SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caffetin COLD® film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Paracetamol	500 mg;
Pseudoephedrine hydrochloride	30 mg;
Dextromethorphan hydrobromide	15 mg;
Ascorbic acid	60 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Film-coated tablets

Blue, oblong, biconvex, film-coated tablets with break-mark on one side.
The break-mark is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of the major symptoms of common cold and influenza (headache, muscle pain, sore throat, nasal congestion, fever or dry cough).

4.2 Posology and method of administration

Adults and adolescents over 12 years old
The recommended dose is one tablet, four times daily. Two tablets could be taken at once. The interval between the administrations should not be less than four hours.
The maximum single dose is 2 tablets, while the daily dose must be limited to a maximum of 2 tablets four times daily (8 tablets in 24 hours).
Drug intake should not continue for more than 5 days without medical advice.

Hepatic dysfunction
Caution should be exercised in patients with hepatic impairment (see section 4.4).
The drug is contraindicated in patients with severe hepatic impairment (see section 4.3).
Renal dysfunction
Caution should be exercised in patients with renal impairment, particularly if accompanied by cardiovascular disease.
The drug is contraindicated in patients with severe renal impairment (see section 4.3).

Paediatric population
Caffetin COLD tablets is not recommended for children aged below 12 years without medical advice.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Severe hypertension or coronary artery disease.
Severe liver or renal impairment.
Concomitant/within the preceding two weeks administration of MAO inhibitors.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with mild to moderate hypertension, heart disease, diabetes, liver and renal diseases, hyperthyroidism, elevated intraocular pressure (glaucoma) or prostatic enlargement, as well as in elderly or debilitated persons.

Concomitant use of other products containing paracetamol could lead to overdose and therefore should be avoided.

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.

Severe Skin reactions
Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of Caffetin COLD should be discontinued and appropriate measures taken if needed.

Ischaemic colitis

Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Cases of dextromethorphan abuse and dependence have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

Serotonin Syndrome
Concomitant administration of Caffetin COLD and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5)..
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Alcohol and caffeine consumption should be avoided.

Paediatric population
Caffetin COLD tablets is not recommended for children aged below 12 years.

4.5 Interactions with other medicinal products and other forms of interaction

Paracetamol
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and reduced by cholestyramine.
The anticoagulant effect of warfarin and other coumarin drugs may be enhanced by prolonged regular use of paracetamol which could increase the risk of bleeding.
Simultaneous use of paracetamol and non-steroidal anti-inflammatory agents increases the risk of impairment kidneys.
Paracetamol may prolong elimination of chloramphenicol.

The use of drugs which induce hepatic microsomal enzymes (anticonvulsants, barbiturates, oral contraceptives and rifampicin) may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentrations of the drug and increased formation of toxic metabolites of paracetamol. Due to increased formation of toxic metabolites of paracetamol, the probability of occurrence of toxic effects on hepatic cells may be increased. Salicylamide prolongs the elimination time of paracetamol, which leads to accumulation of the active substance. Concomitant use of paracetamol and alcohol may increase the hepatotoxicity of paracetamol. 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).

Pseudoephedrine
Pseudoephedrine may partially reverse the hypotensive action of drugs which interfere with sympathetic activity (methyldopa, alpha- and beta-adrenergic blocking agents).
Concomitant use of pseudoephedrine with tricyclic antidepressants, sympathomimetic agents or MAO inhibitors and the use of pseudoephedrine 2 weeks after the end of the treatment with MAO inhibitors, may cause hypertensive crisis, headache, hyperpyrexia and severe cardiac arrhythmias.
When dihydroergotamine and pseudoephedrine are taken at the same time, blood pressure may increase significantly.

Dextromethorphan
Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).
CYP2D6 inhibitors: Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multi-fold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Alcohol may emphasise dextromethorphan adverse reactions, as well as paracetamol hepatotoxicity.

Ascorbic acid
The simultaneous use of ascorbic acid with acetylsalicylic acid leads to increased excretion of ascorbic acid and decreased excretion of acetylsalicylic acid in urine and consequently increased plasma concentration of acetylsalicylic acid.

Concomitant use of ascorbic acid and phenothiazines (fluphenazine) can reduce plasma fluphenazine concentration and its effectiveness.

4.6 Pregnancy and lactation

Pregnancy
Although paracetamol, pseudoephedrine and dextromethorphan have been in widespread use for many years without apparent ill consequence, there are no specific data on their use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment to the mother against any possible hazards to the developing foetus.

Lactation
Pseudoephedrine is excreted in breast milk in small amounts but the effect of this on breast-fed infants is not known. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

Caffetin COLD can cause drowsiness and dizziness in some patients and can have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events that may occur with Caffetin Cold are given by system organ class and frequency.
Frequencies are defined as:
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).

Blood and lymphatic system disorders
Very rare: thrombocytopenia, leukopenia, agranulocytosis.

Immune system disorders
Very rare: hypersensitivity reactions, especially skin rashes, itching, urticaria.

Psychiatric disorders
Rare: restlessness, excitability, drowsiness, insomnia.

Nervous system disorders
Rare: headache, dizziness.
Very rare: tremor.

Eye disorders

Not known: ischaemic optic neuropathy.

Cardiac disorders
Rare: tachycardia

Vascular disorders
Rare: hypertension.
Gastrointestinal disorders:
Rare: dry mouth, nausea, vomiting.
Very rare: epigastric pain.
Not known: ischaemic colitis.
Skin and subcutaneous tissue disorders
Very rare: cases of serious skin reactions (related with paracetamol).
Not known: severe skin reactions, including acute generalized exanthematous pustulosis (AGEP).

Treatment should be discontinued if severe side effects occur.

4.9 Overdose

Paracetamol

Symptoms and signs:
Significantly higher doses of paracetamol than recommended (in adults > 7.5 g) can cause severe damage to the liver and less often to the kidneys. Signs of an acute overdose appear in the first 24 hours as nausea, vomiting, increased sweating and abdominal pain. Signs of liver damage appear only 2 to 4 days after the overdose. Liver failure, encephalopathy, coma and death may occur. Complications include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. An increase in prothrombin time is a reliable sign of impaired liver function.

Management
Treatment is symptomatic. The specific antidote for paracetamol overdose is N-acetylcysteine, which should be given within the first 12 to 24 hours after the overdose.

Pseudoephedrine

Symptoms and signs:
After taking an overdose of pseudoephedrine, adverse effects increase especially restlessness, irritability, tremor, hallucinations, convulsions, hypertension, cardiac arrhythmias, nausea and vomiting. The symptoms are usually occur 4 to 8 hours after overdose and are transient.

Management
Treatment is usually not necessary.

Dextromethorphan

Symptoms and signs:
With acute overdose of dextromethorphan, except for ingestion of very large amounts, serious side effects are rare. Dextromethorphan overdose may be associated with nausea, vomiting, drowsiness, dizziness, irritability, hyperactivity, , dystonia, agitation, insomnia, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, urinary retention, breathing difficulties, toxic psychosis with visual hallucinations, numbness, hyperexcitability.
In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Management
Asymptomatic patients who have overdosed on dextromethorphan in the past hour may receive activated charcoal. For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

Ascorbic acid

Symptoms and signs:
High doses of ascorbic acid can cause increased urinary excretion of oxalic acid salts, lowering of urine pH and their precipitation, and hemolytic anemia in patients with deficiency of the enzyme glucose-6-phosphate dehydrogenase.
Indigestion is the most common side effect of excessive intake of ascorbic acid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides, paracetamol, combinations excl. psycholeptics
ATC code: N02BE51

Paracetamol is an analgesic and antipyretic. The therapeutic effects of paracetamol are thought to be related to inhibition of prostaglandin synthesis, as a result of inhibition of cyclo-oxygenase enzyme.

Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory decongestant. Pseudoephedrine produces its decongestant effect within 30 minutes persisting for at least 4 hours.

Dextromethorphan provides antitussive activity by acting on the medullary cough centre.

Ascorbic acid is a water-soluble vitamin, necessary for collagen formation and tissue repair in the body. Ascorbic acid may be beneficial during infection when vitamin C levels are believed to fall.

5.2 Pharmacokinetic properties

Absorption
Absorption of paracetamol occurs mainly in the small intestine, but gastric emptying is the rate-limiting step in the absorption. Peak plasma concentrations usually occur between 0.5-1.5 hours after oral ingestion.
Pseudoephedrine is well absorbed following oral administration. Peak plasma concentrations occur at approximately 1.5-2.0 hours after oral ingestion.
Dextromethorphan is well absorbed following oral administration with peak plasma levels being seen 2 hours post dose.
Ascorbic acid is readily absorbed from the gastrointestinal tract.

Distribution
Paracetamol is distributed uniformly throughout most body fluids, with an estimated volume of distribution of 0.95 l/kg.
The apparent volume of distribution of pseudoephedrine is approximately 2.8 l/kg.
Ascorbic acid is widely distributed in the body tissues.

Metabolism and elimination
Paracetamol is metabolised by the liver into glucuronide and sulphate conjugates. About 10% of administered paracetamol is converted to a reactive metabolite, acetamidoquinone. This metabolite is rapidly conjugated with glutathione. When large amounts of paracetamol are taken, hepatic glutathione may become depleted causing excessive accumulation of acetamidoquinone leading to hepatic necrosis. The plasma half-life of paracetamol after therapeutic doses is 1.5-2.5 hour.
Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine. The plasma half-life is approximately 5.5 hours.
Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration, by N- and O-demethylation followed by sulphate or glucuronic acid conjugation. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.
It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-Nmethylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.
Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.
It is excreted unchanged and as metabolites in the urine.
Ascorbic acid is reversibly oxidised to dehydroascorbic acid, some is metabolised to ascorbate-2-sulphate; it is excreted in the urine.

Pharmacokinetics in renal impairment

Marked accumulation of the paracetamol glucuronide and sulphate conjugates occurs in chronic renal failure.
In patients with renal impairment, C_{max} for pseudoephedrine increases approximately 1.5 fold, and the half-life of elimination increased 3 -12 fold.

Pharmacokinetics in hepatic impairment
The plasma paracetamol half-life is significantly prolonged (approximately 75%) in patients with severe liver impairment, but clinical significance is unclear, since there is no evidence of hepatotoxicity in patients with liver disease.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the patients which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Starch, pregelatinised
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Silica, colloidal anhydrous
Talc
Magnesium stearate
Film coating:
Opadry II White (polyvinyl alcohol – partially hydrolyzed; macrogol 3350; titanium dioxide (E171); talc);
Opadry II Blue (polyvinyl alcohol – partially hydrolyzed; macrogol 3350; titanium dioxide (E171); talc; FD&C Blue No.2/Indigo carmine aluminium lake (E132)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two (2) years.

6.4 Special precautions for storage

Store below 25°C, in the original package.

6.5 Nature and contents of container

Caffetin COLD film-coated tablets are immediate packed in press-through blisters (Al foil/PVC/PVDC foil) perforated for individual doses, each blister containing 10 film-coated tablets.
The cardboard box contains 10 film-coated tablets (1 blister) and a patient information leaflet.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORIZATION 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 AUTHORIZATION NUMBER(S)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT