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**VARIATIONS APPLIED**  
**Order of the Ministry of**  
**Health of Ukraine**  
**12.10.2020 No. 2313**

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**CITROPAK®-DARNITSA**

***Qualitative and quantitative composition:***

*active substances:* acetylsalicylic acid; paracetamol; caffeine;

1 tablet contains acetylsalicylic acid 240 mg, paracetamol 180 mg, caffeine 30 mg;

*excipients:* citric acid monohydrate, potato starch, povidone, calcium stearate.

**Pharmaceutical form.** Tablets.

*Basic physical and chemical properties:* white to white with creamy or pinkish, flat faced, beveled tablets with scored line.

**Pharmacotherapeutic group.** Analgesics and antipyretics. Acetylsalicylic acid, combinations without psycholeptics. ATC code N02B A51.

***Pharmacological properties.***

*Pharmacodynamic properties.*

Fixed combination.

Due to the presence of acetylsalicylic acid and paracetamol in the tablet, the drug has anti-inflammatory, antipyretic and analgesic effects.

The substances potentiate the effects of each other.

Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory effects, reduces pain, especially caused by inflammation, and moderately inhibits platelet aggregation and thrombogenesis, improves microcirculation in the inflammatory focus.

The antipyretic effect of acetylsalicylic acid is the CNS-mediated inhibition of the PGF2 synthesis in the hypothalamus in response to the exposure to endogenous pyrogens.

Analgesic effect has both peripheral and central origin: the peripheral effect is the inhibition of prostaglandin production in inflamed tissues; the central effect is the impact on hypothalamus centers.

Paracetamol has analgesic, antipyretic and mild anti-inflammatory effects, which are associated with its impact on the thermoregulatory center in the hypothalamus, and a less pronounced ability to inhibit production of prostaglandins in tissues.

Caffeine increases the spinal reflex excitability, stimulates the respiratory and hemodynamic centers, dilates blood vessels of the skeletal muscles, brain, heart, kidneys, reduces platelet aggregation; reduces somnolence, fatigue, increases mental and physical performance. Caffeine weakens effects of hypnotics and narcotics, enhances the action of analgesics and antipyretics.

In this combination, low-dose caffeine has virtually no stimulating effect on the central nervous system, however helps to improve the tone of blood vessels in the brain and speed up the blood flow.

*Pharmacokinetic properties.*

Acetylsalicylic acid.

Acetylsalicylic acid is rapidly and completely absorbed after oral administration. It is mainly hydrolyzed in the gastrointestinal tract, liver and blood to salicylate which is then metabolized primarily in the liver.

Paracetamol.

Paracetamol is absorbed from the gastrointestinal tract with peak plasma concentration 30 to 120 minutes after administration. It is metabolized in the liver and excreted mainly in the urine as the glucuronide and sulfate conjugates. Less than 5 % is excreted as unchanged paracetamol. The elimination half-life is 1 to 4 hours. Plasma protein binding is insignificant at usual therapeutic concentrations but increases with increasing concentrations.

Side hydroxylated metabolite which is usually produced in very small amounts in the liver and usually detoxified by conjugation with liver glutathione may be accumulated following paracetamol overdose and cause liver damage.

Caffeine.

Caffeine peak concentration occurs between 5 and 90 minutes after administration of Citropak®-Darnitsa under fasting condition. There is no evidence of pre-systemic metabolism. In adults, the drug almost completely is metabolised in the liver. The elimination rate in adults is variable. The mean plasma half-life is 4.9 hours with a range of 1.9 to 12.2 hours. Caffeine is uniformly distributed in all body fluids. The mean plasma protein binding of caffeine is 35 %.

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). Among related metabolites include 1-methyluric acid and 5-acetylamino-6-formylamino-3-methyluracil (AFMU).

No cross-interaction of the three active ingredients, as well as no increased risk of interaction with other drugs when using the active ingredients in combination has been observed. Due to the combination of three active substances, the content of either of them is set low, which, accordingly, reduces the drug toxicity.

**Clinical particulars.**

***Therapeutic indications.***

Treatment of mild to moderate pain: headache or toothache, primary dysmenorrhea, migraine, arthralgia, neuralgia, diseases accompanied by hyperthermia of various origin (as an antipyretic drug).

***Contraindications.***

- Hypersensitivity to any of the drug ingredients; hypersensitivity to other xanthine derivatives (theophylline, theobromine), other salicylates;
- medical history of asthma, urticaria or rhinitis caused by acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs;
- erosive and ulcerative gastrointestinal lesions (in the phase of exacerbation), gastrointestinal bleeding or perforation, and history of gastric ulcer;
- blood disorders: hemophilia, hemorrhagic diathesis, hypoprothrombinemia, anemia, leukopenia, increased bleeding tendency, thrombosis, thrombophlebitis, hemorrhagic diseases;
- severe renal or hepatic failure, portal hypertension, congenital hyperbilirubinemia, Gilbert's syndrome;
- glucose-6-phosphate dehydrogenase deficiency;

- organic cardiovascular disorders (in particular, severe atherosclerosis), arrhythmias, cardiac conduction disorders, paroxysmal tachycardia, severe arterial hypertension, severe coronary heart disease, acute myocardial infarction, decompensated heart failure, tendency to vasoconstriction;
- glaucoma, hyperthyroidism, acute pancreatitis, prostatic hypertrophy, severe diabetes mellitus;
- co-administration with monoamine oxidase inhibitors (MAO) and during 2 weeks after discontinuation of MAO inhibitors; concomitant use with tricyclic antidepressants or  $\beta$ -blockers;
- alcoholism, epilepsy, increased excitability, sleep disturbances;
- combination with methotrexate at a dose of  $\geq 15$  mg/week;
- surgical interventions accompanied by major bleeding;
- age over 60 years.

***Special warnings and precautions for use.***

For short-term use. The indicated doses should not be exceeded. This medicinal product should not be combined with other agents containing acetylsalicylic acid or paracetamol.

It is not recommended to use Citropak®-Darnitsa for more than 5 days as an analgesic and more than 3 days as an antipyretic without consulting a doctor.

Citropak®-Darnitsa should not be used in patients with migraine attacks if  $> 20\%$  of the cases are associated with vomiting or if  $> 50\%$  of migraine attacks cases require the bed regime.

If a patient with migraine does not feel better after taking the first 2 tablets of Citropak®-Darnitsa, he/she should seek medical advice.

This medicine should not be used in patients who had headache episodes for 10 days a month during the last 3 months or more.

Caution should be exercised in patients who are at risk of dehydration (for example, in case of vomiting, diarrhea, and before or after major surgery).

Due to its pharmacodynamic properties, Citropak®-Darnitsa can mask the signs and symptoms of infection.

Citropak®-Darnitsa should be used with caution in patients with mild to moderate liver or kidney insufficiency.

***Associated to acetylsalicylic acid.***

Due to acetylsalicylic acid-induced inhibition of platelet aggregation, which persists for several days after administration, the drug may increase the bleeding tendency during and after surgery (including minor surgeries such as tooth extraction). Prior to surgical intervention patients should inform their doctor about the use of the drug. The drug should be discontinued 5 to 7 days before elective surgery.

Low-dose acetylsalicylic acid reduces the excretion of uric acid. In predisposed patients, it can cause a gout attack. The drug should be used with caution in patients with gout and kidney or liver disease, dehydration and diabetes mellitus.

Alcohol should be avoided during the treatment (increased risk of gastrointestinal bleeding).

The drug should be used with extreme caution in the following cases: past history of gastrointestinal ulcers as well as chronic or recurrent peptic ulcer; concomitant treatment with anticoagulants; negative progression of kidney function; negative progression of liver function, congenital hyperbilirubinemias (Gilbert's syndrome, Dubin-Johnson syndrome and Rotor's syndrome); elderly patients. Citropak®-Darnitsa should not be combined with anticoagulants or other drugs that inhibit platelet aggregation. The patients with coagulation disorders should be closely monitored. Caution should be exercised when the drug is used in patients with metrorrhagia or menorrhagia.

If a patient develops gastrointestinal bleeding or ulceration during therapy, Citropak®-Darnitsa should be discontinued immediately. The risk of bleeding may increase with alcohol, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) use.

In patients with impairment of liver and kidney function, the dose should be reduced or dosing interval increased. In patients with hepatic and renal impairment, the dosing interval should be at least 8 hours.

Since acetylsalicylic acid, like all non-selective nonsteroidal anti-inflammatory drugs, irritates the digestive tract mucosa, the drug should be taken only after meals with water, alkaline mineral water, sodium bicarbonate solution (preferably milk).

With long-term treatment, fecal blood should be monitored for ulcerogenic effects and blood tests (effects on platelet aggregation, some anticoagulant activity) should be performed.

For hyperthermia, the drug should be administered only if other analgesic-antipyretic agents are ineffective since there is a risk of Reye's syndrome. If drug-related vomiting occurs, Reye's syndrome should be suspected.

The drug should be used with caution in the treatment of patients with allergic rhinitis, nasal polyps, and urticaria.

Patients with allergic complications, including asthma, allergic rhinitis, urticaria, pruritus, mucosal edema, hay fever, and their association with chronic respiratory infections, and patients with hypersensitivity to nonsteroidal anti-inflammatory drugs may develop bronchospasm or asthma attack.

#### *Associated to paracetamol*

Citropak®-Darnitsa should be used with caution in patients with impaired kidney or liver function or alcohol dependence.

The risk of paracetamol toxicity is increased in patients taking other potentially hepatotoxic drugs or agents that induce microsomal liver enzymes (e.g., rifampicin, isoniazid, chloramphenicol, hypnotics and antiepileptics, including phenobarbitone, phenytoin, and carbamazepine). Patients with history of alcohol dependence are at particular risk of liver damage.

#### *Associated to caffeine*

Citropak®-Darnitsa should be used with caution in patients with gout and hyperthyroidism.

During treatment with Citropak®-Darnitsa, a patient should limit the consumption of products containing caffeine since excessive concentrations of caffeine may cause nervousness, irritability, insomnia and periodic episodes of tachycardia.

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

Possible forms of interactions of active substances.

#### *Acetylsalicylic acid (ASA)*

<i>Combination of acetylsalicylic acid with</i>	<i>Possible outcome</i>
Ibuprofen	Concomitant use of ibuprofen prevents irreversible inhibition of platelets by acetylsalicylic acid. Treatment with ibuprofen in patients who are at risk for cardiovascular diseases may limit the cardioprotective effect of acetylsalicylic acid.
Other nonsteroidal anti-inflammatory drugs (NSAIDs)	There is an increased risk of GI ulcers and bleeding due to synergic effects. If concurrent use is required, gastroprotection should be considered. Therefore, such combination is not recommended.

Corticosteroids	There is an increased risk of GI ulcers and bleeding due to synergic effects. It is advisable to consider the gastroprotection in patients taking ASA and corticosteroids, especially if they are elderly. Systemic glucocorticosteroids reduce blood salicylate levels and increase the risk of overdose after the treatment. Therefore, such combination is not recommended.
Oral anticoagulants (e.g., coumarin derivatives)	Acetylsalicylic acid may increase the anticoagulant effect. Clinical and laboratory monitoring of bleeding time and prothrombin time should be performed. Therefore, such combination is not recommended.
Thrombolytics	There is an increased risk of bleeding. Particularly, treatment with ASA should not be initiated within the first 24 hours after treatment with alteplase in patients with acute stroke. Therefore, such combination is not recommended.
Heparin	There is an increased risk of bleeding. Clinical and laboratory monitoring of bleeding time should be performed. Therefore, such combination is not recommended.
Platelet aggregation inhibitors (ticlopidine, clopidogrel, cilostazol)	There is an increased risk of bleeding. Clinical and laboratory monitoring of bleeding time should be performed. Therefore, such combination is not recommended.
Selective serotonin reuptake inhibitors (SSRIs)	SSRIs may inhibit coagulation or affect platelet function when co-administered with ASA, leading to bleeding complications in general, and, in particular, to a gastrointestinal bleeding. Therefore, concomitant use should be avoided.
Digoxin	Concurrent use increases the plasma concentration of digoxin due to decreased renal excretion.
Phenytoin	ASA increases serum levels of phenytoin. Serum phenytoin levels should be closely monitored.
Valproate	Acetylsalicylic acid inhibits valproate metabolism, hence, it may increase its toxicity. Serum valproate levels should be closely monitored.
Aldosterone antagonists (spironolactone, canrenoate)	Acetylsalicylic acid may reduce their activity due to inhibition of sodium excretion in the urine. Blood pressure should be closely monitored.
Loop diuretics (e.g., furosemide)	Acetylsalicylic acid may reduce their activity 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 ASA, adequate hydration of the patient should be ensured and the kidney function and blood pressure, particularly when starting diuretic treatment, should be monitored.

Antihypertensive drugs (ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers)	Acetylsalicylic acid may reduce their activity due to competition and inhibition of urinary prostaglandins. This combination may lead to acute kidney failure in the elderly or dehydrated patients. At the start of treatment, it is recommended to monitor blood pressure and kidney function tests and ensure adequate hydration of the patient. The bleeding time should be also monitored when co-administered with verapamil.
Uricosurics (e.g., probenecid, sulfinpyrazone)	Acetylsalicylic acid may reduce their activity due to inhibition of tubular resorption leading to high plasma levels of ASA and uric acid.
Methotrexate $\leq 15$ mg/week	The administration of methotrexate at doses $\geq 15$ mg/week increases the hematological toxicity of methotrexate (decrease in renal clearance of methotrexate by anti-inflammatory agents and displacement of methotrexate by salicylates due to plasma protein binding). The concomitant use of NSAIDs is therefore not recommended in patients treated with high-dose methotrexate. The risk of interactions between methotrexate and NSAIDs should also be considered for patients who take low-dose methotrexate, especially those with renal impairment. If combined treatment is required, complete blood count, liver and kidney function tests should be monitored, especially during the first days of such treatment.
Sulphonylureas and insulin	Acetylsalicylic acid increases their hypoglycemic effect, thus some down-titration of the dose of the anti-diabetic medication may be appropriate if high doses of salicylates are used. Very close monitoring of blood glucose levels is recommended.
Alcohol	There is an increased risk of gastrointestinal bleeding. Such combination should be avoided.

