# PRESCRIBING INFORMATION

# [Pr] pms-COLCHICINE

**Colchicine Tablets, USP**

**0.6 mg**

**Gout Therapy**

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montreal, Québec
H4P 2T4

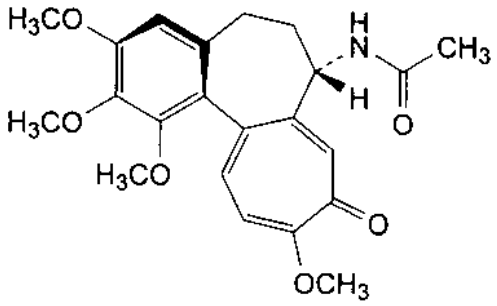
www.pharmascience.com

Date of Revision:
July 05, 2016
Version 1: 2022-11-03

Control No.: 196333

**[Pr] pms-COLCHICINE 0.6 mg per Tablet**
Gout Therapy
Preparations with No Effect on Uric Acid Metabolism

**Structural Formula:**




**Molecular formula:** $C_{22}H_{25}NO_6$

**Molecular Mass:** 399.4 g/mol

## 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 leukocytes, 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 concentration in the 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. .

## Comparative bioavailability study

A pivotal, single center, randomized, single dose, double-blinded, two-sequence, two-treatment, crossover design study was conducted in 34 healthy male volunteers under fasting conditions comparing pms-COLCHICINE 0.6 mg tablets (Pharmascience Inc.) to COLCHICINE-ODAN 0.6 mg tablets (Odan Laboratories Ltd.). A summary of the pharmacokinetic data is presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

| Colchicine<br>(1 x 0.6 mg tablet – Fasting Conditions)<br>From measured data<br>**uncorrected for potency**<br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | 90 % Confidence Interval |
| $AUC_{0-72}$<br>(pg·h/mL) | 15457.6<br>16029.3 (25.8) | 16324.5<br>16713.6 (21.8) | 94.69 | 89.53 – 100.14 |
| $AUC_I$<br>(pg·h/mL) | 17827.6<br>18487.9 (26.2) | 18702.9<br>19154.7 (22.1) | 95.32 | 90.25 – 100.67 |
| $C_{max}$<br>(pg/mL) | 2068.1<br>2208.7 (35.4) | 2130.8<br>2216.6 (27.9) | 97.06 | 88.39 – 106.57 |
| $T_{max}$§<br>(h) | 1.05<br>(0.50 – 2.50) | 1.00<br>(0.75 – 2.03) | | |
| $T_{½}$€<br>(h) | 29.91 (17.5) | 29.68 (15.8) | | |

* pms-COLCHICINE 0.6 mg tablets, Pharmascience Inc., Montreal, Quebec, Canada

† Colchicine 0.6 mg tablets, Odan Laboratories Ltd., Montreal, Quebec, Canada

§ Median (range)

€ Arithmetic mean (CV%)

## INDICATIONS

- Gout: prophylaxis and treatment of gout flares in adults. Colchicine is effective in relieving the pain of acute attacks, especially if therapy is begun early in the attack and in adequate dosage. Many therapists use colchicine as interval therapy to prevent acute attacks of gout.
- Familial Mediterranean Fever (familial recurrent polyserositis).

## CONTRAINDICATIONS

- Patients with serious gastrointestinal, hepatic, renal and cardiac disease.
- Patients with known hypersensitivity to colchicine.
- Patients with renal or hepatic impairment should not be given pms-COLCHICINE in conjunction with P-glycoprotein or strong CYP3A4 inhibitors.
- Avoid pms-COLCHICINE plus cyclosporine or a strong 3A4 inhibitor if patients have renal or hepatic impairment. This can be fatal.

## WARNINGS AND PRECAUTIONS

### Warnings:

**Drug Interactions**
Colchicine is a substrate for both the cytochrome 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.

Colchicine has been shown to induce reversible malabsorption of Vitamin $B_{12}$, apparently by altering the function of ileal mucosa.

**Blood dyscrasias:** myelosuppression, leucopenia, ganulocytopenia, thrombocytopenia, and aplastic anemia have been reported with colchicine used in therapeutic doses.

**Pregnancy:** Cell division in animals and plants can be arrested by colchicine. In certain species of animal under certain conditions it has produced teratogenic effects and has adversely affected spermatogenesis. If the drug is used during pregnancy, or if the patient becomes pregnant while taking it, the woman should be told of the potential hazard to the fetus. While such effects have not been demonstrated in humans, pertinent available information is meager. In view of the above, colchicine is not recommended for use in pregnancy.

**Neuromuscular Toxicity:** 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 (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.

**Precautions:**

Periodic blood tests are suggested since prolonged administration of colchicine could cause blood dyscrasias.

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

Use with care in geriatrics or debilitated patients and those with cardiac, renal or gastrointestinal disease. Dosage reduction may be necessary in these cases and is indicated if weakness, anorexia, nausea, vomiting or diarrhea appears (see Contraindications).

*Pregnancy:* pms-COLCHICINE is not recommended for use in pregnancy (see Warnings).

*Lactation:* It is not known if colchicine is distributed into human milk. pms-COLCHICINE should not be used by women who are breastfeeding.

*Children:* Safety and efficacy of colchicine in treatment of FMF have not been established in patients ≤12 years of age. Colchicine is not recommended in pediatric patients for treatment or prophylaxis of gout flares. Keep colchicine out of reach of children. Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine.

## ADVERSE EFFECTS

Reactions to colchicine appear to be dose related. The most prominent symptoms are referable to the gastrointestinal tract (e.g. nausea, vomiting, abdominal pain, diarrhea) and may be particularity troublesome in the presence of peptic ulcer or spastic colon. At toxic doses colchicine may cause severe diarrhea, generalized vascular damage, and renal damage, with hematuria and oliguria. Muscular weakness, which disappears with discontinuance of therapy, urticaria, dermatitis, and purpura have also been reported. Hypersensitivity to colchicine is a very rare occurrence, but it should be borne in mind. The appearance of any of the aforementioned symptoms may require reduction of dosage or discontinuance of the drug. When given for a prolonged period, colchicine may cause agranulocytosis, aplastic anemia, peripheral neuritis and loss of hair.

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 such patients (see Warnings).

**Post-marketing Experience**

Serious toxic manifestations associated with colchicine include myelosuppression, disseminated intravascular coagulation, and impairment of renal, hepatic, circulatory, and central nervous systems.

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

**Hematological:** leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia

**Hepatobiliary:** elevated AST, elevated ALT

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

**Reproductive:** azoospermia, oligospermia

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## DOSAGE AND ADMINISTRATION

### Dosage

**Gout Flares:**

***Treatment of gout flares in adults (>18 years old):***

The recommended dose of pms-COLCHICINE is 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6mg (1 tablet) one hour later.

The maximum recommended dose is 1.8 mg over one-hour period. Wait 12 hours to resume prophylactic dose. Wait at least three days to repeat.

The treatment of gout flares with pms-COLCHICINE is not recommended in patients receiving prophylactic dose of colchicine and CYP3A4 inhibitors.

***Prophylaxis of gout flares in adults (>18 years old):***

The recommended dosage of pms-COLCHICINE is 0.6 mg once or twice daily. The maximum recommended dose should not exceed 1.2 mg per day. Use with caution in geriatric patients; reduce prophylactic daily dose by 50% in individuals >70 years.

**Familial Mediterranean Fever (FMF):**

***Treatment of FMF in patients >12 years of age***:

The recommended dosage of colchicine for FMF is 1.2 mg to 2.4 mg daily.
The dosage should be increased as needed to control disease and as tolerated in increments of 0.3 mg/day to a maximum recommended daily dose of 2.4 mg. If intolerable side effects develop, the dose should be decreased in increments of 0.3 mg/day. The total daily dose of pms-COLCHICINE may be administered in one to two divided doses.

**Dose Modification for Co-administration of Interacting Drugs**

**Concomitant Therapy:**

Co-administration of colchicine with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) increases the risk of colchicine-induced toxic effects (Table 1). If patients are taking or have recently completed treatment with drugs listed in Table 1 within the prior 14 days, the dose adjustments are as shown on the table below (see Warnings and Drug Interactions).

