BioGripin® PEDIATRIC SYRUP

Each 5 ml (1 cup) includes 120 mg Paracetamol, 50 mg oxolamine citrate and 1 mg chlorpheniramine maleate.
Sodium benzoate, sodium cyclamate, saccharin sodium, ponceau 4R, strawberry essence and banana essence are used as excipients.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic Properties:
Paracetamol: It is a material with analgesic and antipyretic effects. Its analgesic effect is mainly result of the inhibition of prostaglandin synthesis in the central nervous system and less the inhibition of pain impulse generation in periphery. And this occurs by inhibiting the synthesis or effect of prostaglandins and other materials that increase the sensitivity towards mechanical and chemical stimuli of peripheric pain receptors.
Antipyretic effect of Paracetamol is provided by the inhibition of E_2 synthesis of prostaglandin showing stimulant effect on thermoregulation center in the preoptic area of hypothalamus. As a result of this, blood stream to the skin with peripheral vasodilatation and sweating increase, heat loss grows.
Chlorpheniramine maleate: It is a material with antihistaminic and anticholinergic effects. It shows its anticholinergic effect by antagonizing acetylcholine effect in muscarinic (M_3) receptors in the secretary glands of nose mucosa. By this way, it stops the nasal flow and generates dryness in the nose mucosa. Chlorpheniramine antagonizes competitively the histamine effect in the histamine H_1 receptors, and it is effective in healing the allergical symptoms. The sedative effect of the drug is the result of the inhibition of histamine-N-methyltransferase in the central nervous system and blockage of central histaminergic receptors.
Oxolamine citrate: Its cough suppressant effect is provided by inhibiting the receptors starting cough reflex in lungs and bronchial tubes. It is less effective against coughs started by direct stimulation of cough center. Oxolamine increases ciliary activity decreased by harmful factors for the bronchus epithel. Furthermore, it has been experimentally shown that oxolamine has antiinflammatory and antispasmodic effects.

Pharmacokinetic Properties:
Absorbtion:
Paracetamol: It is rapidly and almost completely absorbed through oral way. Peak concentrations are formed within 1/2-2 hours in the plasma, and they are between 5-20 mcg/ml after oral doses up to 650 mg. Analgesic effect is shown within 30 minutes, reaches to maximum in 1-3 hours and continues for 3-4 hours. Meal with rich carbonhydrate value decreases the absorption.
Chlorpheniramine maleate: It is well absorbed by oral way. Because of the first pass effect, it can reach systemic circulation only by 35-60%. After a dose of 4 mg given as solution, average peak concentration is about 5.9 mg/ml, and it is formed between 2-6 hours. Antihistaminic effect is seen within 6 hours and it continues for 24 hours.
Oxolamine citrate: When it is orally administered, it shows its antitussive effect within an hour after the absorption, and this effect continues for 3-4 hours.
Distribution:
Paracetamol: It is distributed to most of the body tissues as uniform. It intervenes to human milk. The ratio of binding to proteins is averagely 25%, but it may vary between 20-50% according to the concentration in the blood. Distribution volume is 0.95 L/kg.
Chlorpheniramine maleate: It is widely distributed to the tissues. Volume of distribution at steady state (VDSS) is 2.5 – 3.2 L/kg in adults, 3.8 L/kg in children, and in vitro protein binding rate is 69– 72%.
Oxolamine citrate: When it is orally administered, it is distributed to bodily tissues after the absorption. Especially by diffusing into the bronchus mucosa, it causes anesthesia effect in afferent nerve endings, and decreases impulse transmission.

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Metabolism:
Paracetamol: 90-95 % of the given dose is metabolized in liver, and excreted as metabolite through urine within 24 hours. Only 3% of the given dose is excreted as unchanged molecule. Main metabolites are sulfate and glucuronide conjugates. Very few of it transforms into N-acetylimidoquinone which is a toxic intermediate. This is normally eliminated by binding to glutathion. However, when this mechanism is saturated, intermediate binds to cell proteins and cause liver necrosis. In case of acute over dose, liver diseases, fasting conditions, in new born babies and infants with decreased clearance and prolonged half life, detoxification mechanism may be insufficient, and liver necrosis risk occurs. Paracetamol dosage may be carefully adjusted and recommended dose limits should not be exceeded.
Chlorpheniramine maleate: When it passes through intestinal mucosa and liver, it is heavily metabolized. 20% of the given dose is excreted through urine without being changed, and the rest of it is excreted as metabolites.
Oxolamine citrate: It is metabolized into diethylamine and a neutral derivative with hidrolytic dissociation. Some portion of the drug is excreted out of the body as unchanged molecule.
Excretion:
Paracetamol: Its half life is 1-4 hours (averagely 2-7 hours). It does not change in kidney deficiency; it may prolong in cases of acute over dose, liver diseases, in premature and new born babies and geriatric patients; it is shorter in children. Renal clearance is 5 mg/minute. Paracetamol can be drawn with dialysis.
Chlorpheniramine maleate: Terminal elimination half life is 12-13 hours in adults, and 9.6 – 13.1 hours in children. Increase in the urine pH value (alkaline urine) and decrease in the urine flow delay the elimination of chlorpheniramine and its dealkylation metabolites.
Oxolamine citrate: 10% of the drug excreted through urine is as unchanged molecule; 0.6 % of it is as neutral derivatives and diethylamine formed by hydrolysis.

INDICATIONS:
BioGripin PEDIATRIC SYRUP is indicated for the symptomatic treatment in case of acute upper respiratory infections as analgesic and antipyretic.

