PRESCRIBING INFORMATION

PrJAMP-COLCHICINE

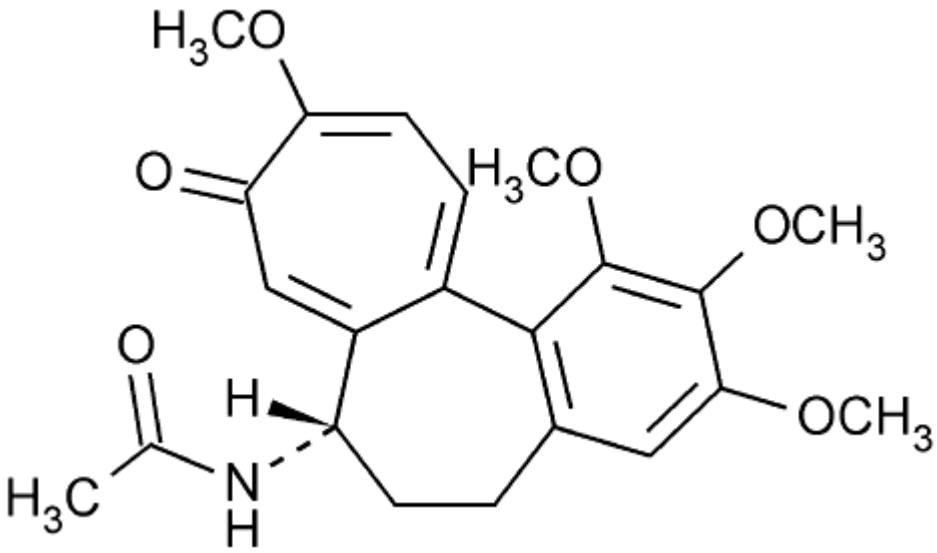
Colchicine Tablets USP

0.6 mg

Health Canada has issued market authorization through this Drug Identification Number for Jamp-Colchicine on September 13, 2011.

PrJAMP-COLCHICINE 0.6 mg per tablet DIN 02373823

Colchicine



$C_{22}H_{25}NO_6$ 399.44

SUMMARY PRODUCT INFORMATION

PRESENTATION

Tablet for oral administration available in bottles of 100's and 500's for hospital and pharmacy use only.

Description: Yellow, round biconvex tablets, embossed 0.6 on one side and scored on the other side.

Non-Medicinal Ingredients: Microcrystalline cellulose, Lactose monohydrate, Crospovidone, Corn Starch (NF), FD&C Yellow # 6, D&C Yellow #10, Colloidal silicon dioxide, Sodium stearyl fumarate

Store between 15 – 30 ^{o}C.

INDICATIONS

Gout: Prophylaxis and treatment of gout flares in adults.

CONTRAINDICATIONS

- Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a strong CYP3A4 inhibitor (Clarithromycin, etc.).
- Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a p-glycoprotein inhibitor (Cyclosporin, etc.).
- Known hypersensitivity to colchicine.
- Serious gastrointestinal, hepatic, renal and cardiac disease.

DOSAGE AND ADMINISTRATION

Oral administration dosages:

- Administer orally with water and maintain adequate fluid intake.
- May be administered without regard to meals.
- May need to supplement with Vitamin B12.
- Avoid grapefruit juice.
- Colchicine is not an analgesic medication and should not be used to treat pain from other causes.

Pr Jamp-Colchicine 0.6 mg tablet	
Use only as prescribed by a physician **Prophylaxis of gout flares in adults:** Adult dose: 1 tablet once or twice daily. The maximum recommended dose for prophylaxis is 2 tablets per 24 hours. Elderly use: use caution; reduce prophylactic daily dose by 50% in individuals >70 years (Terkeltaub, 2009). Dosage for co-administration with Interactive Drugs: • With p-glycoprotein inhibitors (Cyclosporin, etc.): ½ tablet once a day followed by ½ tablet once every other day. • With strong CYP3A4 inhibitors (Clarithromycin, etc.): ½ tablet once a day followed by ½ tablet once every other day. • With moderate CYP3A4 inhibitors (Verapamil, etc.): ½ tablet twice a day or 1 tablet once a day followed by ½ tablet once every other day.	**Use only as prescribed by a physician** **Treatment of gout flares in adults:** Adult dose: 2 tablets at first sign of gout flare followed by 1 tablet an hour later. The maximum recommended dose for treatment is 3 tablets over a 1 hour period. Wait 12 hours and then resume the prophylactic dose. Dosage for co-administration with Interactive Drugs: **All following doses with Interactive Drug should not be repeated for at least 3 days.** • With p-glycoprotein inhibitors (Cyclosporin, etc.): 1 tablet per flare. • With strong CYP3A4 inhibitors (Clarithromycin, etc.): 1 tablet per flare followed by ½ tablet one hour after. • With moderate CYP3A4 inhibitors (Verapamil, etc.): 2 tablets per flare.

Treatment of gout flares with colchicine is not recommended in patients receiving prophylactic dose of colchicine and CYP3A4 inhibitors.

WARNINGS AND PRECAUTIONS

- Keep **[Pr]Jamp-Colchicine** out of reach of children. Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine.

- Colchicine is a toxic substance and must be given only under physician's care. Since the administration of Colchicine is subject to wide variations, the prescribed dosage must be strictly followed.