**Table 1: Colchicine Dose Adjustment for Co-administration with Interacting Drugs if no Alternative Available[1]**

| Drug | Noted or Anticipated Outcome | Gout Flares | | | | FMF | |
|---|---|---|---|---|---|---|---|
| | | Prophylaxis of Gout Flares | | Treatment of Gout Flares | | | |
| | | Original Intended Dosage | Adjusted Dose | Original Intended Dosage | Adjusted Dose | Original Intended Dosage | Adjusted Dose |
| **Strong CYP3A4 Inhibitors[2]** | | | | | | | |
| Atazanavir<br>Clarithromycin<br>Darunavir/ Ritonavir[3]<br>Indinavir<br>Itraconazole<br>Ketoconazole<br>Lopinavir/ Ritonavir[3]<br>Nefazodone<br>Nelfinavir<br>Ritonavir<br>Saquinavir<br>Telithromycin<br>Tipranavir/ Ritonavir[3] | Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicines plasma levels is anticipated with other strong CYP3A4 inhibitors. | 0.6 mg twice a day<br>0.6 mg once a day | 0.3 mg once a day<br>0.3 mg once every other day | 1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days. | 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (1/2 tablet) 1 hour later. Dose to be repeated no earlier than 3 days. | Maximum daily dose of 1.2 – 2.4 mg | Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day) |
| **Moderate CYP3A4 Inhibitors** | | | | | | | |
| Amprenavir[3]<br>Aprepitant<br>Diltiazem<br>Erythromycin<br>Fluconazole<br>Fosamprenavir[3] (pro-drug of Amprenavir)<br>Grapefruit Juice<br>Verapamil | Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions. | 0.6 mg twice a day<br>0.6 mg once a day | 0.3 mg twice a day or 0.6 mg once a day<br>0.3 mg once every other day | 1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days. | 1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days. | Maximum daily dose of 1.2 – 2.4 mg. | Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day) |
| **P-gp Inhibitors[2]** | | | | | | | |
| Cyclosporine<br>Ranolazine | Significant increase in colchicine plasma levels[1]; fatal colchicine toxicity has been reported with cyclosporine, a P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other P-gp inhibitors. | 0.6 mg twice a day<br>0.6 mg once a day | 0.3 mg once a day<br>0.3 mg once every other day | 1.2 mg (2 tablets) followed by 0.6 mg (1 tablet) 1 hour later. Dose to be repeated no earlier than 3 days. | 0.6 mg (1 tablet) x 1 dose. Dose to be repeated no earlier than 3 days | Maximum daily dose of 1.2 – 2.4 mg | Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day) |

[1] For magnitude of effect on colchicine plasma concentrations
[2] Patients with renal or hepatic impairment should not be given colchicine in conjunction with strong CYP3A4 or P-gp inhibitors
[3] When used in combination with Ritonavir, see dosing recommendations for strong CYP3A4 inhibitors

Treatment of gout flares with pms-COLCHICINE is not recommended in patients receiving prophylactic dose of Colchicine and CYP3A4 inhibitors.

For patients with severe renal or hepatic impairment, a 3-tablet course is recommended. For these patients, wait at least two weeks before repeating the course **(**see Warnings and Drug Interactions).

**Administration:**

- Administer orally with water and maintain adequate fluid intake.
- May be administered without regard to meals.
- May need to supplement with Vitamin $B_{12}$.
- Avoid grapefruit juice.
- pms-COLCHICINE is not an analgesic medication and should not be used to treat pain from other causes.

## OVERDOSE

There is usually a latent period between overdosage and the onset of symptoms, regardless of the route of administration. Deaths have been reported with as little as 7 mg, although higher doses have been taken without fatal results.

The exact dose of colchicine that produces significant toxicity is unknown. 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. 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.

For management of a suspected drug overdose, contact your regional Poison Control Center immediately.

## SUPPLIED

Each yellow, round, biconvex tablet debossed with "C" above "0.6" on one side and scored on the other side contains: 0.6 mg of Colchicine and the following non-medicinal ingredients: D&C Yellow #10, FD&C Yellow #6, magnesium stearate, povidone, sodium starch glycolate and sucrose. Available in HDPE bottle of 100 tablets.

Store at room temperature between 15ºC and 30ºC.

Keep out of reach and sight of children.

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montreal, Quebec, H4P 2T4
www.pharmascience.com

## REFERENCES

Colchicine Prescribing Information, Odan Laboratories Ltd, Canada. Date of revision May 4, 2016. Control number: 190129