CONTRAINDICATIONS:
BioGripin PEDIATRIC SYRUP is contraindicated in patients with hypersensitivity against any of the drug content.
Because of the chlorpheniramine it contains, it is contraindicated in patients with narrow angled glaucoma, acute asthma, prostate hypertrophy, bladder outlet obstruction, pyloric stenosis and taking MAOI. It should not be used in new born, premature and babies younger than 6 months of age.
Because of the paracetamol it contains, it is contraindicated in patients with chronic alcoholism, viral hepatitis, liver diseases (Child Plough A/C) and G6PD deficiency.
It should not be used in nursing mothers, because the active matters in BioGripin PEDIATRIC SYRUP penetrate into human milk.

WARNINGS/PRECAUTIONS:
- In people taking alcohol, maximum daily paracetamol dose should be 2 grams because of hepatotoxicity risk.
- BioGripin PEDIATRIC SYRUP should be administered carefully in patients with impaired kidney and liver function.
- **Usage in pediatric patients:** In infants and little children at early age, especially when the recommended dose is exceeded, chlorpheniramine may cause sedation, drowsiness, paradoxical excitation, hallucination and convulsion. Therefore, in children under 2 years of age, it should not be administered without a mandatory medical justification.
- **Usage in geriatric patients:** In geriatric patients (> 60 years of age), chlorpheniramine is more likely to cause sedation, dizziness and hypotension.
- **Usage in pregnancy:** The category of pregnancy is C. When BioGripin is to be used in pregnancy, benefits to mother and potential risks to fetus should be measured and considered.

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- **Usage in Nursing Period:** Nursing mothers should either stop nursing or taking BioGripin.
- **Effects on ability to drive and use machines: Chlorpheniramine maleate in BioGripin affects central nervous system, and may cause drowsiness, blurred vision and ataxia, so patients should be warned beforehand.**

SIDE EFFECTS/ADVERSE REACTIONS:
Drowsiness, flutter, blurred vision, difficult urination, dry mouth, anorexia, irritability, skin allergy, sweating, tachycardia, tinnitus, heartburn, photosensitivity.

PLEASE CONSULT YOUR DOCTOR IN CASE OF ANY UNXPECTED EFFECT.

DRUG INTERACTIONS:
1) Alcohol, phenothiazines, tricyclic antidrepressants and chlorpheniramine potentiate the depressant effect of each other on central nervous system reciprocally.
2) Antimuscarinic effect of chlorpheniramine is increased by atropine, amantadine, haloperidol, phenothiazins, procainamide and quinidine.
3) MAO inhibitors increase the antimuscarinic and CNS depressant effect of chlorpheniramine.
4) Chlorpheniramine may mask the ototoxic effect of cisplatin, paramomycin, salicylates and vancomycin.
5) Hepatotoxicity risk of paracetamol may increase in patients with chronic alcoholism and in those who are using hepatotoxic drugs.
6) Hepatic enzyme inducers (barbiturates, primidone) may decrease paracetamol's clinical effectiveness by enhancing its metabolism.
7) When it is administered together with levodopa, heart arythmia risk might increase.

DIAGNOSTIC TEST INTERACTIONS:
In patients using paracetamol:
- Blood sugar: Observed low when performed with glucose oxidase/peroxidase method. Observed identical because of Hexokinase/glucose-6-phosphate dehidrogenase method.
- Uric acid in the serum: Observed high when performed with phosphotungstate method.
- The results of the bendiromid test are invalid. Because both paracetamol and bentiromide are metabolized to an arylamine compound which influences the amount of p-aminobenzoic acid.
- Qualitative 5-hidroxyindoleacetic acid (5 HIAA) test performed with nitrosonaphtol reagent in the urine gives fake positive result. Quantitative test is not affected.
- Chlorpheniramine causes fake negative result by affecting the skin histamin test done with allergens. If test is to be performed, administration of BioGripin should be stopped 72 hours before the test.

ADMINISTRATION and DOSAGE:
For adults and children over 12 years of age, the usual dose is: 1-2 cups (5-10 ml) at once. This dose can be repeated for three or four times a day with intervals of 6-8 hours. For 24 hours, the maximum dose is 8 cups.
In people taking alcohol, maximum daily paracetamol dose should be 2 grams because of hepatotoxicity risk.
For children between 6-12 years of age, the usual dose is: 1/2-1 cups (2.5-5 ml) at once. This dose can be repeated for three or four times a day with intervals of 6-8 hours. For 24 hours, the maximum dose is 4 cups.
For children between 2-6 years of age, the usual dose is: 1/2 cups (2,5 ml) at once. This dose can be repeated for three or four times a day with intervals of 6-8 hours. For 24 hours, the maximum dose is 2 cups.
In children under 2 years of age, it should not be administered without a mandatory medical justification.

OVERDOSE and MEASURES:
When noticed in early phase, patient is made to vomit or stomach irrigation is performed. In little children, measures should be taken against aspiration risk. Giving cathartic may be beneficial. Then, according to the course of the case, general supportive and symptomatic treatment (i.v. fluid, oxygen) is applied. In case of hypotension, vasopressors may be used. However, adrenalin should not be given. It decreases blood pressure even more. Analeptics should not be used, because they may cause convulsions. Oral N-acetylcysteine is the specific antidote of paracetamol. Initial dose of acetylcysteine is 140 mg/kg, and then 70 mg/kg dose is given each 4 hours to form total 17 doses. Each dose should be given as 5% solution with a soft drink. The most effective application for acetylcysteine therapy is within 10-12 hours after the over dosage, however; administration within 24 hours may also be beneficial.

STORAGE CONDITIONS:
Keep away from children in its packaging, at room temperature below 25°C. Store at refrigerator after opening.

HOW SUPPLIED:
BioGripin PEDIATRIC SYRUP, in bottles of 100 cc with measuring spoon of 5 cc.

Distributed by:
BioActiveT Pharma, UNITED KINGDOM.