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INSTRUCTION
For medical use

GRIPGO HOTMIX®

Composition:
active substances: paracetamol, phenylephrine hydrochloride, ascorbic acid;
Each sachet contains paracetamol 750 mg, phenylephrine hydrochloride 10 mg, ascorbic acid coated equivalent to ascorbic acid 60 mg;
excipients: sucrose, sodium saccharin, povidone, anhydrous citric acid, sodium citrate, pregelatinised starch, indigo carmine (E 132), carmoisin (E 122), black currant flavour.

Pharmaceutical form. Granules for oral solution with black currant flavour.
Main physical and chemical properties: light violet to violet coloured granular powder with the inclusion of white granules of various shapes.

Pharmacotherapeutic group. Analgesics and antipyretics. Paracetamol, combinations excl. psycholeptics. ATC Code N02B E51.

Pharmacological properties.
Pharmacodynamics.
Gripgo Hotmix® is a combined drug, the action of which is caused by the components that are included to its formulation.
Paracetamol is an analgesic and antipyretic drug, having antipyretic and pain-relief properties connected with its action on heat regulating centre in the hypothalamus and its action as an inhibitor of synthesis of prostaglandins.
Phenylephrine hydrochloride is a sympathomimetic that reduces the swelling of the nasal mucous membrane and paranasal sinuses, the severity of exudative manifestations that improves nasal breathing. It stimulates mainly alpha-adrenergic receptors, ensuring a peripheral vasoconstriction and decreasing their permeability, and decreases secretion of mucus.
Ascorbic acid is a vital vitamin and it is added into the drug composition to replenish the loss of vitamin C, which may occur at the beginning of a viral infection.
Pharmacokinetics.
Paracetamol is rapidly and almost completely absorbed in the gastrointestinal tract and evenly distributed throughout the body. The rate of absorption is reduced when paracetamol is taken with

food. At therapeutic doses, paracetamol binds little to plasma proteins. The drug is metabolized in the liver and almost completely excreted in the urine, mostly in the form of glucuronides and sulfate conjugates. A potentially hepatotoxic intermediate metabolite of N-acetyl-p-benzoquinone (NAPQI), formed in small amounts (~5%), is excreted with cysteine or mercapturic acid after conjugation with glutathione. With large doses of paracetamol, glutathione stores in the liver are depleted, leading to the accumulation of toxic metabolites in the liver. This can lead to hepatocyte damage, death and acute liver failure.
Less than 5% of the taken dose of paracetamol is excreted in unchanged form.
The average half-life of paracetamol is from 1 to 4 hours.
Patients with impaired liver function. The half-life of paracetamol in people with compensated liver failure is the same as in healthy people. In case of severe hepatic insufficiency, the half-life of paracetamol may be increased. The clinical significance of the increase in paracetamol half-life in patients with liver disease is unknown. No accumulation, hepatotoxicity or disruption of glutathione conjugation was observed.
Patients with impaired renal function. More than 90% of the therapeutic dose of paracetamol is usually excreted in the urine as metabolites within 24 hours. In patients with chronic renal failure, the ability to excrete polar metabolites is limited, which may lead to their accumulation. Patients with chronic renal failure are advised to increase the interval between paracetamol doses.
Ascorbic acid (vitamin C) is rapidly absorbed in the gastrointestinal tract and delivered to all tissues of the body, 25% is bound to plasma proteins. Excess ascorbic acid, which exceeds the body's needs, is excreted in the urine as metabolites.
Phenylephrine hydrochloride is easily and quickly absorbed in the gastrointestinal tract. It undergoes primary metabolism by monoamine oxidase in the intestine and liver, its bioavailability reaches 40%. The maximum concentration of the drug in blood plasma is reached in 1–2 hours. The half-life is from 2 to 3 hours. It is excreted in the urine mainly in the form of sulfates.

Clinical characteristics.

Indications.

Short-term relief from symptoms of cold and flu, including headache, fever, nasal congestion, sinusitis and pain associated with it, sore throat, body ache.

Contraindications.

- Hypersensitivity to components of the drug.
- Severe liver impairment, congenital hyperbilirubinaemia, acute hepatitis, Gilbert's syndrome.
- Blood disorders, including severe anemia, leucopenia, glucose-6-phosphate dehydrogenase deficiency, thrombosis, thrombophlebitis.
- Rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrose isomaltose deficiency.
- Severe diseases of cardiovascular system, including severe arterial hypertension, severe atherosclerosis, ischemic heart disease, decompensated heart failure, cardiac conduction disorder, predisposition to angiospasms.
- Severe renal impairments, prostatic hypertrophy.
- Increased irritability, insomnia, epilepsy.
- Hyperthyreosis, severe diabetes mellitus, phenylketonuria.
- Acute pancreatitis.
- Angle-closure glaucoma.
- Alcoholism.
- Children under 12 years; elderly age.
- Pregnancy or lactation.

- Concomitant use with:
  - monoamine oxidase inhibitors (MOI) and for 2 weeks after discontinuation of MOI inhibitors;
  - tricyclic antidepressants;
  - β-blockers or antihypertension medicinal products;
  - drugs that suppress or increase appetite;
  - amphetamine-like psychostimulants.

Interaction with other medicinal products and other forms of interactions.
Concomitant use with other drugs containing paracetamol or other active substances that are included into the formulation of Gripgo Hotmix®, should be avoided.
Peculiarities of interaction are caused by the components that are included into its formulation.
Paracetamol.
The absorption rate of paracetamol may be increased during concomitant use with metoclopramide or domperidone and may be reduced during concomitant use with cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding in case of simultaneous long-term regular daily use of paracetamol. Periodic administration according to the recommended regime of administration has no clinical effect. Barbiturates reduce the antipyretic effect of paracetamol.
Anti-seizure drugs (including phenytoin, barbiturates, carbamazepine), that stimulate the activity of microsomal liver enzymes, may increase the toxic effect of paracetamol on the liver due to increasing in the degree of drug conversion to hepatotoxic metabolites.
Simultaneous administration of high doses of paracetamol with isoniazid increases the risk of hepatotoxic syndrome. Simultaneous use of paracetamol with hepatotoxic agents increases the toxic effects of drugs on the liver.
Paracetamol reduces the effectiveness of diuretics. Do not use with alcohol.
Phenylephrine hydrochloride.
The interaction of phenylephrine with monoamine oxidase inhibitors causes hypertensive effect, with tricyclic antidepressants (e.g. amitriptyline) increases the risk of cardiovascular side effects, with digoxin and cardiac glycosides leads to impaired heartbeat or myocardial infraction. Phenylephrine with other sympathomimetics increases the risk of the cardiovascular adverse reactions. Phenylephrine may reduce the effectiveness of beta-blockers and other antihypertensive agents (reserpine, methyldopa) and increase the risk of hypertension and other cardiovascular side effects. α-blockers (phentolamine), phenothiazines, furosemide and other diuretics prevent vasoconstriction. Rauwolfia alkaloids decrease the therapeutic effect of phenylephrine hydrochloride.
Ascorbic acid (vitamin C).
When taken orally ascorbic acid increases absorption of penicillin, iron, decreases the effectiveness of heparin and indirect anticoagulants, increases the risk of crystalluria in the treatment of salicylates. Antidepressants, antiparkinsonian drugs and antipsychotics, derivatives of phenothiazine increase the risk of urine retention, dry mouth, constipation. Glucocorticosteroids increase the risk of glaucoma.
The absorption of vitamin C is decreased when applied simultaneously with oral contraceptives, fruit or vegetable juices, alkaline drinks. Simultaneous application of vitamin C and deferoxamine increases the tissue toxicity of iron, especially in the cardiac muscle that may lead to circulatory decompensation. Vitamin C should be taken only 2 hours after deferoxamine injection. Long-term use of large doses of ascorbic acid inhibits the reaction disulfiram-alcohol. Large doses of the drug decrease the efficiency of tricyclic antidepressants. Large doses of the drug decrease the efficiency of neuroleptics – derivatives of phenothiazine, tubular reabsorption of amphetamine, violate excretion of mexiletine by kidneys, affect resorption of vitamin B_{12}. Ascorbic acid when taken

orally increases the absorption of aluminium in intestinal tract, therefore it should be considered in case of simultaneous treatment with antacids that contain aluminium.

Special precautions.
Consult with a doctor before using the drug.
Do not exceed the recommended dose.
It contains paracetamol. Concomitant use with other paracetamol-containing drugs may lead to overdose. Paracetamol overdose can cause liver failure, which may necessitate a liver transplantation or lead to death.
Avoid concomitant use with other drugs prescribed for symptomatic treatment of cold and flu, vasoconstrictor agents for treatment of rhinitis, drugs containing paracetamol.
The risk of overdose occurs in patients with non-cirrhotic alcoholic liver disease. During the treatment alcohol consumption should be excluded.
It should be considered that in patients with alcohol-induced liver injury the risk of hepatotoxic effects of paracetamol increases; the drug may affect the results of laboratory tests for blood glucose and uric acid.
The patients taking analgesics on a daily basis in mild arthritis should consult with a doctor.
If the patients take warfarin or similar drugs having anticoagulant effect, they should consult with a doctor before taking a drug.
The use of the drug for people who are starving may cause the risk of liver damage.
Patients with pheochromocytoma; patients with prostate hypertrophy, as they may be prone to urinary retention; patients with Raynaud's disease (which may be manifested by pain in the fingers and toes in response to cold or stress); patients with hypertension, cardiovascular disease, diabetes, liver and kidney dysfunction should consult a doctor before using the drug.
The drug should be used with caution in patients prone to high blood pressure, difficulty urinating, Raynaud's disease, patients with bronchial asthma, elderly patients. Phenylephrine, one of the drug components, can cause anginal attacks.
If due to recommendation of the doctor the drug is used for a long period, it is necessary to monitor the functional state of the liver and peripheral blood.
Cases of hepatic dysfunction/insufficiency have been reported in patients with low glutathione levels, such as patients with severe malnutrition, anorexia, low body mass index, or chronic alcohol dependence.
In patients with severe infections such as sepsis, which are accompanied by a decrease in glutathione levels, the risk of metabolic acidosis when taking paracetamol increases. The symptoms of metabolic acidosis are deep, accelerated or difficult breathing, nausea, vomiting, loss of appetite. You should consult your doctor immediately if these symptoms occur.
This drug should not be used in patients taking other sympathomimetics (eg, anti-edema drugs, appetite suppressants, and amphetamine psychostimulants).
Consult a doctor if the headache becomes permanent.
If the signs of the disease do not begin to disappear within 3 days of treatment with the drug or, on the contrary, the health will deteriorate, it is necessary to consult a doctor.
Keep the drug out of sight and reach of children.
Carmoisine (E 122), which is part of the drug, can cause allergic reactions.
In addition, if a patient has an intolerance to certain sugars, a doctor should be consulted before taking this medicine because it contains sucrose.
Use in pregnancy and lactation.
Do not take this medicine during pregnancy.
Paracetamol and phenylephrine can be excreted in breast milk, so if it is necessary to use the drug, breastfeeding should be discontinued.

Influence on velocity reactions in driving motor transport or operating other machines.
During treatment with the drug the patient should refrain from driving a car or equipment that requires increased concentration.

Administration and dosage.
The drug is intended for internal use. Empty contents of sachet into a glass, half fill with very hot water, stir well and add cold water as necessary. Stir until completely dissolved. Take it warm.
Adults and children aged 12 years and over: single dose – 1 sachet. If necessary, the dose may be taken every 4–6 hours. Do not take more than 4 sachets per day.
The interval between takings should be not less than 4 hours.
The treatment course should be not more than 3–5 days. The duration of treatment is defined by the doctor.
Do not exceed the recommended dose. The lowest necessary effective dose should be taken.
Do not use with any other paracetamol-containing products.

Children.
The drug is contraindicated for children under 12 years.

Overdose.
Symptoms.
Signs and symptoms of overdose of some components of Gripgo Hotmix® may be divided as follows:
Paracetamol.
Liver damage is possible in adults who have taken 10 g or more of paracetamol and in children who have taken more than 150 mg/kg body weight. Administration of 5 g or more of paracetamol may lead to liver damage if the patients have risk factors (long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes; alcohol abuse; glutathione cachexia, for example eating disorders, HIV infection, starvation, cystic fibrosis, cachexia).
Symptoms of overdose in the first 24 hours are pale skin, nausea, vomiting, anorexia and abdominal pain. Symptoms of liver damage are observed in 12–48 hours after overdose. Disorders of glucose metabolism and metabolic acidosis may occur. In case of severe poisoning hepatic impairment may progress and inflict development of toxic encephalopathy with hemorrhage, hypoglycaemia, coma and have lethal outcome. Acute renal failure with acute tubular necrosis may show strong back pain, haematuria, proteinuria and develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have also been observed.
Long-term treatment in high doses may lead to aplastic anaemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia. CNS adverse reactions at high doses are dizziness, psychomotor agitation and disorientation; urinary system disorders − nephrotoxicity (renal colic, interstitial nephritis, capillary necrosis).
Phenylephrine hydrochloride.
Overdose caused by the action of phenylephrine may lead to excessive sweating, psychomotor agitation or central nervous system depression, headache, dizziness, somnolence, impairment of consciousness, heart rhythm disorder, tachycardia, premature ventricular contraction, tremor, hyperreflexia, spasms, nausea, vomiting, irritability, anxiety, increase in arterial blood pressure, hallucination.
Ascorbic acid.
Overdose caused by ascorbic acid may have the following manifestations: nausea, vomiting, abdominal bloating and pain, pruritus, skin rash, overexcitement. High doses of ascorbic acid (more than 3000 mg) may cause temporary osmotic diarrhea and gastrointestinal distress,

aberration of zinc and cupric metabolism, glucosuria, crystalluria, formation of concrements in kidneys.
Treatment.
In case of overdose first medical aid is required. The patient should be immediately brought to the hospital, even if early symptoms of overdose have not been observed. 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.
In addition to the above, it is recommended to perform symptomatic or supportive therapy.

Adverse reactions.
Immune system disorders: hypersensitivity reactions, including anaphylaxis, anaphylactic shock, allergic reactions (including angioneurotic edema).
Skin and hypoderm disorders: allergic dermatitis, itching, rashes on skin and mucous membranes (usually erythematous, Urticaria), angioneurotic edema, exudative erythema multiform (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), purpura, haemorrhaging.
Central nervous system disorders: headache, tremor, paraesthesiae, vertigo, dizziness.
Mental disorders: psychomotor agitation, disorientation, anxiety, nervousness, fear, irritability, sleep disturbances, insomnia, drowsiness, confusion, depression, hallucinations, sedative state, anxiety; impaired concentration during the next day, especially with insufficient sleep duration after taking the drug.
Ear disorders: tinnitus.
Visual organs disorders: mydriasis, blurred vision and accommodation, increased intracranial pressure, acute angle-closure glaucoma (more common in patients with glaucoma).
Gastro-intestinal tract disorders: nausea, vomiting, epigastric pain and discomfort, heartburn, loss of appetite, constipation, diarrhea, flatulence, dry mouth, ulcers of the mucous membrane of the mouth, hypersalivation, hemorrhage.
Hepatobiliary system disorders: abnormal liver function, increased liver enzymes, usually without the jaundice development, hepatonecrosis (dose-response effect), hepatic insufficiency.
Endocrine system adverse effects: hypoglycemia, hypoglycemic coma.
Blood and lymphatic system adverse effects: anemia (including hemolytic), sulfhemoglobinemia and methemoglobinemia (cyanosis, shortness of breath, cardiac pain), thrombocytopenia, thrombocytosis bruise or bleeding, leucopenia, agranulocytosis, pancytopenia.
Kidney and urinary system adverse effects: impaired urination incontinence, urinary retention (most likely in patients with prostate hypertrophy), renal colic, nephrotoxicity (interstitial nephritis, papillary necrosis), oliguria, aseptic pyuria.
Cardiovascular system adverse effects: increase in blood pressure (arterial hypertension), heart pain, palpitations, tachycardia, shortness of breath, edema, reflex bradycardia.
Respiratory system adverse effects: bronchospasm in patients sensitive to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs.
The drug may have a slight laxative effect.

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25°C in the original package.
Keep out of reach of children.

Package.
5 g in a sachet. 5 or 10, or 50 sachets in a carton pack.

Conditions of supply.
Without prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD

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