- Colchicine is a substrate for both, the cytocrome P450 3A isoform subfamily (CYP3A) and the efflux transporter, P-glycoprotein (P-gp), Clarithromycin and other macrolides are known to inhibit CYP3A4 and P-gp. When Colchicine and Clarithromycin are administered together, inhibition of P-gp and/or CYP3A4 by Clarithromycin may lead to increased exposure to Colchicine which could result in clinically significant safety concerns. Patients should be monitored for clinical symptoms of Colchicine toxicity. There have been post-marketing reports of Colchicine toxicity with concurrent use of Colchicine and Clarithromycin. In patients with impaired renal function and/or who are elderly, Colchicine and Clarithromycin should not be used concurrently due to the risk of Colchicine toxicity. Deaths have been reported in some of these patients.

- Blood dyscrasias: myelosupporession, leucopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported with colchicine used in therapeutic doses.

- **[Pr]Jamp-Colchicine** must not be used by women who are pregnant or breastfeeding.

- 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 bezafibrate (themselves associated with myotoxicity) or cyclosporine with colchicine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

- **[Pr]Jamp-Colchicine** must be used with caution in aged and feeble patients and those with mild to moderate cardiac, renal, hepatic or gastrointestinal disease (see Contraindications).

- Periodic blood tests are suggested since prolonged administration of **[Pr]Jamp-Colchicine** could cause blood dyscrasias.

KNOWN ADVERSE REACTIONS

Postmarketing Experience

Serious toxic manifestations associated with colchicine include myelosupression, disseminated intravascular coagulation, and impairment of renal, hepatic, circulatory, and central nervous systems. There have been post-marketing reports of colchicine toxicity with concomitant use of Clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some of these patients (see **WARNINGS AND PRECAUTIONS**).

The following adverse reactions have been reported with colchicine. These have been generally reversible upon temporarily interrupting treatment or lowering the dose of colchicine.

Neurological: sensory motor neuropathy

Dermatological: alopecia, maculopapular rash, purpura, rash

Digestive: abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting, hematuria, oliguria, vascular and renal disturbances

Haematological: leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia

Hepatobiliary: elevated AST, elevated ALT

Musculoskeletal: myopathy, elevated CPK, myotonia, muscle weakness, muscle pain, rhabdomyolysis

Reproductive; azoospermia, oligospermia

OVERDOSE

Management: For management of suspected drug overdose contact your regional Poison Control Centre.

The exact dose of colchicine that produces significant toxicity is unknown. Fatalities have occurred after ingestion of a dose as low as 7 mg over a 4-day period, while other patients have survived after ingesting more than 60 mg. a review of 150 patients who overdosed on colchicine found that those who ingested less than 0.5 mg/kg survived and tended to have milder toxicities, such as gastrointestinal symptoms, whereas those who took 0.5 to 0.8 mg/kg had more severe reactions, such as myelosuppression. There was 100% mortality in those who ingested more than 0.8 mg/kg.

Symptoms: The first stage of acute colchicine toxicity typically begins within 24 hours of ingestion and includes gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, diarrhea, and significant fluid loss, leading to volume depletion. Peripheral leukocytosis may also be seen. Life-threatening complications occur during the second stage, which occurs 24 to 72 hours after drug administration, attributed to multi-organ failure and its consequences. Extensive vascular damage may result in shock. Renal dysfunction may occur. Hematuria and oliguria are common manifestations. Muscular weakness is marked and ascending CNS paralysis may develop and delirium and convulsions may occur. Death is usually a result of respiratory depression and

cardiovascular collapse. If the patient survives, recovery of multi-organ injury may be accompanied by rebound leukocytosis and alopecia starting about 1 week after the initial ingestion.

Treatment: Induce emesis or perform gastric lavage. Symptomatic and supportive treatment. No specific antidote is known. Colchicine is not effectively removed by dialysis.

PHARMACOLOGY:

Colchicine is an alkaloid extracted from plants of the genus Colchicum (*Colchicum automnale*) and is a water soluble pale yellow powder which blackens with exposure to light.

Oral Colchicine intake undergoes an entero-hepatic cycle. It is absorbed rapidly by the Gastro-Intestinal Tract. The drug and its metabolites are distributed in the leucocytes, the kidneys, the liver, the spleen and the intestine.

Peak plasma concentration is obtained from 0.5 to 2 hours after ingestion. The half-life of this drug is approximately 20 minutes in the plasma and 60 hours in the leucocytes. The drug is 50% bound to proteins. The interleucocyte concentrations are higher than the concentrations in plasma.

Its metabolism is not well understood. Colchicine is metabolized in the liver and is excreted mainly in the feces; 10 – 20% of the drug finds its way in the urine. The Colchicine binding results in its accumulation in tissues as soon as the daily dosage exceeds 1 mg, which, in turn, could result in toxic effects. A serious renal ailment could prolong the half-life for its elimination.

Colchicine crosses the placenta and passes into the breast milk.

Although its exact mode of action in the relief of gout is not completely understood, colchicine is known to decrease the inflammatory response to urate crystal deposition by inhibiting migration of leukocytes, to interfere with urate deposition by decreasing lactic acid production by leukocytes, to interfere with kinin formation and to diminish phagocytosis and the subsequent anti-inflammatory response.

The anti-inflammatory effect of Colchicine is relatively selective for acute gouty arthritis. It is neither analgesic nor a uricosuric and will not prevent progression to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks.

REFERENCES:

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9. Canadian Pharmacists Association Letter; September 2009; vol 25

10. Canadian Pharmacists Association Letter; September 2009; 25(9):250903

11. Canadian Pharmacists Association Letter; September 2009; 27(12):271208

12. Colcrys (Colchicine) Tablet, film coated (AR Scientific Inc.) DailyMed Label Information – Human Prescription Drug Label (http://dailymed.nlm.nih.gov)

13. Prescribing Information: PrCOLCHICINE, Colchicine Tablets USP, 0.6 mg and 1 mg, EuroPharma International Canada Inc., Date of Revision: January 27, 2014.

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