APPROVED
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INSTRUCTION
for medical use
GRIPGO®

Composition:
active substances: paracetamol, caffeine anhydrous, phenylephrine hydrochloride, chlorpheniramine maleate;
1 tablet contains paracetamol 500 mg, caffeine anhydrous 30 mg, phenylephrine hydrochloride 10 mg, chlorpheniramine maleate 2 mg;
excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Pharmaceutical form. Tablets.
Main physical and chemical properties: white biconvex capsule-shaped tablets.

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

Pharmacological properties.
Pharmacodynamics.
Gripgo® is a combined medicine, the action of which is caused by its components.
Paracetamol is an analgetic-antipyretic that has anti-inflammatory and analgesic properties; that is related to the effect of paracetamol on hypothalamus center of heat regulation and its possibility to inhibit the synthesis of prostaglandins.
Caffeine is an methylxanthine alkaloid, which has a stimulating effect on the central nervous system, mainly on the cerebral cortex, respiratory and vascular centers, increases mental and physical performance, reduces drowsiness, fatigue and weakens the action of drugs that depress the central nervous system. Increases the analgesic effect of paracetamol.
Phenylephrine hydrochloride is a sympathomimetic agent that reduces swelling of the nasal mucosa and paranasal sinuses, as well as the severity of exudative manifestations that promotes the improvement of nasal breathing. It stimulates mainly alpha-adrenoceptors, thereby narrowing and reducing the permeability of peripheral blood vessels, as well as decreasing the formation of mucous secretions.
Chlorpheniramine maleate is an antihistamine that has anti-allergic effects. It competitively blocks histamine H_1-receptors and prevents a development of histamine effects, eliminates the cold, nasal itch and eyes pruritus.
Pharmacokinetics.

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract (GIT). The maximum concentration in blood plasma is reached in 30–60 minutes. The half-life is 1–4 hours. It is evenly distributed in all body fluids. Plasma protein binding is variable; 20 to 30% may be bound at concentrations formed during acute intoxication. It is excreted mainly by the kidneys in the form of conjugated metabolites.
Caffeine and its water-soluble salts are rapidly absorbed in the intestine (including the large intestine) and are quickly distributed in all organs and tissues of the body. Binding to blood proteins (albumins) is 25–36%.
The plasma half-life is about 5–10 hours. The main part is demethylated and oxidized. About 10% is excreted unchanged by the kidneys. Caffeine and its metabolites are excreted by the kidneys (in adults 1–2% of caffeine is excreted unchanged).
Phenylephrine hydrochloride has low bioavailability due to uneven absorption and exposure to monoamine oxidase in GIT and liver during the first pass. It is excreted by the kidneys as metabolites. Acidification of urine accelerates excretion from the body.
Chlorpheniramine maleate is slowly absorbed from GIT; the maximum concentration in blood plasma is reached after 2.5–6 hours, 70% of it is bound to plasma proteins. Bioavailability is from 25% to 50% of the dose. Chlorpheniramine is metabolized during the first pass in the liver, and is largely metabolized in the liver with the formation of metabolites of desmethyl- and didesmethyl chloropheniramine. Chlorpheniramine is distributed throughout the body and crosses the blood-brain barrier. Metabolites and the drug are excreted mainly in the urine unchanged for 4–6 hours. Excretion depends on the pH of the urine and the degree of excretion. In children, there is a faster and more extensive absorption, excretion and half-life.

Clinical characteristics.

Indications.

Treatment of symptoms of flu and acute respiratory viral diseases, such as fever, headache, nasal congestion, rhinitis, sinusitis, sore throat, muscles pain, and cough.

Contraindications.

- Hypersensitivity to any component of the drug, other xanthine derivatives (theophylline, theobromine), opioids, antihistamines, sympathomimetic amines, Stevens-Johnson syndrome;
- severe cardiovascular disease, including unstable angina, decompensated heart failure, disturbance of rhythm and conduction, congenital prolonged QT interval or long-term use of drugs that prolong the QT interval, arrhythmias, bradycardia, severe atherosclerosis, including coronary heart disease, predisposition to vasospasm, severe coronary heart disease; severe hypertension, acute myocardial infarction, organic diseases of the cardiovascular system, thrombosis, thrombophlebitis;
- severe hepatic impairment (including congenital hyperbilirubinemia; Gilbert's syndrome);
- severe renal impairment;
- prostate disease (prostate adenoma with difficulty urinating, acute urinary retention in prostate hypertrophy, prostatic hyperplasia, bladder neck obstruction);
- diseases of the gastrointestinal tract (gastric and duodenal ulcers in the acute stage, stenotic gastric and duodenal ulcers, pyloroduodenal obstruction; acute pancreatitis);
- epilepsy;
- blood diseases (including severe anemia; leukopenia; hematopoietic disorders);
- endocrine diseases (hyperthyroidism, diabetes, pheochromocytoma, thyrotoxicosis, phenylketonuria);
- diseases of the respiratory system (including bronchial asthma; chronic bronchitis; chronic obstructive pulmonary disease; emphysema; risk of respiratory failure);

