SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CAFFETIN® tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Paracetamol	250 mg;
Propyphenazone	210 mg;
Caffeine	50 mg;
Codeine	7.1 mg

(in a form of codeine phosphate sesquihydrate 10 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Tablets

White, rounded, flat tablets with seal Alkaloid on one side and seal Caffetin on the another side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caffetin is indicated for symptomatic and short-term treatment of pain such as headache, toothache, migraine, postoperative and posttraumatic pain, dismenorrhoea, neuralgia, ishialgia, myalgia.

4.2 Posology and method of administration

Caffetin as a combined analgesic should be used as needed, and it is not intended for long-term therapy (no longer than 3 days).
Adults and children over 16 years old: the single dose is 1-2 tablets, according pain intensity. The dose can be repeated 3 times daily. Maximal daily dose is 6 tablets.
Children 12-16 years old: ½-1 tablet, with a possibility to repeat the dose 3 times daily.

4.3 Contraindications

- Hypersensitivity to paracetamol, propyphenazone, codeine, caffeine, , opioid analgesics, or the excipients, listed in section 6.1.
- Severe hepatic or renal impairment.
- Glucose-6-phosphate dehydrogenase deficiency.
- Acute intermittent porphyria .
- Pregnancy and lactation.
- Children under 12 years old.
- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).
- In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and special precautions for use

Combination analgesics are not suitable for long term treatment of pain. This medicine contains codeine and prolonged regular use for more than 3 days can cause dependence (addiction). f such therapy is necessary, periodic controls of blood count, hepatic and renal functions are necessary.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Caution should be exercised in patients with functional renal or hepatic impairment, in alcohol abusers, as well as in patients with chronic respiratory diseases and asthma. Precautions are to be taken in case of reduced tolerance of analgesics, hypersensitivity to other analgesics (danger of provoking asthma attacks), as weel as in gastrointestinal ulcer and haemorrhagia. Special caution is necessary in patients with blood dyscrasia or bone marrow suppression, and close surveillance for haematological parameters is recommended in these patients. The risk of neutropenia and agranulocytosis is present mostly due to the presence of propyphenazone. If such reaction occurs following Caffetin administration (reduction of blood granulocytes, increased temperature, sore throat, ulcerations and abscesses in the mouth, periannal abscesses), the administration of the drug should be discontinued immediately. The described adverse effects usually are reversible within 1-2 weeks.
Simultaneous consumption of alcohol during Caffetin use should be avoided.
Special care is also needed in patients who are anxious, nervous, or have tremor, hypertension or insomnia. If palpitations or tachycardia occur, the treatment should be discontinued.
Caution should be exercised when the drug is used by children aged over 12 years.
Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.
Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients.
Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.
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.

Pediatric population

Post-operative use in children
There have been reports in the published literature that codeine given post- operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Caffetin and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for

whom alternative treatment options are not possible. If a decision is made to prescribe Caffetin concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicaments and other forms of interaction

There is no evidence about specific interactions of Caffetin with other drugs having significant clinical implications.
Simultaneous administration is not recommended with CNS-stimulant drugs, MAO-inhibitors (furasolidine, procarbazine, selegiline) and drugs or beverages containing caffeine.
Co-administration of Caffetin and alcohol, hypnotics, or anxiolytics and sedatives, tricyclic antidepressants, MAO inhibitors should be avoided due to the central depressive activity of codeine.
Alcohol, phenobarbital, phenytoin, carbamazepione, isoniazide and rifampicin enhance the hepatotoxicity of paracetamole.
Concomitant use with oral anticoagulants (acenocumarole, warfarin) or NSAIDs may lead to undesirable gastrointestinal adverse reactions.
If paracetamole preparations are used concomitantly with Caffetin, the risk of paracetamole overdosing is possible.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.
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).

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4.6 Pregnancy and lactation

There are no controlled studies concerning use of combined analgesics during pregnancy and lactation.

Pregnancy
Considering the fact that the possible risk should not be completely excluded, the drug is contraindicated during pregnancy, this includes maternal use during labor because of the potential for respiratory depression in the neonate.The safety of Caffetin during pregnancy has not been established relative to the possible adverse effects of foetal development and should

not be used during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

Lactation
As the active ingredients of the drug are breast excreted, the drug is contraindicated in nursing mothers.
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.
However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

4.7 Effects on ability to drive and use machines

Caffetin administered in therapeutic doses do not affect the driving ability or operating machinery. Caution should be exercised using the maximum daily doses (6 tablets daily), especially concomitantly with alcohol. Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

4.8 Undesirable effects

The therapeutic doses of Caffetin are well tolerated and no dose-dependent adverse effects should be expected, because active ingredients are presented in low doses. Possible adverse reactions are classified according *MedDRA* system organ class database.
Cardiac disorders
Palpitations, tachycardia.
Blood and lymphatic system disorders
Thrombocytopenia, leucopoenia, neutropoenia, pancitopoenia, agranulocytosis (propyphenazone, which is a pyrazolone derivative, is the incriminated ingredient of Caffetin for possible incidence of agranulocytosis, because it is well known for blood dyscrasias associated with aminopyrine - one of the first pyrazolone derivatives, although such reactions have been described with paracetamole as a single agent).
Nervous system disorders
Insomnia, nervousness, dizziness, worsening of headache with prolonged use, drowsiness. When the recommended paracetamol-caffeine-codeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.
Psychiatric disorders
Drug dependence can occur after prolonged use of codeine.
Gastrointestinal disorders
Nausea, vomiting, constipation, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy, bloating, abdominal pain.
Renal and urinary disorders
Renal disturbances.
Skin and subcutaneous tissue disorders
Sweating, pruritus, erythema, urticaria. Cutaneous hypersensitivity reactions including skin

rashes, angioedema. Very rare cases of serious skin reactions (Stevens Johnson syndrome/Toxic epidermal necrolysis) have been reported.
Respiratory, thoracic and mediastinal disorders
Bronchospasm
There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.
Immune system disorders
Anaphylactic reaction.
Hepatobiliary disorders
Hepatic dysfunction, including hepatic impairment (hepatotoxicity is usually associated with the overdose of paracetamol).

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency. Withdrawal symptoms such as restlessness and irritability may result when treatment is stopped.

Codeine
The effects in codeine overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms:
An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory center can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

Management
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

Paracetamol
Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).
Risk Factors:
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.
Or
Regularly consumes ethanol in excess of recommended amounts.

Or
Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:
Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management:
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration 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.

Caffeine
Symptoms:
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

Management:
Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose, but can be considered for up to four hours after the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Caffetin is an established analgesic combination as hundreds such combinations in the world, as well as in countries with most developed pharmacology. The analgesic effect has been proven for paracetamol, propyphenazone and codeine, while caffeine may be considered as an adjuvant, which ameliorates the effect of the analgesics.

Paracetamol

Paracetamol has analgesic and antipyretic effect. Paracetamol is an effective and widely used analgesic in mild and moderate pain. It is an effective antipyretic agent, and because of the association of aspirin with Reye's syndrome in children, paracetamol is analgo-antipyretic of choice in this group. The mechanism of action of paracetamol is an inhibition of the enzym cyclo-oxygenase in CNS, while the peripheral properties of the drug are minimal.

Propyphenazone

Propyphenazone has analgesic and antipyretic effect, which are results of prostaglandin E_2 and F_2 - alfa synthesis inhibition.

Codeine

Codeine is a weak analgesic and it is used in analgesic combinations to ensure additive effect, which is accomplished due to the different mechanism of action. The analgesic effect of codeine is a result of interaction with opioid stereospecific binding sites in the CNS and other tissues, as well as the alterations in the rate of release of neurotransmitters.

Caffeine

The addition of caffeine in analgesic combination containing paracetamol and propyphenazone is based to its ability to enhance the absorption of the other ingredients. Caffeine is central nervous system stimulant and competitive inhibitor of the enzyme phosphodiesterase.

This combination enables the utilization of the advantages of analgesic synergism using relatively small doses of the particular ingredients and the minimisation of possible adverse effects.

5.2 Pharmacokinetic properties

The pharmacokinetics of this combined preparation has limited range, since it is not meant for chronic therapy, during which is necessary maintaining of the therapeutic concentrations in plasma, but as a drug used when needed.

Paracetamol

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 to 60 minutes after oral administration. Paracetamol is metabolised predominantly in the liver and excreted via the urine mainly as the glucuronide and sulphate conjugates. A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine) which is usually produced in very small amounts by mixed-function oxidases in the liver and kidney is usually detoxified by conjugation with glutathione. In case of intended or accidental intoxication N-acetyl-p-benzoquinoneimine may accumulate following paracetamol overdosage because of lack of endogenous gluthatione and may cause necrosis of the liver and renal tubules. The elimination half-life of paracetamol varies from 1-3 hours.

Propyphenazone

Propyphenazone has similar pharmacokinetic profile, which justifies the rationality of the combination. It is readily absorbed from the gastrointestinal tract with peak plasma

concentrations occurring about 0.5 to 0.6 hours after oral administration. It is metabolised extensively in the liver and excreted in the urine and bile as metabolites. The elimination half-life of propyphenazone varies from about 2.1 to 2.4 hours. Combined with paracetamole, propyphenazone extends paracetamol elimination half-life for 40% (2-3h), which enables extended duration of paracetamole effect and diminished dose frequency.

Codeine

Codeine is well absorbed after oral administration and maximal plasma concentration is achieved within 1-2 hours; analgesic effect in achieved in 30-60 minutes, duration of analgesia is 4-8 hours. Codeine is metabolised in the liver and the excretion is predominantly via kidneys (90%). The half-life is 2.5- 3.5 hours.

Caffeine

Caffeine is readily and completely absorbed, it is distributed in all tissues including the brain with peak plasma concentrations occurring about 15-45 minutes; caffeine is metabolised in the liver, with half life of elimination of 5 hours. Caffeine ameliorates the absorption of other active ingredients in analgesic combined preparations.

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. Long term studies of different analgesic combinations in animals to evaluate carcinogenic, mutagenic and embriotoxic potential have not been performed.

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 Basc 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.

Codeine

Codeine has been reported to show no evidence of carcinogenicity or mutagenicity in a variety of test systems, including the micronucleus and sperm abnormality assays and the Salmonella assay. Animal foetal studies on codeine had shown ossification disturbances.

Codeine crosses placental barrier; so, the use during pregnancy in humans may cause foetal physical addiction, resulting in withdrawal syndrome in the new-born.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three (3) years.

6.4 Special precautions for storage

Store at a temperature below 25°C.

6.5 Nature and contents of container

Caffetin tablets are immediate packed in strip (Al/PE printed foil), each strip containing 6 or 10 tablets.
The cardboard box contains 1 strip (each containing 6 or 10 tablets) or 2 strips (each containing 6 tablets) and a leaflet inside.

6.6 Instructions for use/handling

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

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST MARKETING AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT