Product Information

Colchicine Tablets

Composition

Active ingredients: 0.5 mg Colchicine

List of excipients: starch corn, lactose, povidone K25, magnesium stearate

Indication

Prevention and treatment of gout and FMF (familial mediterranean fever).

Dosage and administration

Gout:

The patient should be instructed to always have colchicines at hand, so that therapy can be started at the first sign of an impending attack. Initiation of colchicines therapy in the later stages of an attack may not completely abate the condition.

The initial dose to relieve an attack is 1 or 2 tablets, followed by 1 tablet each hour or 2 tablets every 2 hours, until the pain is relieved, or nausea, vomiting or diarrhea develops. The total amount of colchicines usually required is variable. A course of therapy may range from 3-6 mg. as intermittent treatment,

A total dose of 6mg should not be exceeded. The course should not be repeated within three days.

Familial Mediterranean Fever

The recommended dosage of COLCHICINE for FMF in adults is 1 mg to 2 mg daily. COLCHICINE should be increased as needed to control disease and as tolerated in increments of 0.25 mg/day to maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in increments of 0.25 mg/day. The total daily COLCHICINE dose may be administered in one to two divided doses.

Renal Impairment:

For mild/moderate renal impairment (creatinine clearance 10-50 ml/minute), reduce dose or increase interval between doses (see section Contraindications).

Elderly:

To be given with great care.

Children:

FMF: The recommended dosage of colchicine for FMF in pediatric patients 4 years of age and older is based on age. The following daily doses may be given as a single or divided dose twice daily:
Children 4 – 6 years: 0.25 mg to 1.5 mg daily
Children 6 – 12 years: 1 mg to 1.5 mg daily

Contraindications

The use of colchicine is contraindicated in patients with hypersensitivity to colchicines. The use of colchicine is contraindicated in pregnancy. Colchicine should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion. Colchicine should not be used in patients with severe renal impairment (creatinine clearance less than 10ml/minute).

Special warnings and precautions for use

Colchicine should be given with care to elderly and debilitated patients as there is a greater risk of cumulative toxicity.

Care should also be exercised in those with cardiac or blood problems, hepatic, gastrointestinal disease or if patients are breast-feeding.

Reduce dose in patients with mild to moderate renal impairment (see Method of Administration and Contraindications).

For patients on long-term therapy, compete blood counts are mandatory at periodic intervals. Reduction in dosage is indicated if weakness, anorexia, nausea, vomiting or diarrhea appear.

Colchicine-induced myoneuropathy in patients with altered renal functions is not infrequent. Colchicines withdrawal resulted in a spontaneous remission of symptoms within 4-6 weeks.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug interactions

Co-administration with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) increases the risk of colchicines-induced toxic effects. If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicines may need to be reduced or interrupted. Use of colchicine with P-gp or strong CYP3A4 inhibitors is contraindicated in patients with renal or hepatic impairment. (Strong CYP3A4 inhibitors:atazanavir, clarithromycin,indinavir, itraconazole, ketoconazole,nefazodone, nelfinavir, ritonavir,saquinavir,telithromycin). (Moderate CYP3A4 inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole,fosamprenavir, grapefruit juice, verapamil). (P-gp inhibitors: cyclosporine, ranolazine).

Vitamins: the absorption of Vitamin B_{12} may be impaired by chronic administration or high doses of colchicine; requirement may be increased.

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

Concurrent use of alcohol with orally administered colchicines increases the risk of gastrointestinal toxicity, especially in alcoholics; also, alcohol increases blood uric acid concentrations and may decrease the efficacy of prophylactic gout therapy.

Additive bone marrow depression may occur; dosage reductions may be required when 2 or more bone marrow depressants, including radiation, are used concurrently or consecutively.

Pregnancy and lactation

Do not use in pregnancy as there is a risk of foetal chromosome damage. Colchicines may be used with caution during breast-feeding.

Adverse Reactions
Colchicine frequently causes nausea, vomiting and abdominal pain. Larger doses may cause profuse diarrhea, gastrointestinal hemorrhage, skin rashes and renal and hepatic damage. Rarely peripheral neuritis, myopathy, rhabdomyolysis, alopecia, inhibition of spermatogenesis and, with prolonged treatment, bone marrow suppression with agranulocytosis, thrombocytopenia and aplastic anaemia occur. Peripheral neuritis and depilation have also been reported. Dermatoses and hypersensitivity reactions occur infrequently.
Pharyngolaryngeal pain was seen in 3% of patients treated for gout flares.

Overdose
a) Symptoms
Symptoms of acute overdosage with oral colchicine may not appear for 2 to 72 hours. The first signs of toxicity may be a feeling of burning and rawness in the mouth and throat and difficulty in swallowing. These are followed by nausea, vomiting and diarrhoea. The diarrhoea may be severe and haemorrhagic and accompanied by colic and tenesmus. These symptoms, coupled with vascular damage, may lead to dehydration, hypotension and shock. Multiple organ failure may occur and may be manifest as CNS toxicity, bone marrow depression, hepatocellular damage, muscle damage, respiratory distress, myocardial injury and renal damage. Death may be due to respiratory depression, cardiovascular collapse or sepsis.
In surviving patients, alopecia, rebound leucocytosis and stomatitis may occur about 10 days after the acute overdose.

b) Treatment
Patients should be carefully monitored for some time after overdosage or acute poisoning with colchicine to allow for the delayed onset of symptoms.

In acute poisoning multiple doses of activated charcoal should be administered. Respiration may need assistance. Because of the high degree of tissue binding, colchicine is not dialysable. Circulation should be maintained and fluid and electrolyte imbalance corrected. Morphine sulphate 10mg, intramuscularly, may be given to relieve severe abdominal cramps.

Pharmacodynamics
The anti-inflammatory effect of colchicine in acute gouty arthritis is selective for this disorder. Although its mode of action is not clearly understood, it is thought that colchicine causes the inhibition of the migration of granulocytes into the inflamed area. This reduces the release of lactic acid and pro-inflammatory enzymes that occurs during phagocytosis and breaks the cycle that leads to the inflammatory response**.**

Pharmacokinetics
Colchicine is readily absorbed from the gastrointestinal tract and peak concentrations occur in plasma by half an hour to two hours. The kidney, liver and the spleen also contain high concentrations of colchicine, but it is apparently largely excluded from the heart, skeletal muscle and brain. It is partially deacetylated in the liver. Colchicine and its metabolites are excreted in the urine and faeces.

Storage: Store below 25^{o}C
Packaging: 30 tablets
Manufacturer: Rafa Laboratories Ltd. POB 405 Jerusalem 91003.

The format and content of this document have been approved by the Ministry of Health in January 2011