric and duodenal peptic ulcer; alcohol intoxication; glaucoma; insomnia; pregnancy; lactation in women; children under 12 years of age.

4.4 Special warning and precautions for use

Use cautiously in:
Moderate hepatic or renal impairment; older age; alcoholism; epilepsy and susceptibility to seizures; history of gastric and duodenal ulcer; benign hyperbilirubinemia (including Gilbert's syndrome, Dubin-Johnson syndrome, Rotor's syndrome), children under 12 years of age.
Prolonged use of the drug (more than 5 days) requires monitoring of the peripheral blood parameters and liver function. Alcohol should not be consumed during treatment with Caffetin SC (increased risk of gastrointestinal bleeding).
Patients with renal impairment should use this drug under medical supervision with creatinine clearance monitoring.
When using Caffetin SC, it is not recommended to take other drugs containing paracetamol and/or pyrazolone derivatives, including metamizole sodium.
Excessive use of products containing caffeine (coffee, tea) while taking the drug can cause symptoms of caffeine overdose.
Acute abdominal pain syndrome may be difficult to diagnose while taking the drug.
Mild paracetamol overdose (5 g or more) in patients with glutathione deficiency due to nutritional disorders, diet-related fibrosis, HIV infection, starvation, exhaustion can lead to the development of severe liver damage.
Tell your doctor that you are using this medicine in case you need to undergo uric acid and blood glucose tests. Caffetin SC can alter the results of doping control tests in athletes.
Using the drug for headache relief for longer than recommended can lead to chronic headache.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of paracetamol with hepatic microsomal enzyme-inducing drugs, such as some sleeping pills (barbiturates), antiepileptic drugs (phenobarbital, phenytoin, carbamazepine), rifampicin, ethanol, can increase the risk of hepatotoxicity, even when used

in therapeutic doses.
- Paracetamol increases chloramphenicol half-life by 5 times.
- Concomitant use with metoclopramide and domperidone increases the rate of paracetamol absorption.
- Concomitant use of high doses of paracetamol with anticoagulants increases anticoagulant effects, thus increasing the risk of bleeding.
- Myelotoxic agents increase hematotoxic effects of paracetamol.
- Concomitant use with acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs increases the risk of kidney damage.
- Cholestyramine and antacids reduce paracetamol absorption.
- Paracetamol efficacy can be reduced if concomitantly used with cholestyramine, cholinolytics, antidepressants, alkaline substances.
- Concomitant use of paracetamol with zidovudine increases the risk of neutropenia.
- Paracetamol use can affect uric acid and blood glucose test results.
- Caffeine increases the absorption rate of ergotamine; reduces the absorption of calcium preparations; reduces the effect of narcotic drugs and sleeping pills, increases the excretion of lithium preparations; increases the absorption rate of cardiac glycosides, potentiates their effect and increases their toxicity. Concomitant use of caffeine with beta-blockers can lead to mutual suppression of therapeutic effects; concomitant use of caffeine with beta-adrenergic agonists can lead to additional central nervous system stimulation and other toxic effects. Caffeine reduces the effect of many sedatives, such as barbiturates and antihistamines, and increases tachycardia caused by sympathomimetics and thyroxine.
- Oral contraceptives, cimetidine and disulfiram decrease caffeine metabolism rate; barbiturates and smoking tobacco increase caffeine metabolism rate.
- Concomitant use with DNA gyrase inhibitors (e.g., ciprofloxacin) may slow down the excretion of caffeine and its metabolite paraxanthine.
- When used concomitantly, caffeine decreases the excretion rate of theophylline. Monoamine oxidase inhibitors, furazolidone, procarbazine, selegiline and high doses of caffeine can lead to severe cardiac arrhythmias or a significant increase in blood pressure.
- Mexiletine reduces caffeine excretion by 50%. Caffeine is an adenosine antagonist.
- Concomitant use of caffeine with ephedrine should be avoided since caffeine may interact with ephedrine thus causing clinically significant cardiovascular effects.
- Propyphenazone can increase the effect of oral hypoglycemic agents, sulfanilamides, and anticoagulants and the ulcerogenic effect of glucocorticosteroids, and can reduce the efficacy of potassium-sparing diuretics.