- angle-closure glaucoma, increased intraocular pressure;
- glucose-6-phosphate dehydrogenase deficiency;
- Dubin-Johnson syndrome, Rotor syndrome;
- alcoholism;
- children under 12 years;
- old age (over 60 years);
- pregnancy or breastfeeding;
- increased excitability, sleep disorders, epilepsy;
- concomitant use with:
  - monoamine oxidase inhibitors (MAOIs), and for 2 weeks after discontinuation;
  - tricyclic antidepressants;
  - drugs that suppress or increase appetite and amphetamine-like psychostimulants;
  - vasodilators;
  - beta-blockers and other sympathomimetics.

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® should be avoided.

Peculiarities of interaction are caused by the components that are included into its formulation.

Paracetamol.

The rate of absorption of paracetamol may increase under the action of metoclopramide and domperidone and decrease under the action of cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by concomitant long-term regular daily use of paracetamol, with an increased risk of bleeding. Periodic use has no significant effect.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients risk factors (see "Special warnings and precautions for use" section).

Barbiturates reduce the antipyretic effect of paracetamol.

Anticonvulsants (including phenytoin, barbiturates, carbamazepine), which stimulate the activity of liver microsomal enzymes, may increase the toxic effects of paracetamol on the liver by increasing the rate of conversion of the drug to hepatotoxic metabolites. Concomitant use of paracetamol with hepatotoxic drugs increases the toxic effects of drugs on the liver.

Concomitant use of high doses of paracetamol with isoniazid increases the risk of hepatotoxic syndrome.

Concomitant use of paracetamol with azidothymidine may lead to the development of neutropenia.

Paracetamol reduces the effectiveness of diuretics.

Do not use simultaneously with alcohol.

Caffeine.

Caffeine when used simultaneously enhances the effect of analgesics-antipyretics (improves bioavailability), xanthine derivatives, α- and β-adrenomimetics, psychostimulants, thyrotropic drugs, ergotamine (improves the absorption of ergotamine from the digestive tract).

Cimetidine, hormonal contraceptives, isoniazid increase the effect of caffeine.

Caffeine increases the likelihood of liver damage by hepatotoxic drugs.

Caffeine reduces the effect of opioid analgesics, anxiolytics, hypnotics and sedatives, is an antagonist of drugs for anesthesia and other drugs that depress the central nervous system, a competitive antagonist of drugs adenosine, adenosine triphosphate (ATP); reduces the concentration of lithium in the blood.

Ototoxic and photosensitizing drugs when used concomitantly may exacerbate side effects.

Caffeine reduces the hypotensive effect of guanethidine, which in turn increases the α-adrenostimulatory activity of phenylephrine. Caffeine enhances the action of indirect anticoagulants (coumarin derivatives). Metoclopramide increases, and cholestyramine reduces the rate of caffeine absorption. Antidepressants, antiparkinsonian and antipsychotic drugs, phenothiazine derivatives increase the risk of urinary retention, dry mouth, constipation. Glucocorticosteroids increase the risk of glaucoma.

Phenylephrine hydrochloride.

Phenylephrine hydrochloride should not be used with alpha-blockers, other antihypertensive agents, phenothiazine derivatives (e.g. promethazine), bronchodilator sympathomimetics, guanethidine, foxglove, rauwolfia alkaloids, indomethacin, indomethacin, methyldopa, glucocorticosteroids; drugs that affect appetite, amphetamine-like psychostimulants, labor stimulants, anesthetics, ergot alkaloids, other drugs that stimulate the central nervous system, theophylline.

The use of phenylephrine hydrochloride with indomethacin and bromocriptine can cause severe hypertension. Concomitant use of phenylephrine hydrochloride with sympathomimetic amines, digoxin and cardiac glycosides increases the risk of arrhythmias and myocardial infarction.

There may be an increase in the vasoconstrictive effect of the drug when used concomitantly with labor stimulants and arrhythmias when used with anesthetics. There may be a significant increase in blood pressure with simultaneous intravenous administration of ergot alkaloids.

Atropine sulfate blocks phenylephrine-induced reflex bradycardia and increases the vasopressor response to phenylephrine. Concomitant use of phenylephrine with β-blockers may lead to hypertension and excessive bradycardia with possible heart block. It should be used with caution with thyroid hormones, drugs that affect cardiac conduction (cardiac glycosides, antiarrhythmic drugs). Concomitant use with drugs that increase potassium excretion, such as some furosemide-type diuretics, may increase hypokalemia and reduce arterial sensitivity to vasopressor drugs such as phenylephrine.

It should not be used together with other vasoconstrictors (with any route of administration of the latter).

Concomitant use of phenylephrine and other sympathomimetics can lead to additional stimulation of the central nervous system to an extremely high level, accompanied by nervousness, irritability, insomnia. Seizures are also likely. In addition, concomitant use of other sympathomimetics with phenylephrine may increase the vasoconstrictive effect or cardiovascular effect of either of these two drugs.

Chlorpheniramine maleate.

Chlorpheniramine maleate enhances the anticholinergic effect (dry mouth, urinary retention, constipation) of atropine, antispasmodics, central nervous system depressants (tranquilizers, barbiturates), antiparkinsonian drugs.

Do not use simultaneously with alcohol. Chlorpheniramine maleate when used simultaneously with alcohol potentiate the effect of each other.

Concomitant use with hypnotics, barbiturates, sedatives, neuroleptics and phenothiazine derivatives, tranquilizers, anesthetics, narcotic analgesics, alcohol enhances the effect of chlorpheniramine maleate.

Maprotiline (tetracyclic antidepressant) and other anticholinergic drugs: the anticholinergic effect of these drugs or antihistamines such as chlorpheniramine may be increased.

Special warnings and precautions for use.

Do not exceed the recommended doses.

Do not use concomitantly with sedatives and hypnotics.

Paracetamol.

The medicine contains paracetamol, so it should not be used together with other medicines that contain paracetamol and are used, for example, to reduce fever, treat pain, flu and cold symptoms or insomnia. Concomitant use with other products containing paracetamol may lead to overdose. Overdose with paracetamol can lead to liver failure that may result in liver transplantation or death. Patients diagnosed with hepatic or renal insufficiency should seek medical attention before using the drug.
It should be taken into account that the risk of hepatotoxic effect of paracetamol increases in patients with liver diseases.
Cases of hepatic impairment / liver failure at maximum therapeutic doses of paracetamol have been reported in patients with glutathione deficiency, such as in patients who are severely malnourished, have anorexia, low BMI, are chronic alcohol abusers or have sepsis.
Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis, 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.
In patients with glutathione deficiency, the use of paracetamol may increase the risk of metabolic acidosis. Signs of metabolic acidosis include deep, rapid, difficult breathing, nausea, vomiting, loss of appetite. Contact a doctor immediately if you get these symptoms.
Please see your doctor if your symptoms do not improve. Prolonged use except under medical supervision may be harmful.
Take only when clearly necessary.
Chlorpheniramine maleate.
During treatment, the use of alcohol, which increases the sedative effect of chlorpheniramine maleate, should be excluded.
Phenylephrine hydrochloride.
Phenylephrine may cause rapid pulse, dizziness, or rapid heartbeat; patients, accordingly, should be warned about this.
The use of the drug can lead to a positive analytical result of doping control.
Caffeine.
When using the drug, you should avoid excessive consumption of coffee, strong tea, other tonic drinks, and medicines containing caffeine. This can cause sleep problems, tremors, tension, irritability, palpitations.
The drug can affect the results of laboratory tests on the content of glucose and uric acid in the blood.
In case of an accidental overdose, the patient should immediately consult a doctor, even if the condition has not worsened.
Keep the drug out of the sight and reach of children.

Use in pregnancy and lactation.
Gripgo® is contraindicated during pregnancy. Breastfeeding should be discontinued during treatment.

Influence on velocity reactions in driving motor transport or operating other machines.
Driving, operating machinery and other hazardous activities should be avoided during treatment.

Administration and dosage.
Adults and children over 12 years of age should be prescribed 1 tablet 3–4 times a day with intervals of at least 4 hours between doses. The maximum daily dose is 4 tablets. The maximum period of use without consulting a doctor is 3 days, further therapy should be on doctor’s advice.

Children.

The drug is contraindicated in children under 12 years.

Overdose.

Symptoms.

Below are the overdose symptoms of individual components of Gripgo®.

Associated with paracetamol.

Overdose with paracetamol can lead to liver failure that may result in liver transplantation or death. Experience with overdose indicates that clinical signs of liver damage usually occur 24–48 hours after ingestion and reach maximum after 4–6 days.

Overdose symptoms in the first 24 hours: pallor, nausea, vomiting, anorexia, and abdominal pain. Asymptomatic overdose is also possible. Overdose of paracetamol in a single administration in adults and children can cause reversible or irreversible liver cells necrosis, which can lead to impaired glucose metabolism, metabolic acidosis, hepatocellular failure, encephalopathy, hemorrhages, hypoglycemia, coma, and death. At the same time, there is an increased level of liver transaminases (aspartate aminotransferase, alanine aminotransferase), lactate dehydrogenase and bilirubin, together with increased prothrombin levels 12–48 hours after administration. Liver damage is likely in adults who have taken more than recommended amounts of paracetamol. Increased amounts of the paracetamol metabolite (which is normally neutralized by glutathione at normal doses of paracetamol) are believed to be irreversibly bound to liver tissue. Acute renal failure with acute tubular necrosis can be manifested by severe pain in the lower back, hematuria, proteinuria and can develop even in the absence of severe liver damage. Cardiac arrhythmia and acute pancreatitis were also noted, usually accompanied by liver dysfunction and hepatotoxicity.

In case of long-term use of the drug in large doses, aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia may develop on the part of hematopoietic organs. When taking large doses, there is a possibility of such nervous system side effects as dizziness, psychomotor agitation, and disorientation; along with urinary system side effects, such as nephrotoxicity (renal colic, interstitial nephritis, papillary necrosis).

Symptoms may be limited to nausea and vomiting or may not reflect the severity of the overdose or the risk of organ damage.

Risk factors of paracetamol overdose are:

- long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's wort and other drugs that induce the synthesis of liver enzymes;
- regular abuse of alcohol;
- decrease in the level of glutathione, for example, in case of eating disorders, starvation, exhaustion of the body, cystic fibrosis, HIV.

Management: urgent measures of supportive and symptomatic therapy.

In case of overdose, urgent medical assistance is required. Treatment for overdose or even suspected overdose should be started immediately, the patient should be taken to the hospital, even if there are no early symptoms of overdose, because liver damage may not develop immediately. The concentration of paracetamol in blood plasma should be measured 4 hours or later after intake (earlier concentrations are unreliable).

If an excessive dose of paracetamol (more than 150 mg/kg) was taken within 1 hour, activated charcoal can be used. Treatment with N-acetylcysteine or methionine may be helpful. Symptomatic treatment should also be carried out.

Associated with phenylephrine hydrochloride and chlorpheniramine maleate.

Symptoms of overdose due to phenylephrine and chlorpheniramine maleate: headache, hyperhidrosis, drowsiness, insomnia, behavioral changes, anxiety, irritability, tremor, seizures, hyperreflexia, dizziness, nausea, vomiting, tachycardia, arrhythmias, extrasystoles.

Associated with chlorpheniramine maleate.

With an overdose of chlorpheniramine maleate, the condition can range from depressed to agitated (anxiety and seizures). Atropine-like symptoms may occur, including mydriasis, photophobia, dry skin and mucous membranes, increased body temperature, intestinal atony; depression of the

central nervous system is accompanied by respiratory disorders and disorders of the cardiovascular system.

Associated with caffeine.

Caffeine overdose has the following symptoms: dehydration, hyperthermia, ringing in the ears, epigastric pain, increased diuresis, extrasystole, tachycardia, rapid breathing, arrhythmia, central nervous system effects (dizziness, insomnia, exaltation, irritability, psychomotor agitation, affective state, anxiety, tremor, vomiting, seizures, convulsions, agitation, anxiety, delirium, increased tactile or pain sensitivity).

Management of overdose.

In case of overdose, emergency medical care is required. The patient should be taken to a hospital immediately, even if there are no early symptoms of overdose. Symptoms may be limited to nausea and vomiting or may not reflect the severity of the overdose or the risk of organ damage. Activated charcoal treatment should be considered if an overdose of paracetamol has been taken within 1 hour. Plasma paracetamol concentrations should be measured 4 hours or later after intake (earlier concentrations are inaccurate). N-acetylcysteine treatment can be used within 24 hours after taking paracetamol, but the maximum protective effect occurs when using it within 8 hours after intake. The effectiveness of the antidote decreases sharply after this time. If necessary, the patient should be administered intravenous N-acetylcysteine in accordance with current guidelines. In the absence of vomiting, oral methionine can be used as a suitable alternative in remote areas outside the hospital.

Adverse reactions.

Immune system: hypersensitivity reactions, including anaphylaxis, itchy skin, hyperemia, rash on the skin and mucous membranes (usually generalized rash, erythematous, urticaria), anaphylactic shock, angioneurotic edema, exudative erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrolysis, acute generalized exanthematous pustulosis.

Nervous system and mental disorders: psychomotor agitation and disorientation, anxiety, behavioral changes, fear, anxiety, irritability, sleep disturbances, insomnia, drowsiness, dizziness, mental confusion, hallucinations, depression, tremor, tingling sensation and heaviness in the limbs, tinnitus, headache, dizziness, coma, seizures, hyperexcitability, epileptic seizures, dyskinesia.

Respiratory system: bronchospasm in patients sensitive to aspirin and other NSAIDs, nasal congestion, throat irritation, hoarseness, pharyngitis.

Visual organs: impaired vision and accommodation, mydriasis, increased intraocular pressure, dry eyes.

Gastrointestinal tract: loss of appetite, nausea, vomiting, dry mouth, hypersalivation, heartburn, discomfort and pain in the epigastrium, exacerbation of peptic ulcer disease, flatulence, diarrhea, constipation.

Hepatobiliary system: liver dysfunction, increased activity of hepatic transaminases, usually without jaundice development, hepatonecrosis (at high doses), hepatotoxicity.

Endocrine system: hypoglycemia, up to hypoglycemic coma. With long-term use in high doses, damage to the insular apparatus of the pancreas (hyperglycemia, glucosuria) and disruption of glycogen synthesis up to the appearance of diabetes are possible.

Metabolic disorders: metabolic disorders of zinc, copper.

Blood and lymphatic system: anemia, including hemolytic anemia, bruising or bleeding; sulfhemoglobinemia and methemoglobinemia (cyanosis, shortness of breath, heart pain), thrombocytosis, hyperproteinemia, erythropenia, neutrophilic leukocytosis.

With prolonged use in high doses, aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia are possible.

Kidneys and urinary system: at high doses – nephrotoxicity (including papillary necrosis), urinary incontinence, urinary retention and difficulty urinating, dysuria, interstitial nephritis, increased creatinine clearance, increased excretion of sodium and calcium, aseptic pyuria, renal colic.

With prolonged use in high doses, there is a possibility of damage to the glomerular apparatus of the kidneys, crystalluria, the formation of urate, cystine and/or oxalate stones in the kidneys and urinary tract.
Cardiovascular system: hypertension, tachycardia or reflex bradycardia, arrhythmia, shortness of breath, heart pain, myocardial dystrophy (dose-dependent effect with prolonged use), heart palpitations.
Others: general weakness, increased sweating; possible false increase in uric acid in the blood, determined by the Bittner method; slight increase in the level of 5-hydroxyindoleacetic acid, vanillin mandelic acid and catecholamines in the urine.

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf-life. 4 years.

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

Package.
4 tablets in a blister; 1 blister in a cardboard package No. 4 (4×1).
4 tablets in a blister; 50 blisters in a cardboard package No. 200 (4×50).
10 tablets in a blister; 1 blister in a cardboard package No. 10 (10×1).
10 tablets in a blister; 1 blister in a cardboard package No. 10.
10 cardboard packages in a cardboard box No. 100 (10×1×10).
10 tablets in a blister; 10 blisters in a cardboard package No. 100 (10×10).

Conditions of supply.
Without prescription – No. 4 (4×1), No. 10 (10×1) in blisters.
By prescription – No. 200 (4×50), No. 100 (10×10), No. 100 (10×1×10) in blisters.

Manufacturer.
KUSUM HEALTHCARE PVT LTD

Location of manufacturer and its address of business activity.
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

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