

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use colchicine safely and effectively. See full prescribing information for Colchicine Tablets, USP.

Colchicine Tablets, USP, for oral use**Initial U.S. Approval: 1961****INDICATIONS AND USAGE**

Colchicine Tablets, USP are an alkaloid indicated for:

- Prophylaxis and treatment of gout flares in adults (1.1).
- Familial Mediterranean fever (FMF) in adults and children 4 years or older (1.2).

Colchicine Tablets, USP are not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION

- Gout Flares:**
 - Prophylaxis of Gout Flares:** 0.6 mg once or twice daily in adults and adolescents older than 16 years of age (2.1). Maximum dose 1.2 mg/day.
 - Treatment of Gout Flares:** 1.2 mg (two tablets) at the first sign of a gout flare followed by 0.6 mg (one tablet) one hour later (2.1).
- FMF:** Adults and children older than 12 years 1.2 – 2.4 mg; children 6 to 12 years 0.9 – 1.8 mg; children 4 to 6 years 0.3 – 1.8 mg (2.2, 2.3).
 - Give total daily dose in one or two divided doses (2.2).
 - Once or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose (2.2).

Colchicine Tablets, USP are administered orally without regard to meals.

See full prescribing information for dose adjustment regarding patients with impaired renal function (2.5), impaired hepatic function (2.6), the patient's age (2.3, 8.5) or use of coadministered drugs (2.4).

DOSAGE FORMS AND STRENGTHS

0.6 mg tablets (3).

CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given Colchicine Tablets, USP in conjunction with P-gp or strong CYP3A4 inhibitors (5.3). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses (7).

WARNINGS AND PRECAUTIONS

- Fatal overdoses** have been reported with colchicine in adults and children. Keep Colchicine Tablets, USP out of the reach of children (5.1, 10).
- Blood dyscrasias:** myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anemia have been reported (5.2).
- Monitor for toxicity and if present consider temporary interruption or discontinuation of colchicine (5.2, 5.3, 5.4, 6, 10).
- Drug interaction P-gp and/or CYP3A4 inhibitors:** Coadministration of colchicine with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death (5.3, 7).
- Neuromuscular toxicity:** Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to cause this effect. Consider temporary interruption or discontinuation of Colchicine Tablets, USP (5.4, 7).

ADVERSE REACTIONS

Prophylaxis of Gout Flares: The most commonly reported adverse reaction in clinical trials for the prophylaxis of gout was diarrhea.

Treatment of Gout Flares: The most common adverse reactions reported in the clinical trial for gout were diarrhea (23%) and pharyngolaryngeal pain (3%).

FMF: Most common adverse reactions (up to 20%) are abdominal pain, diarrhea, nausea and vomiting. These effects are usually mild, transient and reversible upon lowering the dose (6).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Coadministration of P-gp and/or CYP3A4 inhibitors (e.g., clarithromycin or cyclosporine) have been demonstrated to alter the concentration of colchicine. The potential for drug-drug interactions must be considered prior to and during therapy. See full prescribing information for a complete list of reported and potential interactions (2.4, 5.3, 7).

USE IN SPECIFIC POPULATIONS

- In the presence of mild to moderate renal or hepatic impairment, adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare and FMF, but patients should be monitored closely (2.5, 8.6).
- In patients with severe renal impairment for prophylaxis of gout flares, the starting dose should be 0.3 mg/day for gout flares, no dose adjustment is required, but a treatment course should be repeated no more than once every two weeks. In FMF patients, start with 0.3 mg/day, and any increase in dose should be done with close monitoring (2.5, 8.6).
- In patients with severe hepatic impairment, a dose reduction may be needed in prophylaxis of gout flares and FMF patients; while a dose reduction may not be needed in gout flares, a treatment course should be repeated no more than once every two weeks (2.5, 2.6, 8.6, 8.7).
- For patients undergoing dialysis, the total recommended dose for prophylaxis of gout flares should be 0.3 mg given twice a week with close monitoring. For treatment of gout flares, the total recommended dose should be reduced to 0.6 mg (one tablet) x 1 dose and the treatment course should not be repeated more than once every two weeks. For FMF patients, the starting dose should be 0.3 mg/day and dosing can be increased with close monitoring (2.5, 8.6).
- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).
- Geriatric Use: The recommended dose of colchicine should be based on renal function (2.5, 8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION: CONTENTS*		8 USE IN SPECIFIC POPULATIONS
1 INDICATIONS AND USAGE	8.1 Pregnancy	
1.1 Gout Flares	8.2 Labor and Delivery	
1.2 Familial Mediterranean Fever (FMF)	8.3 Nursing Mothers	
2 DOSAGE AND ADMINISTRATION	8.4 Pediatric Use	
2.1 Gout Flares	8.5 Geriatric Use	
2.2 FMF	8.6 Renal Impairment	
2.3 Recommended Pediatric Dosage	8.7 Hepatic Impairment	
2.4 Dose Modification for Coadministration of Interacting Drugs		
3 DOSAGE FORMS AND STRENGTHS	9 DRUG ABUSE AND DEPENDENCE	
4 CONTRAINDICATIONS	10 OVERDOSAGE	
5 WARNINGS AND PRECAUTIONS	2.5 Dose Modification in Renal Impairment	
5.1 Fatal Overdose	2.6 Dose Modification in Hepatic Impairment	
5.2 Blood Dyscrasias	11 DESCRIPTION	
5.3 Drug Interactions	12 CLINICAL PHARMACOLOGY	
5.4 Neuromuscular Toxicity	12.1 Mechanism of Action	
6 ADVERSE REACTIONS	12.2 Pharmacokinetics	
6.1 Clinical Trials Experience in Gout	13 NONCLINICAL TOXICOLOGY	
6.2 Postmarketing Experience	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	
7 DRUG INTERACTIONS	14 CLINICAL STUDIES	
	15 HOW SUPPLIED/STORAGE AND HANDLING	
	15.1 How Supplied	
	15.2 Storage	
	17 PATIENT COUNSELING INFORMATION	
	*Sections or subsections omitted from the full prescribing information are not listed.	

FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE****1.1 Gout Flares**

Colchicine Tablets, USP are indicated for prophylaxis and the treatment of acute gout flares.

- Prophylaxis of Gout Flares:** Colchicine Tablets, USP are indicated for prophylaxis of gout flares.
- Treatment of Gout Flares:** Colchicine Tablets, USP are indicated for treatment of acute gout flares when taken at the first sign of a flare.

1.2 Familial Mediterranean Fever (FMF)

Colchicine Tablets, USP are indicated in adults and children four years or older for treatment of familial Mediterranean fever (FMF).

2 DOSAGE AND ADMINISTRATION

The long-term use of colchicine is established for FMF and the prophylaxis of gout flares, but the safety and efficacy of repeat treatment for gout flares has not been evaluated. The dosing regimens for Colchicine Tablets, USP are different for each indication and must be individualized.

The recommended dosage of Colchicine Tablets, USP depends on the patient's age, renal function, hepatic function and use of coadministered drugs [see *Dosage and Administration* (2.4)].

Colchicine Tablets, USP are administered orally without regard to meals.

Colchicine Tablets, USP are not an analgesic medication and should not be used to treat pain from other causes.

2.1 Gout Flares**Prophylaxis of Gout Flares**

The recommended dosage of Colchicine Tablets, USP for prophylaxis of gout flares for adults and adolescents older than 16 years of age is 0.6 mg once or twice daily. The maximum recommended dose for prophylaxis of gout flares is 1.2 mg/day.

An increase in gout flares may occur after initiation of uric acid-lowering therapy, including pegloticase, febuxostat and allopurinol, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Colchicine Tablets, USP are recommended upon initiation of gout flare prophylaxis with uric acid-lowering therapy. Prophylactic therapy may be beneficial for at least the first six months of uric acid-lowering therapy.

Treatment of Gout Flares

The recommended dose of Colchicine Tablets, USP for treatment of a gout flare is 1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later. Higher doses have not been found to be more effective. The maximum recommended dose for treatment of gout flares is 1.8 mg over a one hour period. Colchicine Tablets, USP may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.

2.2 FMF

The recommended dosage of Colchicine Tablets, USP for FMF in adults is 1.2 to 2.4 mg daily.

Colchicine Tablets, USP should be increased as needed to control disease and as tolerated in increments of 0.3 mg/day to a maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in increments of 0.3 mg/day. The total daily Colchicine Tablets, USP dose may be administered in one to two divided doses.

2.3 Recommended Pediatric Dosage**Prophylaxis and Treatment of Gout Flares**

Colchicine Tablets, USP are not recommended for pediatric use in prophylaxis or treatment of gout flares.

FMF

The recommended dosage of Colchicine Tablets, USP for FMF in pediatric patients four 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 to 6 years: 0.3 mg to 1.8 mg daily
- Children 6 to 12 years: 0.9 mg to 1.8 mg daily
- Adolescents older than 12 years: 1.2 mg to 2.4 mg daily

2.4 Dose Modification for Coadministration of Interacting Drugs**Concomitant Therapy**

Coadministration of Colchicine Tablets, USP 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 in the table below [see *Drug Interactions* (7)].

Table 1. Colchicine Tablets, USP Dose Adjustment for Coadministration with Interacting Drugs if no Alternative Available*

Drug	Noted or Anticipated Outcome	Strong CYP3A4 Inhibitors [†]					
		Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares		Original Intended Dosage	Adjusted Dose
Atazanavir/ Ritonavir/ Indinavir/ Ritonavir/ Darunavir/ Ritonavir/ Fosamprenavir/ Ritonavir/ Lopinavir/ Ritonavir/ Nelfinavir/ Ritonavir/ Saquinavir/ Ritonavir/ Telithromycin/ Tiplivanir/ Ritonavir/ Verapamil	Significant increase in colchicine plasma levels [‡] ; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	0.6 mg twice a day	0.3 mg once a 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)

Drug	Noted or Anticipated Outcome	Moderate CYP3A4 Inhibitors					
		Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares		Original Intended Dosage	Adjusted Dose
Amprrenavir/ Agrepitant/ Diltiazem/ Erythromycin/ Fluconazole/ Fosamprenavir* (pro-drug of Amprrenavir)/ Grapefruit juice/ 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	0.3 mg once a 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)

Drug	Noted or Anticipated Outcome	P-gp Inhibitors [§]					
		Gout Flares				FMF	
		Prophylaxis of Gout Flares		Treatment of Gout Flares		Original Intended Dosage	Adjusted Dose
Cyclosporine/ Ranolazine	Significant increase in colchicine plasma levels [‡] ; 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	0.3 mg once a 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)

* For magnitude of effect on colchicine plasma concentrations [see *Clinical Pharmacology* (12.3)]

[†] Patients with renal or hepatic impairment should not be given Colchicine Tablets, USP in conjunction with strong CYP3A4 or P-gp inhibitors [see *Contraindications* (4)]

[‡] When used in combination with Ritonavir, see dosing recommendations for strong CYP3A4 inhibitors [see *Contraindications* (4)]

Table 2. Colchicine Tablets, USP Dose Adjustment for Coadministration with Protease Inhibitors	Protease Inhibitor	Clinical Comment	w/Colchicine – Prophylaxis of Gout Flares	w/Colchicine – Treatment of Gout Flares	w/Colchicine – Treatment of FMF
Atazanavir sulfate (Reyataz)	Patients with renal or hepatic impairment should not be given colchicine with Reyataz.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Darunavir (Prezista)	Patients with renal or hepatic impairment should not be given colchicine with Prezista/ritonavir.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Fosamprenavir (Lexiva) with Ritonavir	Patients with renal or hepatic impairment should not be given colchicine with Lexiva/ritonavir.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Fosamprenavir (Lexiva)	Patients with renal or hepatic impairment should not be given colchicine with Lexiva.	0.6 mg twice a day	0.3 mg once a day	1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
Indinavir (Crixivan)	Patients with renal or hepatic impairment should not be given colchicine with Crixivan.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Lopinavir/ Ritonavir (Kaletra)	Patients with renal or hepatic impairment should not be given colchicine with Kaletra.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Nelfinavir mesylate (Viracept)	Patients with renal or hepatic impairment should not be given colchicine with Viracept.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Ritonavir (Norvir)	Patients with renal or hepatic impairment should not be given colchicine with Norvir.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Saquinavir mesylate (Invirase)	Patients with renal or hepatic impairment should not be given colchicine with Invirase/ritonavir.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)
Tiplranavir (Aptivus)	Patients with renal or hepatic impairment should not be given colchicine with Aptivus/ritonavir.	0.6 mg twice a day	0.3 mg once a day	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 0.6 mg (may be given as 0.3 mg twice a day)

Treatment of gout flares with Colchicine Tablets, USP is not recommended in patients receiving prophylactic dose of Colchicine Tablets, USP and CYP3A4 inhibitors.

2.5 Dose Modification in Renal Impairment

Colchicine dosing must be individualized according to the patient's renal function [see *Use in Specific Populations* (8.6)]. CL_r in mL/minute may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_r = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for female patients}$$

Gout Flares**Prophylaxis of Gout Flares**

For prophylaxis of gout flares in patients with mild (estimated creatinine clearance [CL_r] 50 to 80 mL/min) to moderate (CL_r 30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, in patients with severe impairment, the starting dose should be 0.3 mg/day and any increase in dose should be done with close monitoring. For the prophylaxis of gout flares in patients undergoing dialysis, the starting doses should be 0.3 mg given twice a week with close monitoring [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.6)].

Treatment of Gout Flares

For treatment of gout flares in patients with mild (CL_r 50 to 80 mL/min) to moderate (CL_r 30 to 50 mL/min) renal function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every two weeks. For patients with gout flares requiring repeated courses, consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.6 mg (one tablet). For these patients, the treatment course should not be repeated more than once every two weeks [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.6)].

Treatment of gout flares with Colchicine Tablets, USP is not recommended in patients with renal impairment who are receiving Colchicine Tablets, USP for prophylaxis.

FMF

Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing dialysis. For these patients, the dosage should be reduced [see *Clinical Pharmacology* (12.3)]. Patients with mild (CL_r 50 to 80 mL/min) and moderate (CL_r 30 to 50 mL/min) renal impairment should be monitored closely for adverse effects of colchicine. Dose reduction may be necessary. For patients with severe renal failure (CL_r less than 30 mL/min), start with 0.3 mg/day; any increase in dose should be done with adequate monitoring of the patient for adverse effects of colchicine [see *Use in Specific Populations* (8.6)]. For patients undergoing dialysis, the total recommended starting dose should be 0.3 mg (half tablet) per day. Dosing can be increased with close monitoring. Any increase in dose should be done with adequate monitoring of the patient for adverse effects of colchicine [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.6)].

2.6 Dose Modification in Hepatic Impairment**Gout Flares****Prophylaxis of Gout Flares**

For prophylaxis of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. Dose reduction should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment [see *Use in Specific Populations* (8.7)].

Treatment of Gout Flares

For treatment of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicine. However, for the treatment of gout flares in patients with severe impairment, while the dose does not need to be adjusted, a treatment course should be repeated no more than once every two weeks. For these patients, requiring repeated courses for the treatment of gout flares, consideration should be given to alternate therapy [see *Use in Specific Populations* (8.7)].

Treatment of gout flares with Colchicine Tablets, USP is not recommended in patients with hepatic impairment who are receiving Colchicine Tablets, USP for prophylaxis.

FMF

Patients with mild to moderate hepatic impairment should be monitored closely for adverse effects of colchicine. Dose reduction should be considered in patients with severe hepatic impairment [see *Use in Specific Populations* (8.7)].

3 DOSAGE FORMS AND STRENGTHS

0.6 mg tablets — purple capsule-shaped, film-coated with "AR 374" debossed on one side and scored on the other side.

4 CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given Colchicine Tablets, USP in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors except fosamprenavir). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

5 WARNINGS AND PRECAUTIONS**5.1 Fatal Overdose**

Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine [see *Overdosage* (10)]. Colchicine Tablets, USP should be kept out of the reach of children.

5.2 Blood Dyscrasias

Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia and aplastic anemia have been reported with colchicine used in therapeutic doses.

5.3 Drug Interactions

Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and strong CYP3A4 inhibitors. 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 colchicine may need to be reduced or interrupted [see *Drug Interactions* (7)]. Use of Colchicine Tablets, USP in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors except fosamprenavir) is contraindicated in patients with renal or hepatic impairment [see *Contraindications* (4)].

5.4 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, lovastatin, gemfibrozil, fenofibrate, fenofibric acid or bezafibrate (themselves associated with myotoxicity) or cyclosporine with Colchicine Tablets, USP may potentiate the development of myopathy [see *Drug Interactions* (7)]. Once colchicine is stopped, the symptoms generally resolve within one week to several months.

6 ADVERSE REACTIONS**Prophylaxis of Gout Flares**

The most commonly reported adverse reaction in clinical trials of colchicine for the prophylaxis of gout was diarrhea. Treatment of Gout Flares

The most common adverse reactions reported in the clinical trial with Colchicine Tablets, USP for treatment of gout flares were diarrhea (23%) and pharyngolaryngeal pain (3%).

FMF

Gastrointestinal tract adverse effects are the

Colchicine Tablets, USP are supplied for oral administration as purple, film-coated, capsule-shaped tablets (0.1575" x 0.3030"), debossed with "AR 374" on one side and scored on the other, containing 0.6 mg of the active ingredient colchicine USP. Inactive ingredients: carnauba wax, FD&C blue #2, FD&C red #40, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium starch glycolate, titanium dioxide and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which Colchicine Tablets, USP exert their beneficial effect in patients with FMF has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1 β . Additionally, colchicine disrupts cytoskeletal functions through inhibition of β -tubulin polymerization into microtubules, and consequently prevents the activation, degranulation and migration of neutrophils thought to mediate some gout symptoms.

12.3 Pharmacokinetics

Absorption

In healthy adults, colchicine is absorbed when given orally, reaching a mean C_{max} of 2.5 ng/mL (range 1.1 to 4.4 ng/mL) in one to two hours (range 0.5 to three hours) after a single dose administered under fasting conditions.

Following oral administration of Colchicine Tablets, USP given as 1.8 mg colchicine over one hour to healthy, young adults under fasting conditions, colchicine appears to be readily absorbed, reaching mean maximum plasma concentrations of 6.2 ng/mL at a median 1.81 hours (range: 1.0 to 2.5 hours). Following administration of the nonrecommended high-dose regimen (4.8 mg over six hours), mean to maximum plasma concentrations were 6.8 ng/mL, at a median 4.47 hours (range: 3.1 to 7.5 hours).

After 10 days on a regimen of 0.6 mg twice daily, peak concentrations are 3.1 to 3.6 ng/mL (range 1.6 to 6.0 ng/mL), occurring 1.3 to 1.4 hours postdose (range 0.5 to 3.0 hours). Mean pharmacokinetic parameter values in healthy adults are shown in Table 5.

C _{max} (Colchicine ng/mL)	T _{max} ^a (h)	Vd/F (L)	CL/F (L/hr)	t _{1/2} (h)
Colchicine Tablets, USP 0.6 mg Single Dose (N=13)				
2.5 (28.7)	1.5 (1.0 – 3.0)	341.5 (54.4)	54.1 (31.0)	--
Colchicine Tablets, USP 0.6 mg Twice Daily x 10 Days (N=13)				
3.6 (23.7)	1.3 (0.5 – 3.0)	1150 (18.7)	30.3 (19.0)	26.6 (16.3)

^aT_{max} mean (range)

CL = Dose/AUC_{0-∞} (calculated from mean values)

Vd = CL/Ke (calculated from mean values)

In some subjects, secondary colchicine peaks are seen, occurring between three and 36 hours postdose and ranging from 39 to 155% of the height of the initial peak. These observations are attributed to intestinal secretion and reabsorption and/or biliary recirculation.

Absolute bioavailability is reported to be approximately 45%.

Administration of Colchicine Tablets, USP with food has no effect on the rate of colchicine absorption but does decrease the extent of colchicine by approximately 15%. This is without clinical significance.

Distribution

The mean apparent volume of distribution in healthy young volunteers is approximately 5 to 8 L/kg.

Colchicine binding to serum protein is low, 39 ± 5%, primarily to albumin regardless of concentration.

Colchicine crosses the placenta (plasma levels in the fetus are reported to be approximately 15% of the maternal concentration). Colchicine also distributes into breast milk at concentrations similar to those found in the maternal serum. *(See Use in Specific Populations (8.1, 8.3)).*

Metabolism

Colchicine is demethylated to two primary metabolites, 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) and one minor metabolite, 10-O-demethylcolchicine (also known as colchicine). *In vitro* studies using human liver microsomes have shown that CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC. Plasma levels of these metabolites are minimal (less than 5% of parent drug).

Elimination/Excretion

In healthy volunteers (n=12), 40 to 65% of 1 mg orally administered colchicine was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also postulated to play a role in colchicine elimination. Following multiple oral doses (0.6 mg twice daily), the mean elimination half-lives in young healthy volunteers (mean age 25 to 28 years of age) is 26.6 to 31.2 hours. Colchicine is a substrate of P-gp.

Extracorporeal Elimination

Colchicine is not removed by hemodialysis.

Special Populations

There is no difference between men and women in the pharmacokinetic disposition of colchicine.

Pediatric Patients

Pharmacokinetics of colchicine was not evaluated in pediatric patients.

Elderly

A published report described the pharmacokinetics of 1 mg oral colchicine tablet in four elderly women compared to six young healthy males. The mean age of the four elderly women was 83 years (range 75 to 93), mean weight was 47 kg (38 to 61 kg) and mean creatinine clearance was 46 mL/min (range 25 to 75 mL/min). Mean peak plasma levels and AUC of colchicine were two times higher in elderly subjects compared to young healthy males.

A pharmacokinetic study using a single oral dose of one 0.6 mg colchicine tablet was conducted in young healthy subjects (n=20) between the ages of 18 and 30 years and elderly subjects (n=18) between the ages of 60 and 70 years. Elderly subjects in this study had a median age of 62 years and a mean (±SD) age of 62.93 ± 2.83 years. A statistically significant difference in creatinine clearance (mean ± SD) was found between the two age groups (132.56 ± 23.16 mL/min for young vs 87.02 ± 17.92 mL/min for elderly subjects, respectively). The following pharmacokinetic parameter values (mean ± SD) were observed for colchicine in the young and elderly subjects, respectively: AUC_{0-∞} (ng/hr/mL) 22.39 ± 6.95 and 25.01 ± 6.92; C_{max} (ng/mL) 2.61 ± 0.71 and 2.56 ± 0.97; T_{max} (hr) 1.38 ± 0.42 and 1.25 ± 0.43; apparent elimination half-life (hr) 24.92 ± 5.34 and 30.06 ± 10.78; and clearance (mL/min) 0.0321 ± 0.0091 and 0.0292 ± 0.0071.

Clinical studies with colchicine for prophylaxis and treatment of gout flares and for treatment of FMF did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease or other drug therapy. *(See Dosage and Administration (2.4) and Use in Specific Populations (8.5)).*

Renal Impairment

Pharmacokinetics of colchicine in patients with mild and moderate renal impairment is not known. A published report described the disposition of colchicine (1 mg) in young adult men and women with FMF who had normal renal function or end-stage renal disease requiring dialysis. Patients with end-stage renal disease had 75% lower colchicine clearance (0.17 vs 0.73 L/hr/kg) and prolonged plasma elimination half-life (18.8 hrs vs 4.4 hrs) as compared to subjects with FMF and normal renal function. *(See Dosage and Administration (2.5) and Use in Specific Populations (8.6)).*

Hepatic Impairment

Published reports on the pharmacokinetics of IV colchicine in patients with severe chronic liver disease, as well as those with alcoholic or primary biliary cirrhosis and normal renal function suggest wide interpatient variability. In some subjects with mild to moderate cirrhosis, the clearance of colchicine is significantly reduced and plasma half-life prolonged compared to healthy subjects. In subjects with primary biliary cirrhosis, no consistent trends were noted. *(See Dosage and Administration (2.6) and Use in Specific Populations (8.7)).* No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh G).

Drug Interactions

In Vitro Drug Interactions

In vitro studies in human liver microsomes have shown that colchicine is not an inhibitor or inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 activity.

In Vivo Drug Interactions

The effects of coadministration of other drugs with Colchicine Tablets, USP on C_{max}, AUC and C_{min} are summarized in Table 6 (effect of other drugs on colchicine) and Table 7 (effect of colchicine on other drugs). For information regarding clinical recommendations, see *Table 1* in Dose Modification for Coadministration of Interacting Drugs. *(See Dosage and Administration (2.4)).*

Coadministered Drug	Dose of Coadministered Drug (mg)	Dose of Colchicine Tablets, USP (mg)	N	% Change in Colchicine Concentrations from Baseline (Range: Min - Max)	
				C _{max}	AUC _{0-∞}
Cyclosporine	100 mg single dose	0.6 mg single dose	23	270.0 (62.0 to 606.9)	259.0 (75.8 to 511.9)
Clarithromycin	250 mg twice daily, 7 days	0.6 mg single dose	23	227.2 (65.7 to 591.1)	281.5 (88.7 to 851.6)
Ketoconazole	200 mg twice daily, 5 days	0.6 mg single dose	24	101.7 (19.6 to 219.0)	212.2 (76.7 to 419.6)
Ritonavir	100 mg twice daily, 5 days	0.6 mg single dose	18	184.4 (79.2 to 447.4)	296.0 (53.8 to 924.4)
Verapamil	240 mg daily, 5 days	0.6 mg single dose	24	40.1 (-47.1 to 149.5)	103.3 (-9.8 to 217.2)
Diltiazem	240 mg daily, 7 days	0.6 mg single dose	20	44.2 (-46.0 to 318.3)	93.4 (-30.2 to 338.6)
Azithromycin	500 mg x 1 day, then 250 mg x 4 days	0.6 mg single dose	21	21.6 (-41.7 to 222.0)	57.1 (-24.3 to 241.1)
Grapefruit juice	240 mL twice daily, 4 days	0.6 mg single dose	21	-2.55 (-53.4 to 55.0)	-2.36 (-46.4 to 62.2)

Estrogen-containing oral contraceptives: In healthy female volunteers given ethinyl estradiol and norethindrone (Ortho-Novum 1/35) coadministered with Colchicine Tablets, USP (0.6 mg twice daily x 14 days), hormone concentrations are not affected.

In healthy volunteers given theophylline coadministered with Colchicine Tablets, USP (0.6 mg twice daily x 14 days), theophylline concentrations were not affected.

Coadministered Drug	Dose of Coadministered Drug (mg)	Dose of Colchicine Tablets, USP (mg)	N	% Change in Coadministered Drug Concentrations from Baseline (Range: Min - Max)	
				C _{max}	AUC _{0-∞}
Theophylline	300 mg (elixir) single dose	0.6 mg twice daily x 14 days	27	1.6 (-30.4 to 23.1)	1.6 (-28.5 to 27.1)
Ethinyl Estradiol (Ortho-Novum 1/35)	21-day cycle (active treatment) + 7-day placebo	0.6 mg twice daily x 14 days	27*	-6.7 (-40.3 to 44.7)	-3.0 [†] (-25.3 to 24.9)
Norethindrone (Ortho-Novum 1/35)				0.94 (-37.3 to 59.4)	-1.6 [†] (-32.0 to 33.7)

* Conducted in healthy adult females

[†]AUC_{0-∞}

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two year studies were conducted in mice and rats to assess the carcinogenic potential of colchicine. No evidence of colchicine-related tumorigenicity was observed in mice or rats at colchicine oral doses up to 3 and 2 mg/kg/day, respectively (approximately six and eight times, respectively, the maximum recommended human dose of 2.4 mg on a mg/m² basis).

Mutagenesis

Colchicine was negative for mutagenicity in the bacterial reverse mutation assay. In a chromosomal aberration assay in cultured human white blood cells, colchicine treatment resulted in the formation of micronuclei. Since published studies demonstrated that colchicine induces aneuploidy from the process of mitotic nondisjunction without structural DNA changes, colchicine is not considered clastogenic, although micronuclei are formed.

Impairment of Fertility

No studies of colchicine effects on fertility were conducted with Colchicine Tablets, USP. However, published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Reproductive studies also reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division and normal cleavage in females when exposed to colchicine. Colchicine administered to pregnant animals resulted in fetal death and teratogenicity. These effects were dose-dependent, with the timing of exposure critical for the effects on embryofetal development. The nonclinical doses evaluated were generally higher than an equivalent human therapeutic dose, but safety margins for reproductive and developmental toxicity could not be determined.

Case reports and epidemiology studies in human male subjects on colchicine therapy indicated that infertility from colchicine is rare. A case report indicated that azospermia was reversed when therapy was stopped. Case reports and epidemiology studies in female subjects on colchicine therapy have not established a clear relationship between colchicine use and female infertility. However, since the progression of FMF without treatment may result in infertility, the use of colchicine needs to be weighed against the potential risks.

14 CLINICAL STUDIES

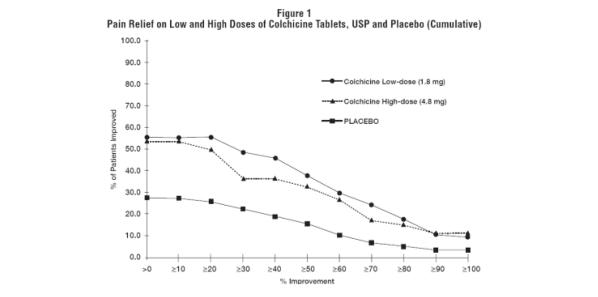
The evidence for the efficacy of colchicine in patients with chronic gout is derived from the published literature. Two randomized clinical trials assessed the efficacy of colchicine 0.6 mg twice a day for the prophylaxis of gout flares in patients with gout initiating treatment with urate-lowering therapy. In both trials, treatment with colchicine decreased the frequency of gout flares.

The efficacy of a low-dosage regimen of oral colchicine (total dose 1.8 mg over one hour) for treatment of gout flares was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel group, one week, dose-comparison study. Patients meeting American College of Rheumatology criteria for gout were randomly assigned to three groups: high-dose colchicine (1.2 mg, then 0.6 mg hourly x six hours [4.8 mg total]); low-dose colchicine (1.2 mg, then 0.6 mg in one hour [1.8 mg total] followed by five placebo doses hourly); or placebo (two capsules, then one capsule hourly x six hours). Patients took the first dose within 12 hours of the onset of the flare and recorded pain intensity (11 point Likert scale) and adverse events over 72 hours. The efficacy of colchicine was measured based on response to treatment in the target joint, using patient self-assessment of pain at 24 hours following the time of first dose as recorded in the diary. A responder was one who achieved at least a 50% reduction in pain score at the 24 hour postdose assessment relative to the pretreatment score and did not use rescue medication prior to the actual time of 24 hour postdose assessment.

Rates of response were similar for the recommended low-dose treatment group (38%) and the nonrecommended high-dose group (33%) but were higher as compared to the placebo group (16%) as shown in Table 8.

Colchicine Tablets, USP Dose Responders n (%)		Placebo n (%) (n=58)	% Differences in Proportion	
Low-Dose (n=74)	High-Dose (n=52)		Low-Dose vs Placebo (95% CI)	High-Dose vs Placebo (95% CI)
28 (38%)	17 (33%)	9 (16%)	22 (8, 37)	17 (1, 33)

Figure 1 shows the percentage of patients achieving varying degrees of improvement in pain from baseline at 24 hours.



The evidence for the efficacy of colchicine in patients with FMF is derived from the published literature. Three randomized, placebo-controlled studies were identified. The three placebo-controlled studies randomized a total of 48 adult patients diagnosed with FMF and reported similar efficacy endpoints as well as inclusion and exclusion criteria. One of the studies randomized 15 patients with FMF to a six month crossover study during which five patients discontinued due to study noncompliance. The 10 patients completing the study experienced five attacks over the course of 90 days while treated with colchicine compared to 59 attacks over the course of 90 days while treated with placebo. Similarly, the second study randomized 22 patients with FMF to a four month crossover study during which nine patients discontinued due to lack of efficacy while receiving placebo or study noncompliance. The 13 patients completing the study experienced 18 attacks over the course of 60 days while treated with colchicine compared to 68 attacks over the course of 60 days while treated with placebo. The third study was discontinued after an interim analysis of six of the 11 patients enrolled had completed the study; results could not be confirmed.

Open-label experience with colchicine in adults and children with FMF is consistent with the randomized, controlled trial experience and was utilized to support information on the safety profile of colchicine and for dosing recommendations.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Colchicine Tablets, USP 0.6 mg are purple, film-coated, capsule-shaped tablets debossed with "AR 374" on one side and scored on the other side.

Bottles of 30 NDC 0254-2008-11

Bottles of 100 NDC 0254-2008-01

16.2 Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from light.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Dosing Instructions

Patients should be advised to take Colchicine Tablets, USP as prescribed, even if they are feeling better. Patients should not alter the dose or discontinue treatment without consulting with their doctor. If a dose of Colchicine Tablets, USP is missed:

- For treatment of a gout flare when the patient is not being dosed for prophylaxis, take the missed dose as soon as possible.
- For treatment of a gout flare during prophylaxis, take the missed dose immediately, wait 12 hours, then resume the previous dosing schedule.
- For prophylaxis without treatment for a gout flare, or FMF, take the dose as soon as possible and then return to the normal dosing schedule. However, if a dose is skipped the patient should not double the next dose.

Fatal Overdose

Instruct patient that fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. Colchicine Tablets, USP should be kept out of the reach of children.

Blood Dyscrasias

Patients should be informed that bone marrow depression with agranulocytosis, aplastic anemia and thrombocytopenia may occur with Colchicine Tablets, USP.

Drug and Food Interactions

Patients should be advised that many drugs or other substances may interact with Colchicine Tablets, USP and some interactions could be fatal. Therefore, patients should report to their healthcare provider all of the current medications they are taking and check with their healthcare provider before starting any new medications, particularly antibiotics. Patients should also be advised to report the use of nonprescription medication or herbal products. Grapefruit and grapefruit juice may also interact and should not be consumed during Colchicine Tablets, USP treatment.

Neuromuscular Toxicity

Patients should be informed that muscle pain or weakness, tingling or numbness in fingers or toes may occur with Colchicine Tablets, USP alone or when it is used with certain other drugs. Patients developing any of these signs or symptoms must discontinue Colchicine Tablets, USP and seek medical evaluation immediately.

COL345 R1 February 2018

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MEDICATION GUIDE

Colchicine Tablets, USP

Read the Medication Guide that comes with Colchicine Tablets, USP before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about Colchicine Tablets, USP when you start taking it and at regular checkups.

What is the most important information that I should know about Colchicine Tablets, USP?

Colchicine Tablets, USP can cause serious side effects or death if levels of colchicine are too high in your body.

- Taking certain medicines with Colchicine Tablets, USP can cause your level of colchicine to be too high, especially if you have kidney or liver problems.
- Tell your healthcare provider about all your medical conditions, including if you have kidney or liver problems. Your dose of Colchicine Tablets, USP may need to be changed.
- Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.
- Even medicines that you take for a short period of time, such as antibiotics, can interact with Colchicine Tablets, USP and cause serious side effects or death.
- Talk to your healthcare provider or pharmacist before taking any new medicine.
- Especially tell your healthcare provider if you take:
 - atazanavir sulfate (Reyataz)
 - clarithromycin (Biaxin)
 - cyclosporine (Neoral, Gengraf, Sandimmune)
 - fosamprenavir (Lexiva)
 - fosamprenavir (Lexiva) with ritonavir
 - indinavir (Crixivan)
 - itraconazole (Sporanox)
 - lopinavir/ritonavir (Kaletra)
 - nefazodone (Serzone)
 - ritonavir (Norvir)
 - telithromycin (Ketek)

- atazanavir sulfate (Reyataz)
- clarithromycin (Biaxin)
- cyclosporine (Neoral, Gengraf, Sandimmune)
- fosamprenavir (Lexiva)
- fosamprenavir (Lexiva) with ritonavir
- indinavir (Crixivan)
- itraconazole (Sporanox)
- lopinavir/ritonavir (Kaletra)
- nefazodone (Serzone)
- ritonavir (Norvir)
- telithromycin (Ketek)
- clarithromycin (Biaxin)
- darunavir (Prezista)
- fosamprenavir (Lexiva)
- fosamprenavir (Lexiva) with ritonavir
- itraconazole (Sporanox)
- lopinavir/ritonavir (Kaletra)
- nelfinavir mesylate (Viracept)
- saquinavir mesylate (Invirase)
- tipranavir (Aptivus)

Ask your healthcare provider or pharmacist if you are not sure if you take any of the medicines listed above. This is not a complete list of all the medicines that can interact with Colchicine Tablets, USP.

- Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.
- Keep Colchicine Tablets, USP out of the reach of children.

What are Colchicine Tablets, USP?

Colchicine Tablets, USP are a prescription medicine used to:

- prevent and treat gout flares in adults
- treat familial Mediterranean fever (FMF) in adults and children age 4 or older

Colchicine Tablets, USP are not a pain medicine, and should not be taken to treat pain related to other conditions unless specifically prescribed for those conditions.

Who should not take Colchicine Tablets, USP?

Do not take Colchicine Tablets, USP if you have liver or kidney problems and you take certain other medicines. Serious side effects, including death, have been reported in these patients even when taken as directed. See “**What is the most important information that I should know about Colchicine Tablets, USP?**”
What should I tell my healthcare provider before starting Colchicine Tablets, USP?

See “What is the most important information that I should know about Colchicine Tablets, USP?”

Before you take Colchicine Tablets, USP tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems.
- are pregnant or plan to become pregnant. It is not known if Colchicine Tablets, USP will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. Colchicine passes into your breast milk. You and your healthcare provider should decide if you will take Colchicine Tablets, USP or breastfeed. If you take Colchicine Tablets, USP and breastfeed, you should talk to your child’s healthcare provider about how to watch for side effects in your child.

Tell your healthcare provider about all the medicines you take, including ones that you may only be taking for a short time, such as antibiotics. See “**What is the most important information that I should know about Colchicine Tablets, USP?**” Do not start a new medicine without talking to your healthcare provider.

Using Colchicine Tablets, USP with certain other medicines, such as cholesterol-lowering medications and digoxin, can affect each other,

causing serious side effects. Your healthcare provider may need to change your dose of Colchicine Tablets, USP. Talk to your healthcare provider about whether the medications you are taking might interact with Colchicine Tablets, USP and what side effects to look for.

How should I take