4.6 Pregnancy and lactation

Pregnancy
There are no controlled studies concerning use of combined analgesics during pregnancy and lactation. Considering the fact that the possible risk can not be completely excluded, the drug is contraindicated during pregnancy.

Lactation
As the active ingredients of the drug are breast excreted, the drug is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

Caution is advised during treatment when operating motor vehicles and engaging in other activities that require increased concentration and psychomotor speed.

4.8 Undesirable effects

The adverse reactions are specified according *MedDRA* frequency convention, as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Central nervous system disorders
Very rare - dizziness, sleep disturbance.
Not known - insomnia, anxiety, headache.
Gastrointestinal tract disorders
Very rare - nausea, vomiting, feeling of abdominal heaviness and discomfort, gastralgia
Hepatobiliary disorders
Very rare – hepatic impairment
Respiratory disorders
Very rare - bronchospasm.
Hematopoietic disorders
Very rare - leukopenia, thrombocytopenia, agranulocytosis, hemolytic anemia, methemoglobinemia, pancytopenia
Immune system disorders
Very rare - skin rash, itching, urticaria, Quincke's oedema, exudative erythema multiforme

There are very rare reports of serious skin reactions with paracetamol use (e.g., drug-induced Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

4.9 Overdose

Symptoms
Symptoms of paracetamol overdose in the first 24 hours: nausea, vomiting, abdominal pain, pallor, loss of appetite. Signs of liver damage (pain in the liver area, increased activity of hepatic microsomal enzymes) may appear within 12-48 hours of overdose. Carbohydrate metabolism disorder and metabolic acidosis may occur. In adult patients, paracetamol may cause liver damage at doses of 10 g paracetamol. Ingestion of 5 g of paracetamol or more may lead to liver damage if the patient has risk factors that may contribute to increased hepatotoxicity. In the event of severe overdose, hepatic failure may progress to encephalopathy, coma, and acute renal failure with acute tubular necrosis (even in the absence of severe liver damage). Cardiac arrhythmias and pancreatitis may occur.

Gastric lavage, activated charcoal treatment and symptomatic treatment are recommended within 1 hour of overdose. Treatment with acetylcysteine is most effective in the first 8 hours of overdose. Its effectiveness may decline over time. If necessary, the patient should be administered SH-group donors and glutathione-methionine synthesis precursors in the next 24 hours of overdose. The treatment of these patients is carried out in a specialized liver diseases department.

The following symptoms may occur as a result of high doses of caffeine: headache, tremors, irritability, gastralgia, anxiety, motor restlessness, confusion, tachycardia, arrhythmia, hyperthermia, dehydration, increased sensitivity to touch and pain, frequent urination, nausea, vomiting (sometimes with blood), tinnitus, seizures (tonic-clonic seizures in acute overdose).

Treatment: gastric lavage, activated charcoal, laxatives; in the event of haemorrhagic gastritis: administration of antacids, gastric lavage with ice-cold 0.9% sodium chloride solution, maintaining lung ventilation and oxygenation; in the event of seizures: intravenous administration of diazepam, phenobarbital, maintaining fluid and electrolyte balance.

It should be taken into account that the occurrence of clinically significant symptoms of caffeine overdose while using this drug is always associated with severe liver damage caused by paracetamol overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Analgesics; Other analgesics and antipyretics; Paracetamol, combinations excl. psycholeptics
ATC code: N02BE51

Mechanism of action
Caffetin SC is a combination drug composed of analgesics (paracetamol and propyphenazone) and a psychostimulant (caffeine).

Paracetamol has an analgesic and antipyretic effect. Paracetamol is a non-narcotic analgesic. It inhibits cyclooxygenase (COG) in the central nervous system (CNS) only, acting on pain centers and thermoregulation (cellular peroxidases neutralize the effect of paracetamol on COG in inflamed tissues), which explains the lack of anti-inflammatory effect. Paracetamol has no effect on the synthesis of prostaglandins (PG) in peripheral tissues thus causing no negative effect on water-salt metabolism (retention of sodium and water) and gastrointestinal (GIT) mucosa.

Propyphenazone is a pyrazolone derivative with analgesic, antipyretic and anti-inflammatory effects. Its mechanism of action is by inhibiting COG, which participates in the formation of prostaglandins from arachidonic acid.