#### Paracetamol

<i>Combination of paracetamol with</i>	<i>Possible outcome</i>
Liver enzyme inducers or potentially hepatotoxic substances (e.g., alcohol, rifampicin, isoniazide, hypnotics and antiepileptics including phenobarbitone, phenytoin and carbamazepine, salicylamide and other stimulants of microsomal oxidation)	Increased toxicity of paracetamol that may lead to liver damage even with otherwise harmless doses of paracetamol. Therefore, liver function tests should be monitored. Concomitant use is not recommended.
Chloramphenicol	There is 5-fold increase of excretion time of chloramphenicol due to paracetamol. Paracetamol may increase the risk of elevated chloramphenicol plasma concentrations. Concomitant use is not

	recommended.
Zidovudine	Paracetamol may increase the tendency to neutropenia, therefore, monitoring of hematopoiesis should be performed. Concomitant use is not recommended unless monitored by a doctor.
Probenecid	Probenecid reduces paracetamol clearance, thus, paracetamol doses should be decreased when combined with this agent. Concomitant use is not recommended.
Oral anticoagulants	The repeated use of paracetamol for more than one week increases anticoagulant effects. Sporadic use of paracetamol does not have a significant effect on coagulation.
Propantheline or other agents that lead to delayed gastric emptying	These agents lead to slower absorption of paracetamol. The analgesic effect may be delayed and less pronounced.
Metoclopramide or other agents that lead to acceleration of gastric emptying	These active substances accelerate the absorption of paracetamol increasing its efficacy and speed up the onset of analgesia.
Cholestyramine	Cholestyramine reduces the absorption of paracetamol, therefore, it should not be given within 1 hour of paracetamol administration if maximal analgesia is to be achieved.

### Caffeine

<i>Combination of caffeine with</i>	<i>Possible outcome</i>
MAO inhibitors	Co-administration of caffeine may lead to a dangerous increase in blood pressure, so such combination is contraindicated.
Hypnotic agents (e.g., benzodiazepines, barbiturates, antihistamines)	Concomitant use can reduce the hypnotic effect or inhibit the anticonvulsive effects of barbiturates. Therefore, the concomitant use is not recommended. If such treatment is required, the combination may be more beneficial if taken in the morning.
Lithium agents	Caffeine lowers the concentration of lithium in the blood. Caffeine withdrawal increases serum lithium levels since caffeine may increase renal clearance of lithium. Therefore, when caffeine is withdrawn, it may be necessary to reduce the dose of lithium. Therefore, the concomitant use is not recommended.
Disulfiram	Patients with alcohol dependence who receive disulfiram therapy should be warned to avoid the use of caffeine in order to prevent the risk of alcohol abstinence syndrome worsening due to caffeine-induced cardiovascular and cerebral excitation.
Ephedrine-type substances	Their combination increases the risk of dependence development. Therefore, the concomitant use is not recommended.
Sympathomimetics or levothyroxine	Their combination may have an enhanced tachycardic effect due to synergic effects. Therefore, the concomitant use is not recommended.
Theophylline	Co-administration may reduce the excretion of theophylline.
Quinolone antibacterials (ciprofloxacin, enoxacin, and pefloxacin), terbinafine, cimetidine,	Increased caffeine half-life due to inhibition of the liver cytochrome P450 pathway. Therefore, patients with hepatic impairment, cardiac arrhythmias or latent epilepsy should avoid caffeine intake.

fluvoxamine and oral contraceptives	
Nicotine, phenytoin and phenylpropanolamine	These substances decrease the half-life of caffeine.
Clozapine	Caffeine increases the serum levels of clozapine probably due to the interaction through both pharmacokinetic and pharmacodynamic mechanisms. Clozapine serum levels should be monitored. Therefore, the concomitant use is not recommended.
Analgesic-antipyretic agents	Their effects become enhanced (improves bioavailability).
Ergotamine	Concomitant use of caffeine together with ergotamine improves the absorption of ergotamine from the gastrointestinal tract.
Derivatives of xanthine, alpha- and beta-adrenomimetics, psychostimulants	It potentiates the effects of xanthine derivatives, alpha- and beta-adrenomimetics, and psychostimulants.

