APPROVED
Order of Ministry of
Health of Ukraine
07.11.2018 № 2032
Registration certificate
№ UA/9202/01/01

INSTRUCTION
for medical use

LOWSPIRIN®

Composition:
active substance: acetylsalicylic acid;
1 tablet contains acetylsalicylic acid 75 mg;
excipients: Microcrystalline cellulose, Pregelled Starch, Colloidal silicon dioxide anhydrous, Stearic acid, Opadry Y-1-7000 White, Acryl-Eze 93O18359 White.

Pharmaceutical form. Enteric coated tablets.
Basic physicochemical properties: round biconvex white film-coated tablets.

Pharmacotherapeutic group. Antithrombotic agents. ATC code B01A C06.

Pharmacological properties.
Pharmacodynamics.
Acetylsalicylic acid inhibits platelet aggregation by blocking thromboxane A_2 synthesis. The mechanism of its action consists in irreversible inactivation of the enzyme cyclooxygenase (COX-1). The indicated inhibitory effect is particularly pronounced for platelets because they are not capable of resynthesis of the enzyme.
Acetylsalicylic acid also exhibits other inhibitory effects on platelets. Due to these effects, it can be used for many vascular diseases.
Acetylsalicylic acid belongs to a group of non-steroidal anti-inflammatory drugs (NSAID) with analgesic, antipyretic and anti-inflammatory properties.
Orally, at higher doses of acetylsalicylic acid, it can be used to relieve pain and in mild fibrillar conditions such as colds and flu, to lower the temperature and relieve pain in the joints and muscles, with acute and chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.
Pharmacokinetics.
After oral administration acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. During and after absorption it is turned to the active metabolite salicylic acid.
The maximal plasma concentration of acetylsalicylic acid is achieved after 10-20 minutes, of salicylic acid after 20-120 minutes, respectively. Due to the enteric coating of Lowspirin® tablets, the active substance is released not in the stomach, but in the alkaline environment of the intestine. Therefore, absorption of acetylsalicylic acid slows to 3-6 hours after the intake of enteric coated tablet compared to conventional tablet of acetylsalicylic acid.
Acetylsalicylic and salicylic acids are completely bound to plasma proteins and rapidly distributed in the body. Salicylic acid penetrates into the placental barrier and distributes into breast milk.
Salicylic acid is metabolised mainly in the liver. The metabolites of salicylic acid are salicyluric acid, salicylphenol gluconurid and salicylacil gluconurid, gentisin acid and gentisin-uric acid.
Kinetics of salicylic acid excretion is dose-dependent, since metabolism is limited by the activity of liver enzymes. The half-life is dose-dependent, and increases from 2-3 hours after using low doses to 15 hours after using high doses. Salicylic acid is excreted mostly by the kidneys.

Clinical characteristics.

Indications.

To decrease the risk of:

- lethal outcome in patients with suspected acute myocardial infarction;
- morbidity and lethal outcome in patients who have had myocardial infarction;
- transitory ischemic attacks (TIA) and stroke in patients with TIA;
- morbidity and lethal outcome in stable and unstable angina;
- myocardial infarction in patients at high risk of cardiovascular complications (diabetes mellitus, controlled arterial hypertension) and individuals at multifactor risk of cardiovascular diseases (hyperlipidaemia, adiposity, smoking, old age).

For prevention of:

- thrombosis and embolism after vessel surgery (percutaneous transluminal catheter angioplasty (PCTA), carotid endarterectomy, coronary arterial bypass grafting (CABG), arteriovenous shunting);
- deep vein thrombosis and pulmonary embolism after a long-term immobilization (after surgical operation);

For secondary prevention of strokes.

Contraindications.

- Hypersensitivity to acetylsalicylic acid and other salicylates or any other drug component.
- Asthma caused by the use of salicylates or substances with a similar action, particularly NSAIDs, in the anamnesis.
- Hemorrhagic diathesis.
- Acute peptic ulcers.
- Severe renal failure.
- Severe hepatic failure.
- Severe cardiac failure.
- Gout.
- Combination with methotrexate at a dose of 15 mg/week and more (see section “Drug interactions and other type of interactions”).
- Age up to 18 years. Acetylsalicylic acid can cause Reye syndrome.
- The last trimester of pregnancy.

Drug interactions and other types of interactions.

Contraindicated combinations for simultaneous use.

Methotrexate (at doses of 15 mg/week or more):

The use of acetylsalicylic acid and methotrexate at a dose of 15 mg/week and more increases haematological toxicity of methotrexate (anti-inflammatory agents decrease renal clearance of methotrexate and salicylates displace methotrexate from plasma protein binding sites).

Unrecommended combinations for simultaneous use.

Uricosuric agents (benzobromarone, probenecid)

Salicylates reduce the therapeutic efficacy of uricosuric drugs in removing uric acid. This may provoke the development of gout in patients with reduced uric acid excretion. The combined use of acetylsalicylic acid and uricosuric drugs should be avoided.

Combinations to be used with caution.

Anticoagulants, thrombolytics/other platelet aggregation inhibitors/hemostasis.

With the simultaneous use of acetylsalicylic acid and anticoagulants, thrombolytics/other platelet aggregation inhibitors/hemostasis, their effects are increased and the risk of bleeding increases.

Selective inhibitors reuptake of serotonin.

When applied with selective inhibitors reuptake serotonin, the risk of gastrointestinal bleeding increases as a result of a possible synergistic effect.

Oral antidiabetic drugs.
Salicylates can increase the hypoglycemic effect of antidiabetic drugs from the group of sulfonylureas derivatives.
Digoxin/Lithium
At the simultaneous application of acetylsalicylic acid with digoxin/lithium, their concentration in blood plasma is increased due to a decrease in renal excretion. At the beginning and in the event of discontinuation of treatment with acetylsalicylic acid, monitoring of plasma concentrations of digoxin/lithium is recommended, since dosage adjustment may be necessary.
Diuretics and antihypertensive drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid, can reduce the antihypertensive effect of diuretics and other antihypertensive drugs. The use of NSAIDs with angiotensin converting enzymes (ACE) inhibitors increases the risk of acute renal failure. Patients who are taking acetylsalicylic acid and mentioned drugs at the same time are advised to carefully monitor blood pressure and adjust the dose if it is necessary.
Diuretic drugs.
The co-administration of acetylsalicylic acid with diuretics may cause to acute renal failure due to decreased glomerular filtration due to decreased prostaglandin synthesis. Patient hydration and monitoring the function of the kidneys at the beginning of therapy is recommended.
Inhibitors of carbohydrazide (acetazolamide)
Concomitant use of carboanidrase inhibitors with acetylsalicylic acid may lead to severe acidosis and increased toxicity to the central nervous system.
Systemic corticosteroids.
The combined use of acetylsalicylic acid and systemic corticosteroids may increase the risk of ulceration and bleeding in the gastrointestinal tract.
Methotrexate at doses less than 15 mg/week.
When applying acetylsalicylic acid and methotrexate at doses less than 15 mg/week, hematologic toxicity of methotrexate is increased (reduction of renal clearance of methotrexate by anti-inflammatory agents and displacement of methotrexate by salicylates in connection with blood plasma proteins). A weekly blood circulation check is required during the first weeks of therapy. For patients with impaired renal function, even moderate severity, as well as for elderly people, careful monitoring is recommended.
Other NSAIDs
The combined use of acetylsalicylic acid and other NSAIDs may be accompanied by increased activity and adverse reactions. The risk of ulceration and bleeding increases in the gastrointestinal tract.
Ibuprofen
Simultaneous administration with ibuprofen prevents irreversible platelet inhibition by acetylsalicylic acid. Treatment with ibuprofen in patients at risk for cardiovascular disease may limit the cardioprotective effect of acetylsalicylic acid (see section "Peculiarities of use").
Ciclosporin, tacrolimus.
Concomitant use of NSAIDs with cyclosporine or tacrolimus may increase the nephrotoxicity of cyclosporine and tacrolimus. Simultaneous use of these preparations and acetylsalicylic acid it is necessary to control a renal function.
Antacids
The simultaneous use of acetylsalicylic acid with antacids may lead to increased withdrawal (due to increasing pH in urine).
Antiepileptic drugs (phenytoin, valproate)
Increased levels of phenytoin and valproate in plasma. When used simultaneously with valproic acid, acetylsalicylic acid displaces it from the plasma proteins. As a result, plasma levels of valproate are increased, which leads to an increase in the incidence of adverse reactions to signs of intoxication such as tremor, nystagmus, ataxia and personality changes.
Penicillin
Prolongation of the half-life period of penicillin blood plasma.
Alcohol.
The co-administration of acetylsalicylic acid with alcohol may increase the risk of ulceration and bleeding in the gastrointestinal tract.

Peculiarities of use.
Acetylsalicylic acid in a dose of 75 mg is not intended to be used as an anti-inflammatory/analgesic/antipyretic agents.
It is recommended for use by adults. The drug is contraindicated for use in patients under the age of 18 due to the risk of developing Reye syndrome (see "Contraindications" and "Children").
Reye syndrome
Reye syndrome may occur with the use of acetylsalicylic acid in children with acute upper respiratory tract viral infection (URTI), which is accompanied or not accompanied by an temperature rise, without consulting a physician. In some viral diseases, especially with influenza A, influenza B and chickenpox, there is a risk of Reye syndrome, which is a very rare but life-threatening illness requiring urgent medical intervention. The risk may be increased if acetylsalicylic acid is used as an adjunct drug, but the cause-effect relationship in this case is not proven. If these conditions are accompanied by constant vomiting, this may be a manifestation of Reye syndrome.
Use the drug with caution in the following situations:
- hypersensitivity to analgesic, anti-inflammatory, anti-rheumatic drugs, as well as allergies to other substances;
- nasal polyps;
- presence of symptoms of chronic gastric or duodenal dyspepsia or their relapse;
- ulcers of the gastrointestinal tract, including chronic and recurrent stomach ulcers or gastrointestinal bleeding in history;
- arterial hypertension;
- simultaneous application of anticoagulants;
- in patients with impaired kidney function or patients with cardiovascular disorders (e.g. kidney vascular pathology, congestive heart failure, hypovolemia, extensive surgery, sepsis or severe bleeding), since acetylsalicylic acid may also increase the risk of impaired renal and acute renal function insufficiency;
- in patients with severe deficiency of glucose-6-phosphate dehydrogenase, acetylsalicylic acid may cause hemolysis or hemolytic anemia. Especially in the presence of factors that may increase the risk of hemolysis, such as high doses of the drug, fever or acute infectious process;
- impaired liver function.

Ibuprofen.
Ibuprofen may inhibit the effect of low doses of acetylsalicylic acid on platelet aggregation when used concurrently with acetylsalicylic acid (see section "*Drug interactions and other types of interactions*"). In case of using Lowspirin before taking ibuprofen as an analgesic, consult with your doctor.
Hypersensitivity
Acetylsalicylic acid may cause the development of hypersensitivity reactions, including bronchospasm/bronchial asthma attack or other reactions. Risk factors of hypersensitivity reactions for acetylsalicylic acid include a history of asthma, hay fever, nasal polyposis or chronic respiratory disease, allergic reactions (e.g. skin reactions, itching, urticaria) that appear in the use of other substances. The drug should be used with caution in hypersensitivity to analgesic, anti-inflammatory, anti-rheumatic drugs, as well as in the presence of allergies to other substances.
The use of the drug should be discontinued when the first signs of hypersensitivity reactions occur (e.g., skin rash, blennosis).
Serious side effects from the skin.
Rare cases of severe side effects from the skin, including Stevens-Johnson syndrome, have been reported with the use of acetylsalicylic acid (see section "Adverse reactions"). The use of the drug should be discontinued in the event of any clinical symptoms of hypersensitivity reactions, including rashes on the skin and mucous membranes.
The risk of the bleeding/increased bleeding in surgical interventions
The antiplatelet effect of acetylsalicylic acid persists for several days after administration, which may increase the probability of bleeding or increased bleeding during surgical operations (including minor surgical interventions such as tooth extraction). There is a probability of temporary discontinue use the drug.

Gastrointestinal bleeding/ulcers
Patients should tell their doctor about any unusual bleeding symptoms. In case of gastrointestinal bleeding or ulceration, treatment should be discontinued.
Menorrhagia.
Acetylsalicylic acid is not recommended for women with menorrhagia (during menstruation), since it can increase menstrual bleeding.
Disorders of kidney or liver function
Acetylsalicylic acid should be used with caution in patients with moderate renal or hepatic impairment (contraindicated in severe cases) or in patients with signs of dehydration, since the use of NSAIDs may impair renal function. Patients with hepatic insufficiency (weak or moderate) should monitor liver function tests.
Elderly patients
Older patients are particularly susceptible to adverse reactions when using NSAIDs, including acetylsalicylic acid, in particular gastrointestinal bleeding and perforations that may be lethal (see section "Administration and dosage"). In case of need for long-term treatment with acetylsalicylic acid, patients should be monitored regularly.
Gout
With the use of small doses of acetylsalicylic acid, the excretion of uric acid may decrease. This can lead to an attack of gout in patients who are liable to it. The use of acetylsalicylic acid is contraindicated in patients with gout (see section "Contraindications").
Medicinal products that change haemostasis
Due to the increased risk of bleeding, the concomitant use of acetylsalicylic acid with other medical drugs that change hemostasis (such as anticoagulants such as warfarin, thrombolytics, antiplatelet agents, anti-inflammatory drugs, selective serotonin reuptake inhibitors) is not recommended accept such combination which is strictly necessary (see section "Interaction with other drugs and other Interactions"). If such a combination is used, close monitoring of the patient for the detection of bleeding symptoms is recommended.
Ulcerogenic effect
Due to the increased risk of ulcerogenic effect, caution should be taken when using acetylsalicylic acid with oral corticosteroids, selective serotonin reuptake inhibitors, and deferasiroxes (see section "Interaction with other drugs and other Interactions").
Hypoglycemia
Acetylsalicylic acid may potentiate hypoglycemic effects of sulfonylureas and insulin when used at high doses, which may increase the risk of hypoglycaemia (see section "Interaction with other drugs and other Interactions").

Use during pregnancy or breastfeeding.
Pregnancy.
Care should be taken while applying salicylates in the 1st and 2nd trimesters of pregnancy. The use of salicylates is contraindicated in the third trimester of pregnancy.
The inhibition of prostaglandin synthesis may have negatively effect on pregnancy and/or embryo/fetal development. Available data from epidemiological studies indicate the risk of miscarriage and fetal malformations (heart failure and gastroschisis) after the use of prostaglandin synthesis inhibitors at the beginning of pregnancy. The risk increases depending on the dosage increasing and duration of therapy. According to available data, the association between acetylsalicylic acid and increased risk of miscarriage has not been confirmed.
Available epidemiological data on developmental malformations are not consistent, but the increased risk of gastroschisis cannot be excluded in the use of acetylsalicylic acid. The results of a prospective early-pregnancy study (1-4 month) involving approximately 14,800 female-child pairs did not indicate any association with the increased risk of malformations.
Animal studies indicate reproductive toxicity.
During the I and II trimester of pregnancy, acetylsalicylic acid preparations should not be prescribed without a clear clinical need. In women who are likely pregnant or during the I and II trimester of

pregnancy, the dose of acetylsalicylic acid should be as low as possible and the duration of treatment is as short as possible.
Implantation disorders, embryotoxic and fetotoxic effects, and effects on the ability of a child to study after prenatal exposure with salicylates have been reported.
According to studies in animals, the use of salicylates results in fetal adverse reactions (such as increased mortality, growth disturbances, intoxication with salicylates), however, controlled trials involving pregnant women have not been performed.
According to previous experience, the risk is low in the use of the drug in therapeutic doses.
During the III trimester of pregnancy all prostaglandin synthesis inhibitors may affect the foetus follows:
on foetus as follows:

- cardiopulmonary toxicity (with premature closure of arterial ducts and pulmonary hypertension);
- renal impairment with possible further development of renal failure with oligohydramnios;

on a woman and foetus at the end of pregnancy as follows:

- possibility of prolongation of bleeding time, antiplatelet effect which may occur even after very low dose;
- inhibition of uterine contractions, which may lead to delays or increased duration of childbirth.

In view of this, acetylsalicylic acid is contraindicated during the III trimester of pregnancy.
Breastfeeding.
Salicylates and their metabolites are excreted into breast milk.Concentrations in breast milk are equivalent or even higher than concentrations in the mother's blood plasma. During compulsory use during lactation, breastfeeding should be discontinued in case of regular high doses (> 300 mg/day).

Effects on the ability to drive and use other mechanisms.
No studies were conducted.

Administration and dosage.
The drug should be taken internally, 30-60 minutes before eating, without chewing, drinking enough fluids.

Indication	**Daily dose**	**The number of perceptions per day**	**Periodicity of perceptions**
Reducing the risk of fatal consequence in patients with suspected acute myocardial infarction*	75 –300 mg	1 time	daily
Reducing the risk of morbidity and mortality in patients who have suffered myocardial infarction	75 –300 mg	1 time	daily
Secondary stroke prevention	75 –300 mg	1 time	daily
Reducing the risk of transient ischemic attacks (TIA) and stroke in patients with TIA	75 –300 mg	1 time	daily
Reducing the risk of developing the disease and the lethal effect in patients with stable and unstable cardiac angina	75 –300 mg	1 time	daily
Prevention of deep venous thrombosis and embolism of pulmonary artery after long-term immobilization (after surgery) - 100-200 mg per day or 300 mg per day on alternate days.	75 –300 mg	1 time	daily
	300 mg	1 time	on alternate days
Prevention of thromboembolism after surgery on vessels (percutaneous transluminal catheter angioplasty, endarterectomy of the arteria carotis, coronary artery bypass graft surgery (CABG), arteriovenous shunting) **	75 –150 mg	1 time	daily
	300 mg	1 time	on alternate days

Prevention of myocardial infarction in patients at high risk of developing cardiovascular complications (diabetes mellitus, controlled arterial hypertension), and those with multi-factorial risk of cardiovascular disease (hyperlipidemia, obesity, smoking, old age)**	75 –150 mg	1 time	daily
	300 mg	1 time	on alternate days

* - During 30 days after a heart attack, continue to take a maintenance dose of 75-300 mg per day. After 30 days, consideration should be given to further prevention of recurrence of myocardial infarction. The initial dose should be chewed to achieve rapid absorption.
** - use one of the treatment regimens.

Elderly patients
In general, acetylsalicylic acid should be used with caution in elderly patients who have a greater tendency to develop adverse reactions (see section "Peculiarities of use"). In the absence of severe renal or hepatic insufficiency, the usual dose for adults is recommended. Treatment should be reviewed at regular intervals.

Children.
According to the indications (see section "Indications"), the Lowspirin® drug should not be used by children.
The use of acetylsalicylic acid in children under the age of 18 years can lead to serious side effects (including Reye syndrome, one of the symptoms of which is persistent vomiting). Please read the information provided in the section "Peculiarities of use".

Overdose.
Symptoms of severe poisoning can develop slowly, for example, within 12-24 hours after application. After oral administration of an ASA dose to 150 mg/kg body weight, moderate intoxication may be developed, and at a dose of > 300 mg/kg body weight - severe.
Chronic poisoning with salicylates may have a latent nature, as its symptoms are nonspecific. Moderate chronic intoxication occurs, as a rule, only after repeated doses of large doses.
Acute intoxication is indicated by a pronounced change in acid-base balance, which may vary depending on the age of the patient and the severity of intoxication. The most common manifestation in children is metabolic acidosis. The severity of the condition can not be assessed solely on the basis of the concentration of salicylates in the plasma. Absorption of acetylsalicylic acid may be delayed due to delayed gastric release, the formation of concretions in the stomach, or in the case of receiving a preparation in the form of enteric coated tablets.
Warning.
Local signs of irritation, which are commonly dominated by an overdose of ASA, such as nausea, vomiting and stomach ache, may be absent as this form of ASA has an enteric coating and resorption occurs only in the intestinum tenue.
Symptoms.
Headache, nausea, hypocalcemia, or hypoglycemia, skin rash, dizziness, gastrointestinal bleeding, thrombosis inhibition to coagulopathy, cardiovascular disorders (from arrhythmia, arterial hypotension to cardiac arrest), tinitis, visual and auditory impairment, tremor, confusion of consciousness , hyperthermia, increased sweating, hyperventilation, acid-alkali balance and electrolyte imbalance, dehydration, coma and respiratory failure.
Tinnitus is possible at a concentration of salicylates in the plasma of more than 150-300 μg/ml. Serious side-effects are observed at concentrations of salicylates in plasma above 300 μg/ml.
Treatment.
Due to life threatening conditions caused by severe intoxication, all necessary precautions should be taken immediately: prevention or reduction of resorption, gastric lavage in the early stages (up to one hour after ingestion), activated carbone, control and appropriate correction of the electrolytes. The use of glucose. Sodium bicarbonate is using for correction of acidosis and for acceleration of withdrawal (urine pH > 8). Glycine: the initial dose is 8 g orally, then 4 g every 2 hours for 16 hours. Possible hemoperfusion or hemodialysis (the need for application can be established in the toxicological center).

