For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Chlorpheniramine Maleate, Phenylephrine Hydrochloride, Paracetamol, Sodium Citrate & Menthol Syrup

(Brand Name: KOLQ® Syrup)

Paracetamol: Box Warning About Its Liver Toxicity

Taking more than daily dose may cause serious liver damage or allergic reactions (e.g., swelling of the face, mouth and throat, difficulty in breathing, itching or rash). The risk of liver injury primarily occurs when patient take multiple products containing paracetamol/acetaminophen at one time and exceed the current maximum dose of 4000 mg within a 24-hour period.

2. Qualitative and Quantitative Composition

Each 5 ml contains:

Chlorpheniramine Maleate IP ……... 0.5 mg
Phenylephrine Hydrochloride IP …….…..... 5 mg
Paracetamol IP ……..… 125 mg
Sodium Citrate IP ……..……. 60 mg
Menthol IP ……...……. 1 mg
In a Flavoured Syrupy Base ……...…….. q.s.
Colours: Carmoisine and Caramel

3. Dosage Form and Strength

Dosage Form: Oral liquid.

Dosage Strength: Chlorpheniramine maleate 0.5 mg, phenylephrine hydrochloride 5 mg, paracetamol 125 mg, sodium citrate 60 mg, and menthol 1 mg per 5 ml of liquid.

4. Clinical Particulars

4.1 Therapeutic Indication

KOLQ Syrup is indicated for symptomatic treatment of common cold and flu-like syndrome.

4.2 Posology and Method of Administration

For oral administration. Shake well before use.

- **Children between 4 to 6 years:** 2.5 ml to be administered every 4 to 6 hours daily
- **Children > 6 to 12 years:** 5 ml to be administered every 4 to 6 hours daily
- **Adults and adolescents > 12 years:** 10 ml to be administered every 4 to 6 hours daily

Or, as prescribed by the physician.

4.3 Contraindications

KOLQ Syrup is contraindicated in the following:

- Known hypersensitivity to chlorpheniramine maleate or to phenylephrine or to paracetamol or to sodium citrate or to menthol or to any component of the formulation.
- In patients who have been treated with monoamine oxidase (MAO) inhibitors within the last 14 days.
- In patients who are currently receiving other sympathomimetic drugs.
- Cardiovascular disorders.
- In patients with peripheral vascular insufficiency.
- In patients with hyperthyroidism.
- In patients with glaucoma.
- In patients with prostate problem.
- Pheochromocytoma.
- In patients having aluminum toxicity, untreated Addison's disease, heart disease, hyperkalemia, renal impairment, dehydration (due to its sodium citrate content).

4.4 Special Warnings and Precautions for Use

Chlorpheniramine Maleate

Chlorpheniramine maleate may cause drowsiness and may have additive CNS effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Antihistamines should be used with caution in patients with peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.

Chlorpheniramine maleate, in common with other drugs having anticholinergic effects, should be used with caution in the following conditions: Epilepsy; raised intra-ocular pressure including glaucoma; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment. Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g., increased energy, restlessness, nervousness).

Chlorpheniramine maleate should not be used with other antihistamine-containing products.

Phenylephrine

Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, heart disease (angina), peripheral vascular disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy.

Phenylephrine should not be used with other sympathomimetics (such as decongestants, appetite suppressants, and amphetamine-like psychostimulants).

Sympathomimetics may act as cerebral stimulants giving rise to insomnia, nervousness, hyperpyrexia, tremor, and epileptiform convulsions.

Paracetamol

Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.
Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.

Sodium Citrate
Sodium citrate should not generally be given to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria.
As it contains sodium, sodium citrate should be used with caution in patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism.

Menthol
Menthol may give rise to hypersensitivity reactions including contact dermatitis.
There have been reports of apnoea and instant collapse in infants after the local application of menthol to their nostrils. Thus, this formulation should be kept out of reach of infants and children.

4.5 Drug Interactions
Chlorpheniramine Maleate
Alcohol, Hypnotics, Anxiolytics, Sedatives, Opioid Analgesics, and Neuroleptics: Concurrent use of chlorpheniramine maleate with any of these drugs may enhance the sedative effect.
Phenytoin: Chlorpheniramine maleate inhibits phenytoin metabolism and can lead to phenytoin toxicity.
MAO Inhibitors and Tricyclic Antidepressants: The antimuscarinic effects of chlorpheniramine maleate are enhanced by other antimuscarinic drugs and both antimuscarinic and sedative effects are enhanced by MAO inhibitors (concurrent therapy is contraindicated) and tricyclic antidepressants.

Phenylephrine
MAO Inhibitors: Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and MAO inhibitors, thus concomitant use is contraindicated.
Sympathomimetic Amines: Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.
Beta-Blockers and Other Antihypertensives (Including Debrisoquine, Guanethidine, Reserpine, and Methyldopa): Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased.
Tricyclic Antidepressants (Amitriptyline): Concomitant use of phenylephrine with amitriptyline may increase the risk of cardiovascular side effects.

Ergot Alkaloids (Ergotamine and Methylsergide): Concomitant use of phenylephrine with these drugs increases risk of ergotism.
Digoxin and Cardiac Glycosides: Co-administration of phenylephrine with these drugs increases risk of irregular heartbeat or heart attack.

Paracetamol
Cholestyramine: The rate of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.
Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
Warfarin: The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Chloramphenicol: Concurrent administration of paracetamol and chloramphenicol may markedly retard the elimination of chloramphenicol and thus, increases plasma concentration of chloramphenicol which leads to risk of its harmful effects. Monitoring of chloramphenicol plasma levels is recommended while combining paracetamol with chloramphenicol injection.
Alcohol, Anticonvulsants, and Isoniazid: Concomitant administration of alcohol, anticonvulsants, and isoniazid with paracetamol may increase risk of hepatotoxicity.

Sodium Citrate
Acidic Drugs: Alkalinisation of the urine leads to increased renal clearance of acidic drugs such as salicylates, tetracyclines, and barbiturates. Conversely, it prolongs the half-life of basic drugs and may result in toxicity.
Aluminium-Containing Compounds: Citrate salts taken orally can enhance the absorption of aluminium from the gastrointestinal tract (GIT). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations, including many effervescent or dispersible tablets are best avoided by patients with renal failure taking aluminium-containing compounds.
Lithium or Tetracyclines (e.g., Doxycycline): Effectiveness of these drugs may be decreased when coadministered with sodium citrate.
Anorexiants (e.g., Phentermine) or Sympathomimetics (e.g., Pseudoephedrine): Co-administration of these drugs may results in increased side effects.
Miscellaneous: Sodium citrate increases intra-gastric pH, thus it may reduce or increase the rate and/or extent of absorption of a number of drugs.

Menthol
Drugs Metabolised by CYP3A4: Menthol is a moderate inhibitor of CYP3A4 enzyme. Thus, menthol may alter plasma levels of drugs metabolised mainly by CYP3A4 enzymes. However, no clinically significant drug interactions have been reported.

4.6 Use in Special Populations
Pregnant Women

It is not known whether components of KOLQ Syrup can cause fetal harm when administered to a pregnant woman. Use of chlorpheniramine maleate during the third trimester of pregnancy may result in reactions in the newborn or premature neonates. Thus, KOLQ Syrup should not to be used during pregnancy unless considered mandatory by the physician.

Lactating Women

Paracetamol and phenylephrine are excreted in breast milk, but not in a clinically significant amount. Chlorpheniramine maleate may inhibit lactation and may be secreted in breast milk. Because of higher risk of intolerance of antihistamines in small infants (newborns and premature), KOLQ Syrup should not be administered to a nursing mother. Accordingly, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Patients

Elderly patients with normal renal and hepatic function should be given the same dose as recommended for adults. The risk of toxic reactions with this formulation may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

4.7 Effect on Ability to Drive and Use Machines

The anticholinergic properties of chlorpheniramine maleate content of this formulation may cause drowsiness, dizziness, blurred vision and psychomotor impairment, which can seriously hamper the patients' ability to drive and use machinery. Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable Effects

Chlorpheniramine Maleate

Central Nervous System (CNS): Sedation (varying from slight drowsiness to deep sleep), headaches, inability to concentrate, lassitude, dizziness, twitching, muscular weakness and inco-ordination, tinnitus, depression, irritability and nightmares may occur infrequently. Paradoxical excitation in children and confusional psychosis in the elderly can occur. The effects of alcohol may be increased.
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, dyspepsia, anorexia.
Anticholinergic: Urinary retention, dryness of mouth, blurred vision.
Cardiovascular: Tachycardia, arrhythmias, hypotension, tightness in chest.
Hepatic: Jaundice.
Hematological: Haemolytic anaemia; other blood dyscrasias.
Allergic: Urticaria, exfoliative dermatitis, photosensitivity reactions.

Phenylephrine

Phenylephrine may elevate blood pressure with headache, vomiting and rarely palpitations, tachycardia or reflex bradycardia, tingling and coolness of the skin. There have been rare reports of allergic reactions.

Paracetamol

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including thrombocytopenic purpura, methaemoglobenemia and agranulocytosis, but these were not necessarily related to paracetamol. Overdosage with paracetamol can result in severe hepatotoxicity and sometimes acute renal tubular necrosis. If there is a pre-existing liver insufficiency, paracetamol can be hepatotoxic even in normal dosage. Increased levels of aspartate aminotransferase and hepatic transaminases may occur. Nausea, vomiting, abdominal pain, diarrhea, constipation, dyspepsia, dry mouth, heartburn have also been reported commonly with the use of paracetamol.

Sodium Citrate

Side effects of sodium citrate may include nausea, vomiting, diarrhea, and abdominal pain.

Menthol

Ingestion of significant quantities of menthol is reported to cause symptoms such as severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma.

4.9 Overdose

Chlorpheniramine Maleate

Symptoms: The estimated lethal dose of chlorpheniramine maleate is 25 to 50 mg/kg body weight. Overdose with chlorpheniramine maleate is associated with antimuscarinic, extrapyramidal, gastrointestinal, and CNS effects. In children, CNS stimulation predominates over CNS depression, causing ataxia, excitement, tremors, psychosis, hallucinations, and convulsions. Hyperpyrexia may also occur. Other symptoms of overdose in children include dilated pupils, dry mouth, facial flushing. In adults, CNS depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse including arrhythmias.

Treatment: In severe overdose the stomach should be emptied. If overdose is by the oral route, treatment with activated charcoal should be considered (treatment is most effective if given within an hour of ingestion). Convulsions may be controlled with intravenous diazepam or phenytoin, although it has been suggested that CNS depressants should be avoided. Other treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia, and intravenous fluids. Vasopressors such as noradrenaline or phenylephrine may be used to counteract hypotension. Forced diuresis, peritoneal dialysis or haemodialysis appear to be of limited benefit. Haemoperfusion may be used in severe cases.

Phenylephrine

Symptoms: Overdose symptoms may include hypertension and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures, and arrhythmias may occur.

Treatment: Treatment measures include early gastric lavage and symptomatic and supportive measures. The hypertensive effects may be treated with an α-receptor blocking agent (such as phentolamine mesylate, 6 to 10 mg) given intravenously, and the bradycardia treated with atropine, preferably only after the pressure has been controlled.

Paracetamol

Symptoms: Ingestion of 5 gram or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycaemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Treatment: Immediate treatment is essential in the management of paracetamol overdose. 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 (FDA approved antidote) may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion.

Sodium Citrate

Symptoms: Excessive use of sodium citrate may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Excessive doses of sodium salts may also lead to sodium overloading and hyperosmolality. Symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop, especially in hypocalcemic patients.

Treatment: Treatment of metabolic alkalosis consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium ions may be of particular importance.

Menthol

Symptoms: Ingestion of significant quantities of menthol is reported to cause symptoms such as severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, epileptiform convulsions, CNS depression, and coma.

Treatment: Supportive care, including anticonvulsant therapy, is the mainstay of treatment of menthol intoxication. Gastric lavage may be considered if the patient presents within 1 hour of ingestion; any convulsions must be controlled first. Activated charcoal may be given orally. Haemodialysis with a lipid dialysate or haemoperfusion have been tried, but are of doubtful value.

5. Pharmacological Properties

5.1 Mechanism of Action

Chlorpheniramine Maleate – Antihistamine.

Chlorpheniramine maleate is H_1 receptor antagonist (antihistamine effect). Chlorpheniramine maleate diminishes or abolishes the actions of histamine in the body by competitive (reversible) blockade of histamine H_1 receptor sites on tissues. Chlorpheniramine maleate prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Phenylephrine - Sympathomimetic Nasal Decongestant.

Phenylephrine is a nasal decongestant with a potent postsynaptic α-receptor agonist activity. Dilated blood vessels can cause nasal blocks or stuffy nose. Phenylephrine shrinks blood vessels in the nasal passages and thus, reduces nasal congestion. A direct action at the receptors accounts for the greater part of its effects, whereas only a small part of effect is due to its ability to release norepinephrine.

Sympathomimetic amines, such as phenylephrine, act on α-adrenergic receptors of the respiratory tract to produce vasoconstriction effect. This result in temporarily reduction of swelling associated with inflammation of the mucous membranes lining the nasal and sinus passages. This allows the free drainage of the sinusoidal fluid from the sinuses. In addition to reducing mucosal lining swelling, phenylephrine also suppresses the production of mucous, therefore preventing a buildup of fluid within the nasal cavities.

Paracetamol – Analgesic and Antipyretic

Analgesic Effect: The mechanism of analgesic action of paracetamol has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic Effect: Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

Sodium Citrate: Expectorant

Expectorants such as sodium citrate are considered to increase the volume of secretions in the respiratory tract thereby facilitating their removal by ciliary action and coughing.

Menthol: Demulcent

Menthol produces demulcent effect by reducing irritation of mucous membranes of the throat and trachea. Menthol diminishes the effects of local mechanical, chemical or bacterial irritants. Menthol provides soothing action on the throat and reduces impulses from the inflamed/irritated mucosa.

5.2 Pharmacodynamic Properties

Chlorpheniramine Maleate

Chlorpheniramine maleate produces antihistamine effect by blocking H_1 receptor. Chlorpheniramine maleate also possesses anticholinergic activity.

Phenylephrine

Phenylephrine is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa.

Paracetamol

Paracetamol is a centrally acting analgesic and antipyretic agent.

Sodium Citrate

Sodium citrate produces expectorant effect.

Menthol

Menthol provides cooling and soothing effect on the pharyngeal mucosa. Menthol also exerts a mild local anesthetic action; thereby minimizes triggering of cough episode (demulcent action). Menthol can also relieve pain in inflamed or irritated mucous membranes.

5.3 Pharmacokinetic Properties

Chlorpheniramine Maleate

Absorption: Chlorpheniramine maleate is almost completely absorbed after oral administration with peak plasma concentrations occurring at about 2.5 to 6 hours. Bioavailability is low with values of 25 to 50% having been reported.

Distribution: Chlorpheniramine is widely distributed in the body, and enters the CNS. About 70% of chlorpheniramine in the circulation is protein-bound.

Metabolism and Excretion: Chlorpheniramine maleate undergoes some first pass metabolism (10%) and enterohepatic recycling. Chlorpheniramine maleate is extensively metabolised, principally to inactive desmethylated metabolites which are excreted primarily in the urine (50%), together with about 35% unchanged drug. Only trace amounts are excreted in the faeces. The mean elimination half-life has been reported to be about 30 hours, with mean values ranging from 2 to 43 hours.

Phenylephrine

Absorption: After oral administration, phenylephrine is rapidly absorbed from the GIT and undergoes first-pass metabolism by MAO in the gut and liver. As a consequence, systemic bioavailability of oral route is only about 40%. Following oral administration, peak plasma concentration is achieved in 1 to 2 hours.

Distribution: Distribution in the brain appears to be minimal.

Metabolism and Excretion: Following absorption, the drug is extensively metabolised in the liver as the sulphate conjugate. Both phenylephrine and its metabolites are excreted in the urine. The mean plasma half-life is in the range 2 to 3 hours.

Paracetamol

Paracetamol is readily absorbed from the GIT with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, but increases with increasing concentrations.

Sodium Citrate

After absorption, sodium citrate is metabolised to bicarbonate. Bicarbonate ions are excreted in the urine, which is rendered alkaline, and there is accompanying diuresis.

Menthol

After absorption, menthol is excreted in the urine and bile as a glucuronide.

6. Nonclinical Properties

6.1 Animal Toxicology

Chlorpheniramine Maleate

Toxicity: LD50 values reported for chlorpheniramine maleate by oral route in rats, mice, and guinea pigs were 118, 121, and 186 mg/kg respectively.

Chlorpheniramine maleate was administered by gavage to groups of 12 female Sprague-Dawley rats for 29 days at doses of 0, 2, 5, 10, or 25 mg/kg body weight and in feed (average daily dose, 1 mg/kg) for three successive generations to male and female Sprague-Dawley rats. No clinical, hematologic, or pathologic alterations were apparent in either study.

No compound-related effects were reported after chlorpheniramine maleate was administered by gavage to groups of 8 male and 8 female rats 5 days per week for 6 weeks at doses of 5 or 10 mg/kg per day. Similar experiments in which two rhesus monkeys were administered 20 mg/kg per day 5 days per week for 7 weeks resulted in no apparent adverse effects.

Mutagenicity: Chlorpheniramine maleate was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of S9 metabolic activation systems prepared from the livers of Aroclor 1254-treated male Sprague-Dawley rats or male Syrian hamsters.

Carcinogenicity: A 2-year oncogenicity study of chlorpheniramine maleate was conducted in which groups of 50 male and 50 female CD albino rats were fed diets containing SCH 190 (Chlor-trimeton') for 103 weeks. The doses (approximately 2, 10, or 20 mg/kg per day) were formulated based on group mean values for body weight and feed consumption. There were no reported increases in the incidences of neoplastic lesions attributed to dosing with chlorpheniramine maleate.

Phenylephrine

Toxicity: LD50 values for phenylephrine have been determined in several species by various routes of administration. In Wistar rats, the LD50 value by intraperitoneal injection was 17 mg/kg and by subcutaneous injection was 33 mg/kg. The LD50 values in male Swiss mice were 89 mg/kg (intraperitoneal) and 22 mg/kg (subcutaneous). New Zealand rabbits had LD50 values of 0.5 mg/kg (intravenous), 7.2 mg/kg (intramuscular), and 22 mg/kg (subcutaneous).

Mutagenicity: Phenylephrine hydrochloride was not mutagenic in four tester strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, and TA98) in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9.

Carcinogenicity: In the mouse study, the mean daily dose (males and females) in the low dose animals was 133 mg/kg and in the high dose animals 270 mg/kg. The study demonstrated no evidence of carcinogenicity in rats and mice under the testing conditions employed.

Paracetamol

Preclinical data reveal no special hazard for humans with paracetamol based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenicity. Studies for the evaluation of toxicity to reproduction and development are not available.

Sodium Citrate

Chronic Toxicity: In a 1-year oral repeated-dose toxicity study, two successive generations of rats were exposed to 0.1% citric acid, sodium salt (approximately 50 mg/kg/day) in the diet. No adverse effects were seen in rats. A limited number of tissues were examined microscopically. LOAEL (lowest observed adverse effect level i.e., lowest dose at which there was an observed toxic or adverse effect) > 0.1% citric acid, sodium salt (approximately 50 mg/kg/day based on no effects at one concentration).
In a 32-week oral repeated-dose toxicity study, 20 male rats were treated with 5% citric acid, sodium salt (about 2,500 mg/kg/day) in the diet. No overt signs of toxicity were observed. LOAEL > 2500 mg/kg/day (based on no effects at the only concentration tested).
Reproductive Toxicity: In a fertility study, rats were exposed to 0.1% citric acid, sodium salt (approximately 50 mg/kg/day) in their daily diet. Exposure began 29 weeks prior to mating and continued for a few months after mating. No reproductive effects were detected. LOAEL for reproductive toxicity > 0.1% (approximately 50 mg/kg/day, based on no treatment related effects on reproduction).
Developmental Toxicity: In a developmental toxicity study, pregnant rats were exposed to 241 mg/kg/day citric acid by oral gavage daily on days 6 to 15 of gestation. No adverse effects were observed on fertilization, maternal, or fetal survival. LOAEL for maternal and developmental toxicity > 241 mg/kg/day (based on no observed effects at the only dose level tested).
Mutagenesis: In several *in vitro* and *in vivo* tests, citric acid/sodium citrate was not mutagenic.

Menthol

Toxicity: Menthol show low acute oral toxicity with LD50 values normally greater than 2000 mg/kg body weight (rats and mice). Only limited studies are available investigating dermal toxicity. In one study the LD50 of menthol in rabbits was above 5000 mg/kg body weight. In a second investigation a dermal dose of 34500 mg menthol liquid / kg body weight was lethal to a mouse.
Mutagenesis: Menthol was not mutagenic in the Ames test with the standard tester strains *Salmonella typhimurium* TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537, TA 2637 with and without metabolic activation and including cytotoxic concentrations.
Carcinogenicity: Menthol was tested in a well performed study for carcinogenicity (103 weeks) in doses of 3750 and 7500 ppm in the feed in F344 rats and of 2000 and 4000 ppm in the feed in B6C3F1 mice. In male and female rats the survival rate was not affected by treatment and no carcinogenic effects of menthol were found in any organ.
Impairment of Fertility: There is no evidence indicating a potential of menthol to interfere adversely with reproduction. Histopathological examinations of the reproduction organs of rats and mice showed no changes in repeated dose toxicity studies with menthol and also in carcinogenicity studies with menthol.

7. Description

KOLQ Syrup is a Pink-Red coloured clear liquid.

Each 5 ml of KOLQ Syrup contains 0.5 mg of chlorpheniramine maleate, 5 mg of phenylephrine hydrochloride, 125 mg of paracetamol, 60 mg of sodium citrate, and 1 mg of menthol for oral administration.

Chlorpheniramine Maleate

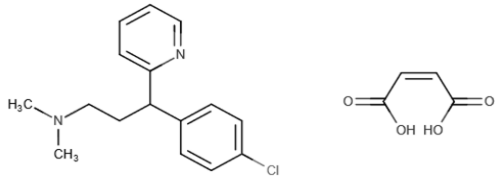
Chlorpheniramine maleate appears as odorless white crystalline solid or white powder with a bitter taste.

Molecular Weight: 390.9 g/mol.

Molecular Formula: C20H23ClN2O4.

Chemical Name: (2Z)-but-2-enedioic acid; [3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl] dimethylamine.

Structural Formula:



Phenylephrine Hydrochloride

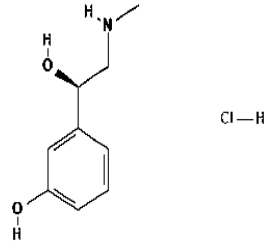
Phenylephrine hydrochloride is an odorless white microcrystalline powder with a bitter taste.

Molecular Weight: 203.66 g/mol.

Molecular Formula: C9H14ClNO2.

Chemical Name: 3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol; hydrochloride.

Structural Formula:



Paracetamol

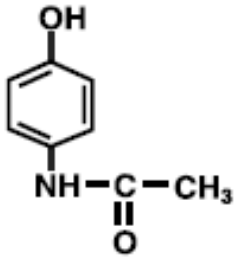
Paracetamol, also called as acetaminophen, is a slightly bitter, white, odorless, crystalline powder. Paracetamol is a non-opiate, non-salicylate analgesic and antipyretic agent.

Molecular Weight: 151.16 g/mol.

Chemical Name: 4'-hydroxyacetanilide.

Molecular Formula: C8H9NO2.

Structural Formula:

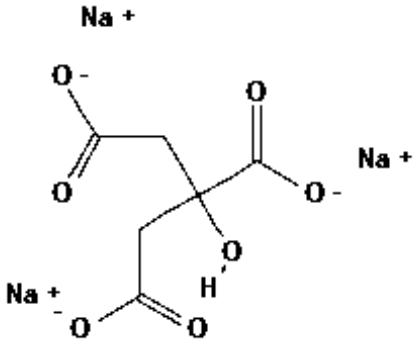


Sodium Citrate

Sodium citrate is the sodium salt of citric acid having expectorant effect. It is white, crystalline powder or white, granular crystals, slightly deliquescent in moist air, freely soluble in water, practically insoluble in alcohol.

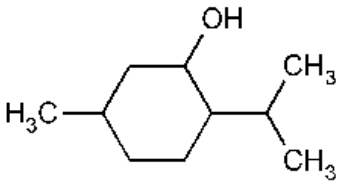
Molecular Weight: 258.07 g/mol.

Chemical Name: Trisodium; 2-hydroxypropane-1,2,3-tricarboxylate.
Molecular Formula: C6H5Na3O7.
Structural Formula:



Menthol

Menthol is an organic compound made synthetically or obtained from peppermint or mint oils with flavoring, demulcent, and local anesthetic properties.
Menthol is a white crystalline solid with a peppermint odor and taste.
Chemical Name: Cyclohexanol, 5-methyl-2-(1-methylethyl).
Molecular Weight: 156.27 g/mol
Molecular Formula: C10H20O.
Structural Formula:



Inactive ingredients (excipients) of KOLQ Syrup contain Sodium Benzoate, Xanthan Gum, Poly Ethylene Glycol 400, Propylene Glycol, Glycerin, Sucralose, Lactic Acid, Colour Caramel, Colour Carmoisine & Flavour Mixed Fruit

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

18 Months

8.3 Packaging Information

60 ml PET bottle with 10 ml measuring cup.

8.4 Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions to Patients / Caregivers

- Use this medication exactly as prescribed by your doctor. Don't exceed the recommended dose or duration of treatment. Shake well before each use.
- This medicine is not recommended in children below 2 years of age.
- Avoid use of this medicine during pregnancy and lactation.
- Not to share this medication with other patients even though symptoms are similar. Also, don't use medication prescribed for other patients.
- Not to use with any other medicine containing paracetamol (prescription or over-the-counter - OTC). Users to ask a doctor or pharmacist, if they are not sure about presence of paracetamol in the drug taken for other illnesses. Also, not to use this medicine with other cough and cold relief products without consulting your doctor.
- This medicine (as it contains chlorpheniramine maleate) may cause drowsiness. Patients should be warned not to engage in activities requiring mental alertness such as driving a car or operating machinery after taking this medicine.

10. Details of Manufacturer

Akums Drugs & Pharmaceuticals Ltd.
22, Sector - 6A, I.I.E., SIDCUL, Haridwar - 249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 123/UA/2007. Date of FDA Product Permission: 13/07/2017

12.Date of Revision

December 2023.

Marketed by:
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Division of
BLUE CROSS LABORATORIES PVT LTD.
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