*Effect on laboratory tests:*

- High doses of acetylsalicylic acid can affect the results of several clinical and chemical laboratory tests.
- Paracetamol may affect the results of the uric acid test when using the phosphotungstic acid method as well as results of tests for glycemia when using the glucose oxidase/peroxidase method.
- Caffeine can reverse the effects of dipyridamole on myocardial blood flow, thereby interfering with the results of this test. It is recommended that the administration of caffeine is suspended at least 8 till 12 hours prior to the test.

***Special warnings and precautions for use.***

*Regarding paracetamol:* prior to the use of the drug, a doctor should be consulted if the patient is taking warfarin or similar drugs that have an anticoagulant effect, as well as when the patient has liver or kidney disease.

The risk of overdose is greater in patients with non-cirrhotic alcoholic liver disease. The medicinal product may affect the results of laboratory tests for blood glucose and uric acid.

Patients who take analgesics every day for mild arthritis should consult a doctor. In patients with severe infections such as sepsis, which are associated with the depleted glutathione levels, paracetamol increases the risk of metabolic acidosis. Symptoms of metabolic acidosis are deep, rapid or difficult breathing, nausea, vomiting, and loss of appetite. If such symptoms occur, medical advice should be sought immediately.

Excessive amounts of caffeinated beverages (e.g., coffee, tea, etc.) are not recommended during treatment with the medicinal product. This can result in sleep disturbances, tremor, chest discomfort due to palpitations.

The indicated doses of the drug should not be exceeded.

Do not take with other paracetamol-containing medicines.

If symptoms persist, medical advice should be sought.

If headache persists, medical advice should be sought.

*Regarding acetylsalicylic acid:* caution should be exercised in patients with impaired renal function or cardiovascular disorders (e.g., renal vascular disease, congestive heart failure, hypovolemia, major surgeries, sepsis or heavy bleedings) since acetylsalicylic acid may also increase the risk of renal impairment and acute renal failure.

Ibuprofen may reduce the inhibitory effect of acetylsalicylic acid on platelet aggregation. If the drug is used prior to ibuprofen as an analgesic, the patient should consult a doctor.

Medicines containing acetylsalicylic acid should not be used in children with acute respiratory viral infection (ARVI), whether or not accompanied by fever. Some viral diseases, especially influenza A, influenza B, and chickenpox pose the risk of Reye's syndrome which requires immediate medical attention. The risk may rise if acetylsalicylic acid is used as a concomitant medicine but a causal relationship has not been established. If these conditions are associated with prolonged vomiting, it may be a sign of Reye's syndrome. Keep the medicine out of sight and reach of children.

*Fertility, pregnancy and lactation.*

The medicinal product should not be used during pregnancy.

Acetylsalicylic acid has a teratogenic effect; it leads to the malformation such as cleft palate when used during the I trimester of pregnancy, and to inhibition of labor (inhibition of prostaglandin production), closure of ductus arteriosus in the fetus causing pulmonary hyperplasia and hypertension in blood vessels of small circulation, renal impairment with possible subsequent renal failure with oligohydramnios, bleeding time prolongation, antiplatelet effect which may occur even after very low doses, when used in the III trimester.

Caffeine increases the risk of spontaneous abortion.

Breast-feeding should be discontinued during treatment. The drug is excreted into breast milk that increases the risk of bleeding in babies due to platelet dysfunction.

*Effects on ability to drive and use machines.*

With high-dose treatment, driving or using other machines should be avoided due to possible adverse CNS reactions (dizziness, psychomotor agitation and disorientation and impaired attention).

***Posology and method of administration.***

Citropak<sup>®</sup>-Darnitsa should be taken as one tablet 2 to 3 times daily after meals. The maximum daily dose is 6 tablets (2 tablets 3 times daily). Citropak<sup>®</sup>-Darnitsa tablets should not be used for more than 5 days as an analgesic and more than 3 days as an antipyretic.

The recommended dose should not be exceeded. Do not take with other paracetamol-containing medicines.

Drink a full glass of water with each dose.

Although the effects of liver or kidney disease on the pharmacokinetics of Citropak<sup>®</sup>-Darnitsa have not been evaluated, the drug may enhance the renal or hepatic impairment due to the mechanism of action of acetylsalicylic acid and paracetamol and that should be taken into account by patients with liver or kidney failure. Thus, Citropak<sup>®</sup>-Darnitsa is contraindicated in patients with severe liver or kidney failure and should be used with caution in patients with mild to moderate liver or kidney failure.

*Children.*

The drug is contraindicated in children under 16 years of age unless specifically indicated otherwise (Kawasaki disease).

***Overdose.***

Symptoms of overdose may occur with long-term use of the drug or when used in doses which are many times higher than recommended.

Since Citropak<sup>®</sup>-Darnitsa is a fixed combination the overdose should be considered for each active substance contained in it.

*Acetylsalicylic acid.*

Salicylate poisoning is usually associated with plasma concentrations > 350 mg/L (2.5 mmol/l). Most deaths occur in patients whose ASA concentrations are > 700 mg/l (5.1 mmol/l). Single doses lower than 100 mg/kg per BW are unlikely to cause serious poisoning.

Symptoms of an overdose. Adverse reactions such as nausea, vomiting, dehydration, tinnitus, dizziness, deafness, hyperhidrosis, burning sensation in the extremities, tachycardia, premature beats and hyperventilation, and acid-base imbalance are very common. Mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH is observed in adults and children. Acidosis can increase salicylate transfer across the blood-brain barrier.

Less common are hematemesis, hyperpyrexia, hypoglycemia, hypokalemia, thrombocytopenia, increased prothrombin time, intravascular coagulation, renal failure, and non-cardiac pulmonary edema. CNS adverse reactions such as disorientation, psychomotor excitation or depression of the central nervous system, somnolence, impaired consciousness, dizziness, tremor, hyperreflexia, convulsions and coma may develop.

*Symptoms of an overdose with acetylsalicylic acid.*

Salicylate toxicity may be a result of intoxication due to long-term use of therapeutic doses or acute intoxication (with > 100 mg/kg/day for more than 2 days) which is potentially life-threatening (from accidental ingestion by children to accidental poisoning).

Chronic salicylate poisoning may be asymptomatic since it has no specific symptoms. Moderate salicylate intoxication or salicylism usually develops only after repeated administration of high doses.

Symptoms: dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and decreased consciousness may be controlled by the dose down-titration. Tinnitus can occur at the plasma concentration of 150 to 300 µg/ml. Severe side effects occur at concentration > 300 µg/ml. The main feature of acute poisoning is a severe acid-base imbalance which may vary with age and severity of intoxication. The most common symptom in children is metabolic acidosis. The severity of poisoning may not be assessed using only plasma concentrations. Absorption of acetylsalicylic acid may be slowed due to inhibition of gastric emptying, formation of gastric stones or due to the use of gastro-resistant medicines.

Emergency care for acetylsalicylic acid poisoning is based on the severity, stage and clinical symptoms and corresponds to the standard methods of emergency care for poisoning. Urgent measures should be aimed at accelerating drug elimination as well as at restoring electrolyte and acid-base balance.

Due to the complex pathophysiological effects of salicylate poisoning, some symptoms and laboratory abnormalities may occur.

Mild and moderate poisoning: tachypnea, hyperventilation, respiratory alkalosis, sweating, nausea, and vomiting. Laboratory findings: alkalosis, alkaluria.

Severe poisoning: respiratory alkalosis with compensatory metabolic acidosis, hyperpyrexia, tinnitus, deafness. Respiratory disorders: from hyperventilation, non-cardiac pulmonary edema to respiratory arrest and asphyxia; laboratory findings: alkalosis, alkaluria. Cardiovascular disorders: from cardiac arrhythmias, hypotension to cardiac arrest. Fluid and electrolyte loss: dehydration, oliguria, renal failure. Laboratory findings: hypokalemia, hypernatremia, hyponatremia, changes in renal function, prolonged prothrombin time, hypoprothrombinemia. Impaired glucose metabolism, ketosis manifests in laboratory tests as hyperglycemia, hypoglycemia (especially in children), increased levels of ketone bodies. Gastrointestinal disorders: gastrointestinal bleedings. Blood abnormalities: from platelet suppression to coagulopathies.

Neurological disorders: toxic encephalopathy and CNS depression from lethargy, depression of consciousness to coma and seizures.

*Symptoms of an overdose with paracetamol.* Liver damage is possible in adults who have taken ≥ 10 g of paracetamol or in children who have taken more than 150 mg/kg per body weight.

In patients with risk factors (prolonged treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's wort or other liver enzyme-inducing medicinal products; regular consumption of excessive amounts of ethanol; glutathione cachexia (digestive disorders, mucoviscidosis, HIV infection, starvation, cachexia), intake of ≥ 5 g of paracetamol may cause liver damage.

**Symptoms of an overdose.** Within the first 24 hours following symptoms occur: nausea, vomiting, loss of appetite, anorexia, abdominal pain, and skin pallor. Liver damage, impaired glucose metabolism, and metabolic acidosis may occur within 12 to 48 hours. With a significant overdose, liver disorders can cause encephalopathy, hemorrhages, hypoglycemia, cerebral edema, coma, and death. Acute renal failure with acute tubular necrosis can manifest as severe low back pain, hematuria, proteinuria and may develop even in the absence of severe kidney damage.

With the long-term use of the medicinal product in high doses, hematopoietic disorders such as aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, and thrombocytopenia may develop.

Also, hyperhidrosis, somnolence, impaired consciousness, tachycardia, premature beats, tremor, hyperreflexia, convulsions, cardiac arrhythmias, pancreatitis, psychomotor agitation or central nervous system depression have been reported. With higher doses, urinary tract disorders have been reported: nephrotoxicity (renal colic, interstitial nephritis, capillary necrosis); central nervous system disorders: dizziness, disorientation, psychomotor agitation.

**Treatment.** Acute medical management is required in the event of an overdose. The patient should be taken to a hospital immediately, even if there are no early symptoms of an overdose. Symptoms may be limited to nausea and vomiting or may not reflect the severity of an overdose or the risk of organ damage. Plasma paracetamol concentration should be measured in 4 hours or later after dosing (earlier concentrations are unreliable). Treatment should start with gastric lavage followed by activated charcoal (if an excessive dose has been taken within the last 1 hour) and symptomatic therapy. N-acetylcysteine is a specific antidote for a paracetamol overdose. If there is no vomiting, the administration of oral methionine or intravenous N-acetylcysteine is effective within the first 24 hours, however, the maximum protective effect is achieved within 8 hours after an overdose. The efficacy of the antidote declines drastically after this time passes. General supportive measures should be taken as well. If necessary, alpha-blockers may be used.

**Symptoms of an overdose with caffeine.** Central and peripheral nervous system disorders: irritability, nervousness, restlessness, insomnia, dizziness, increased emotional excitability, involuntary muscle contractions, convulsions, and rapid breathing. Gastrointestinal disorders: gastric or abdominal pain. Cardiovascular disorders: tachycardia, arrhythmia. Other: flushing, frequent urination.

**Treatment.** Gastric lavage, ipecacuanha preparations in case of suppression of the vomiting reflex, activated charcoal, high cleansing enema, correction of acid-base balance and plasma electrolytes, forced diuresis, oxygen therapy, hemodialysis in severe cases. Symptomatic therapy. Diazepam is used for convulsions.

In the first hours of acute poisoning, acetylcysteine is administered at a dose of 140 mg/kg if oral route is possible; if oral route is impossible, the first intravenous dose is 150 mg/kg, then the dose is increased up to 300 mg/kg/day.

### ***Undesirable effects.***

Some patients may experience side effects specific to acetylsalicylic acid, paracetamol or caffeine.

Most of the following side effects are clearly dose-dependent and vary from one person to another.

Possible side effects:

	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000
<i>Infections and infestations</i>			Pharyngitis

<i>Eye disorders</i>			Eye pain; visual disturbance
<i>Ear and vestibular disorders</i>		Tinnitus	
<i>Respiratory, thoracic and mediastinal disorders</i>			Epistaxis; hypoventilation; rhinorrhea
<i>Gastrointestinal disorders</i>	Nausea; abdominal discomfort	Dry mouth; diarrhea; vomiting	Decreased appetite; burping; bloating; dysphagia; oral paresthesia; drooling
<i>Nervous system disorders</i>	Dizziness	Tremor; paresthesia; headache; anxiety	Dysgeusia; impaired attention; amnesia; abnormal coordination; hyperesthesia; sinus headache
<i>Psychiatric disorders</i>	Nervousness	Insomnia	Anxiety; euphoric mood; tension
<i>Cardiovascular disorders</i>		Arrhythmia	Hyperemia; peripheral vascular disorders
<i>Skin and subcutaneous tissue disorders</i>			Hyperhidrosis; pruritus; urticaria
<i>Musculoskeletal and connective tissue disorders</i>			Musculoskeletal stiffness; neck pain; back pain; muscle cramps
<i>General disorders</i>		Fatigue;	Malaise; chest discomfort
<i>Laboratory findings</i>		Increased heart rate	

Data on side effects obtained during post-marketing research (frequency unknown):

*Ear and vestibular disorders:* deafness, disorientation.

*Respiratory, thoracic and mediastinal disorders:* rhinitis, nasal congestion, dry cough, dyspnea, asthma, bronchospasm in patients sensitive to acetylsalicylic acid and other NSAIDs.

*Gastrointestinal disorders:* dyspeptic disorders, including nausea, vomiting, epigastric discomfort and pain, heartburn, abdominal pain, gastralgia; gastrointestinal inflammation, erosive and ulcerative gastrointestinal lesions which can cause gastrointestinal bleeding and perforation with corresponding laboratory and clinical signs in separate cases, oral mucosal ulcers.

*Hepatobiliary disorders:* hepatotoxicity, elevated liver enzymes, usually without development of jaundice, hepatonecrosis (dose-dependent effect), transient liver failure with elevated liver transaminases.

*Renal and urinary disorders:* nephrotoxicity, kidney damage with papillary necrosis; renal colic, interstitial nephritis with high doses.

*Endocrine disorders:* hypoglycemia leading even to hypoglycemic coma.

*Nervous system disorders:* dizziness, headache, tremor, involuntary muscle contractions, psychomotor agitation and disorientation and impaired attention, insomnia, sleep disturbances, nervousness, irritability, hyperexcitability, anxiety, restlessness, fatigue, and paresthesias.

*Psychiatric disorders:* fear, anxiety.

*Cardiovascular disorders:* tachycardia, palpitations, hypertension, hypotension, arrhythmia.

*Blood and lymphatic system disorders:* anemia, sulfhemoglobinemia and methemoglobinemia (cyanosis, dyspnea, heartache), hemolytic anemia, bruising or bleeding; with long-term use in high doses: aplastic anemia, pancytopenia, neutropenia, leukopenia, thrombocytopenia, agranulocytosis. Due to its antiplatelet effect, acetylsalicylic acid increases the risk of bleeding, decreased platelet aggregation, hypocoagulation, hemorrhagic syndrome, and purpura. Bleeding such as intraoperative hemorrhage, hematomas, genitourinary bleeding, nosebleeds, gum bleeding, gastrointestinal bleedings and cerebral hemorrhages (especially in patients with uncontrolled hypertension and/or on concurrent antihypertensive drugs) which were life-threatening in individual cases, have been observed. Bleedings may lead to the acute and chronic post-hemorrhagic anemia/iron deficiency anemia (due to the so-called occult microhemorrhage) with corresponding laboratory signs and clinical symptoms such as asthenia, skin pallor, and hypoperfusion.

*Immune system disorders:* hypersensitivity reactions, including skin and mucosal rashes (usually generalized rash, erythematous rash, urticaria rash), urticaria, skin itching, edema, angioedema, exudative erythema multiforme (incl. Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), anaphylaxis, anaphylactic shock, non-cardiac pulmonary edema.

Patients with individual hypersensitivity to salicylates may develop allergic skin reactions, including such symptoms such skin hyperemia, fever, rash, urticaria, edema, pruritus, angioedema, rhinitis, and nasal congestion. Asthmatic patients may experience an increased incidence of bronchospasm; mild to moderate allergic reactions which can affect the skin, respiratory tract, digestive tract, cardiovascular system and manifest as rashes, urticaria, edema, and pruritus.

*Skin and subcutaneous tissue disorders:* itchy skin, skin and mucosal rashes (usually generalized rash, erythematous rash, urticaria), angioedema, exudative erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome).

*General disorders:* asthenia.

Moreover, for the drugs containing similar active substances the following side effects have been reported (frequency unknown): hypertension, anemia, sulfhemoglobinemia and methemoglobinemia (cyanosis, dyspnea, heartache), hemolytic anemia, feeling of fear, agitation, sleep disturbances, inflammation of digestive tract, hypoglycemia up to hypoglycemic coma, hepatonecrosis (dose-dependent effect), hypoperfusion, non-cardiogenic pulmonary edema.

There is no information available to suggest that the extent and type of side effects of the individual active substances is enhanced or their spectrum is broadened when the fixed combination is used under the condition that it is used as prescribed.

Increased risk of hemorrhages can persist for 4 to 8 days after the last dose of acetylsalicylic acid. Very rarely severe hemorrhages (e.g., intracerebral hemorrhage) have been observed, especially in patients with untreated hypertension and/or those on concurrent anticoagulant therapy. In individual cases, these events can be life-threatening.

#### Reporting of suspected side effects.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

***Shelf life.*** 2 years.

**Special precautions for storage.**

Store in the original package at temperature not above 25°C.

Keep out of reach of children.

**Nature and contents of container.**

6 or 10 tablets in a blister; 1 blister in a carton box; 6 or 10 tablets in blisters.

**Category of release.**

Non-prescription medicine.

**Manufacturer.** PrJSC Pharmaceutical Firm "Darnitsa".

**The manufacturer's location and address of the place of business.**

13, Boryspilska Street, Kyiv, 02093, Ukraine.

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