Adverse reactions.
Blood and lymphatic system: thrombocytopenia, agranulocytosis, pancytopenia, leukopenia, anemia (post-hemorrhagic/iron deficiency, aplastic) with appropriate laboratory parameters and clinical manifestations; hemolysis and hemolytic anemia (in patients with severe forms of insufficiency of glucose-6-phosphate dehydrogenase), prolongation of bleeding time.
Immune system: reactions of high sensitivity including asthmatic conditions, skin reactions, respiratory tract, gastrointestinal and cardiovascular disorders, rash, edema, itching, cardio-respiratory failure, anaphylactic shock; erythematous/eczematous skin reactions, severe skin reactions, including exudative multivormal erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis; angioneurotic edema, allergic edema, rhinitis, nasal congestion, decreased blood pressure to shock.
Metabolic disorders: hyperuricemia with appropriate laboratory parameters and clinical manifestations (gout attacks), hypoglycemia, violations of acid-alkali balance.
Nervous system: headache, dizziness, disturbance of orientation, confusion of consciousness.
Organs of vision: visual impairment.
Auditory organs: hearing impairment, ringing in the ears (tinitus).
Gastrointestinal tract: microbleeding (70%), dyspepsia, nausea, vomiting, diarrhea; pain in the epigastric region, abdominal pain, heartburn, anorexia, inflammation of the gastrointestinal tract, gastrointestinal bleeding, gastrointestinal ulcers, which can rarely lead to hemorrhage and perforation, with relevant clinical symptoms and changes in laboratory parameters.
Vascular system disorders: hemorrhagic vasculitis, bleeding (intraoperative haemorrhage, hematoma, bleeding of the urogenital system, nasal bleeding, bleeding gums, haemorrhage of the gastrointestinal tract, blood vomiting, melena, hidden gastrointestinal bleeding, brain haemorrhage (especially in patients with uncontrolled hypertension and/or when concomitant use of anticoagulants) with corresponding clinical symptoms, including asthenia, skin pallor, hypoperfusion.
Liver and biliary tract disorders: hepatic dysfunction, transient hepatic insufficiency, increased liver transaminases.
Kidney and urinary tract disorders: renal dysfunction, acute renal failure.
Respiratory system disorders: rhinitis, dyspnea, bronchospasm, asthma attacks.
Reproductive system: menorrhagia.
Skin and subcutaneous tissue: purpura, nodular erythema, multiforme erythema.
Others: Reye syndrome (see section "Peculiarities of use").

Shelf-life. 4 years.

Storage conditions.
Store in the original package at the temperature below 25°C.
Keep it out of reach of children.

Package.
10 tablets are in a strip; 3, 8 or 10 strips are in a carton pack.
30 tablets are in a strip; 1, 2, 3 or 4 strips are in a carton pack.

Conditions of supply. Without prescription.

Manufacturer.
LLC “KUSUM PHARM”.
or
KUSUM HEALTHCARE PVT LTD.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy Oblast, Sumy, Skryabina Str., 54.
or
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

Date of last revision. 20.06.2024