Caffeine increases reflex spinal cord excitability, stimulates respiratory and vasomotor centers, dilates blood vessels in skeletal muscles, brain, heart, kidneys, reduces platelet aggregation, and reduces drowsiness and fatigue. The small dose of caffeine in this combination practically has no CNS-stimulating effect, but it helps regulate cerebral vascular tone, reduces drowsiness and improves the analgesic efficacy of the other drug components. Caffetin SC has a pronounced analgesic and antipyretic effect and rapid onset of action. Its analgesic effect occurs 30 minutes following ingestion, lasting for several hours.

5.2 Pharmacokinetic properties

Paracetamol
Paracetamol has a high absorption rate. The extent of plasma protein binding of paracetamol is 15%. The time to peak plasma concentration (tmax) is 20-30 minutes. Paracetamol crosses the blood-brain barrier. The amount of drug excreted in breast milk is less than 1% of the maternal dose. The therapeutic plasma concentration of paracetamol is achieved with administration of 10-15 mg/kg/dose.
Paracetamol is metabolized in the liver: 80% undergoes glucuronidation and sulfation resulting in the formation of inactive metabolites; 17% undergoes hydroxylation resulting in the formation of inactive metabolites, which are then conjugated with glutathione. In the event of glutathione deficiency, these metabolites can block hepatocyte enzyme systems and cause necrosis. Paracetamol elimination half-life is 2-3 hours.
Paracetamol clearance in older patients is decreased, while half-life is increased. 3% of paracetamol is excreted unchanged via the kidneys.

Propyphenazone
Peak plasma concentration of propyphenazone is reached in 30 minutes. Propyphenazone is metabolized in the liver and has a half-life of 1-1.5 hours. Combined with paracetamol, propyphenazone extends paracetamol elimination half-life by 40%, which enables dose reduction during the day. Drug excretion occurs via the kidneys.
Combined with paracetamol, propyphenazone extends paracetamol elimination half-life for 40% (2-3h), which enables extended duration of paracetamol effect and diminished dose frequency

Caffeine
Peak concentration is achieved in 1 hour; caffeine half-life is 3.5 hours; 65-80% of caffeine is excreted via the kidneys mainly in the form of 1-methylxatin, 1-methyl uric acid and acetylated uracil derivatives; small amount of caffeine is converted to theophylline and theobromine.

5.3 Preclinical safety data

Chronic administration of analgesic combination containing caffeine to dogs and rats has revealed no drug related toxicity. No blood or urine changes were observed, nor were there any macroscopic or microscopic pathological changes detected.

Paracetamol
Although some animal studies suggested that high paracetamol doses, administered in a prolonged period, may have cancerogenic effects, no clinical data confirm this hypothesis. Paracetamol has been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basic test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.
Animal toxicological studies with high paracetamol doses showed testicular atrophy and spermatogenesis inhibition, but the relevance of these data in humans is not confirmed.

Propyphenazone
Animal toxicological studies on propyphenazone showed no significant toxic effects. No signs of existence of teratogenity, embriotoxicity or carcinogenicity have been noted.

Caffeine
The ability of caffeine to catalyse N-nitrosamine production in the digestive tract actuates the question about caffeine carcinogenicity, but still this hypothesis is at a level of a speculation.
High doses of caffeine, administered during pregnancy in animals, have caused skeletal abnormalities of the fingers and phalanxes.
Caffeine crosses placental barrier; enormous coffee consumption in human may increase the risk of abortion and intrauterine foetal retardation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate;
Cellulose, microcrystalline;
Povidone;
Croscarmellose sodium;
Silica, colloidal anhydrous;
Sodium starch glycolate (type A);
Glycerol dibehenate;
Sodium laurilsulfate;
Magnesium stearate.

Incompatibilities

Not applicable.

6.2 Shelf life

3 (three) years.

6.3 Special precautions for storage

Store below 25°C.

6.4 Nature and contents of container

Caffetin SC tablets are immediate packed in strip packaging (Al/PE printed foil), each strip containing 6 tablets. The cardboard box contains 1 or 2 strips (6 or 12 tablets) and a patient leaflet.

6.5 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Alkaloid AD Skopje
Blvd. Aleksandar Makedonski 12,
1000 Skopje, Republic of North Macedonia
Tel.: + 389 2 31 04 000
Fax: + 389 2 31 04 021

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT