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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use colchicine safely and effectively. See full prescribing information for COLCRYS™.

COLCRYS™ (colchicine, USP) tablets for Oral use
Initial U.S. Approval: 1961

INDICATIONS AND USAGE

COLCRYS (colchicine, USP) tablets are an alkaloid indicated for

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

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION

- **Gout Flares**: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 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).
  - Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose (2.4).
- See full prescribing information for dose adjustment regarding patients with impaired renal function (2.5) or hepatic function (2.6).

DOSAGE FORMS AND STRENGTHS

- 0.6 mg tablets (3).

CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given COLCRYS 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 COLCRYS out of the reach of children (5.1, 10).
- *Blood dyscrasias:* myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported.
- 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 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 COLCRYS. (5.4, 7).

ADVERSE REACTIONS

Gout Flares: Most common adverse reaction is diarrhea (23%) and pharyngolaryngeal pain (3%). (6).

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 Mutual Pharmaceutical Company, Inc. at 1-888-351-3786 or drugsafety@urlpharma.com 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 COLCRYS. 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 patients with severe hepatic or renal impairment, close monitoring is recommended in both gout flares and FMF patients; a dose reduction may not be needed in gout flares but should be considered in FMF patients, based on the patient's estimated creatinine clearance. (2.5, 2.6, 8.6, 8.7)
- In the presence of renal impairment, dosing for gout flares should be repeated no more than once every two weeks, whereas dosing for FMF should be continued but adjusted based upon the patients estimated creatinine clearance. (2.5, 8.6).
- For patients undergoing dialysis, the total recommended dose for gout flares should be reduced to 0.6 mg (1 tablet) x 1 dose, whereas for FMF patients the starting dose should be 0.3 mg per day. For gout flares, a treatment course should be repeated no more than once every 2 weeks with no increase in dosage but for FMF patients, 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.

Revised: 7/2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Gout Flares
COLCRYS™ (colchicine, USP) tablets are indicated for treatment of acute gout flares when taken at the first sign of a flare.

1.2 Familial Mediterranean fever (FMF)
COLCRYS™ (colchicine, USP) tablets are indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).

2 DOSAGE AND ADMINISTRATION

The long term use of colchicine is established for FMF but the safety and efficacy of repeat treatment in gout flares has not been evaluated. The dosing regimens for COLCRYS are different for the two indications and must be individualized.

The recommended dosage of COLCRYS depends on the patient's age, renal function, hepatic function, and use of other co-administered drugs [see *Dose Modification for Co-administration of Interacting Drugs (2.4)*].

COLCRYS tablets are administered orally, without regard to meals.

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

2.1 Gout Flares
The recommended dose of COLCRYS for treatment of a gout flare is 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 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 1 hour period.

2.2 FMF
The recommended dosage of COLCRYS for FMF in adults is 1.2 mg to 2.4 mg daily.
COLCRYS 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 COLCRYS dose may be administered in one to two divided doses.

2.3 Recommended Pediatric Dosage

Gout Flares:
COLCRYS is not recommended for pediatric use in gout flares.

FMF:
The recommended dosage of COLCRYS 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: 0.3 mg to 1.8 mg daily
- Children 6 – 12 years: 0.9 mg to 1.8 mg daily
- Adolescents older than 12 years: 1.2 mg to 2.4 mg daily

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2.4 Dose Modification for Co-administration of Interacting Drugs

Concomitant Therapy:
Co-administration 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 of COLCRYS should be reduced as shown below[See *DRUG INTERACTIONS (7)*].

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

Drug	Noted or Anticipated Outcome	Clinical Comment	
Strong CYP3A4 Inhibitors			
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	Significant increase in colchicine plasma levels[1]; 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.	**Gout Flares** 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.	**FMF** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Moderate CYP3A4 Inhibitors			
amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	**Gout Flares** 1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days.	**FMF** Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
P-gp Inhibitors			
cyclosporine, 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.	**Gout Flares** 0.6 mg (1 tablet) x 1 dose. Dose to be repeated no earlier than 3 days.	**FMF** 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 [See *Pharmacokinetics (12.3)*]

2.5 Dose Modification in Renal Impairment

Clcr in mL/minute may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

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Gout Flares:
For treatment of gout flares in patients with mild (estimated creatinine clearance Clcr 50 – 80 mL/min) to moderate (Clcr 30 – 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 dose does not need to be adjusted, but a treatment course should be repeated no more than once every 2 weeks. For these patients, requiring repeated courses, consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for gout flares should be reduced to a single dose of 0.6 mg (1 tablet). For these patients, a treatment course should not be repeated more than once every 2 weeks [*See Clinical Pharmacology (12.3) and Renal Impairment (8.6)*].

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 (Clcr 50 – 80 mL/min) and moderate (Clcr 30 – 50 mL/min) renal impairment should be monitored closely for adverse effects of COLCRYS. Dose reduction may be necessary. For patients with severe renal failure (Clcr less than 30 mL/minute), 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 Renal Impairment (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 *Renal Impairment (8.6)*].

2.6 Dose Modification in Hepatic Impairment

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, in patients with severe impairment, the dose does not need to be adjusted, but a treatment course should be repeated no more than once every 2 weeks. For these patients, requiring repeated courses, consideration should be given to alternate therapy. [*See Hepatic Impairment (8.7)*].

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 Hepatic Impairment (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 in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

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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)*]. COLCRYS should be kept out of the reach of children.

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

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 COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors 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, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy [*See DRUG INTERACTIONS (7)*]. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

6 ADVERSE REACTIONS

Gout Flares:
The most common adverse reaction is diarrhea (23%). Pharyngolaryngeal pain was seen in 3% of patients treated for gout flares.

FMF:
Gastrointestinal tract adverse effects are the most frequent side effects in patients initiating colchicine, usually presenting within 24 hours, and occurring in up to 20% of patients given therapeutic doses. Typical symptoms include cramping, nausea, diarrhea, abdominal pain, and vomiting. These events should be viewed as dose-limiting if severe as they can herald the onset of more significant toxicity.

6.1 Clinical Trials Experience in Gout
Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

In a randomized, double-blind, placebo-controlled trial in patients with a gout flare, gastrointestinal adverse reactions occurred in 26% of patients using the recommended dose (1.8 mg over 1 hour) compared to 77% of patients taking a non-recommended high-dose (4.8 mg over 6 hours) and 20% of patients taking placebo. Diarrhea was the most commonly reported drug-related gastrointestinal adverse event. As shown in Table 2, diarrhea is associated with treatment. Diarrhea was more likely to occur in patients taking the high-dose regimen than the low-dose regimen. Severe diarrhea occurred in 19% and vomiting occurred in 17% of patients taking the non-recommended high-dose colchicine regimen but did not occur in the recommended low-dose colchicine regimen.

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Table 2

Number (%) of Patients with at Least One Drug-Related Treatment Emergent Adverse Events with an Incidence of ≥ 2% of Patients in Any Treatment Group

MedDRA System Organ Class MedDRA Preferred Term	Colchicine Dose		Placebo (N=59) n (%)
	High (N=52) n (%)	Low (N=74) n (%)	
Number of Patients with at Least One Drug-Related TEAE	40 (77)	27 (37)	16 (27)
Gastrointestinal Disorders	40 (77)	19 (26)	12 (20)
Diarrhea	40 (77)	17 (23)	8 (14)
Nausea	9 (17)	3 (4)	3 (5)
Vomiting	9 (17)	0	0
Abdominal Discomfort	0	0	2 (3)
General Disorders and Administration Site Conditions	4(8)	1(1)	1 (2)
Fatigue	2 (4)	1 (1)	1 (2)
Metabolic and Nutrition Disorders	0	3 (4)	2 (3)
Gout	0	3 (4)	1 (2)
Nervous System Disorders	1 (2)	1 (1.4)	2 (3)
Headache	1 (2)	1 (1)	2 (3)
Respiratory Thoracic Mediastinal Disorders	1 (2)	2 (3)	0
Pharyngolaryngeal Pain	1 (2)	2 (3)	0

6.2 Postmarketing Experience

Serious toxic manifestations associated with colchicine include myelosuppression, disseminated intravascular coagulation, and injury to cells in the renal, hepatic, circulatory, and central nervous systems. These most often occur with excessive accumulation or overdosage [See *OVERDOSAGE (10)*].

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

7 DRUG INTERACTIONS

COLCRYS (colchicine) is a substrate of the efflux transporter P-glycoprotein (P-gp). Of the cytochrome P450 enzymes tested, CYP3A4 was mainly involved in the metabolism of colchicine. If COLCRYS is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicine are likely. Fatal drug interactions have been reported.

Physicians should ensure that patients are suitable candidates for treatment with COLCRYS and remain alert for signs and symptoms of toxicities related to increased colchicine exposure as a result of a drug interaction. Signs and symptoms of COLCRYS toxicity should be evaluated promptly and, if toxicity is suspected, COLCRYS should be discontinued immediately.

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Table 3 provides recommendations as a result of other potentially significant drug interactions. Table 1 provides recommendations for strong and moderate CYP3A4 inhibitors and P-gp inhibitors.

Table 3
Other Potentially Significant Drug Interactions

Concomitant Drug Class or Food	Noted or anticipated Outcome	Clinical Comment
HMG-Co A Reductase Inhibitors: atorvastatin, fluvastatin, pravastatin, simvastatin	Pharmacokinetic and/or pharmacodynamic interaction: the addition of one drug to a stable long-term regimen of the other has resulted in myopathy and rhabdomyolysis (including a fatality)	Weigh the potential benefits and risks and carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy; monitoring CPK (creatine phosphokinase) will not necessarily prevent the occurrence of severe myopathy.
Other Lipid Lowering Drugs: fibrates, gemfibrozil		
Digitalis Glycosides: digoxin	P-gp substrate; rhabdomyolysis has been reported	

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with colchicine in pregnant women. Colchicine crosses the human placenta. While not studied in the treatment of gout flares, data from a limited number of published studies found no evidence of an increased risk of miscarriage, stillbirth, or teratogenic effects among pregnant women using colchicine to treat familial Mediterranean fever (FMF). Although animal reproductive and developmental studies were not conducted with COLCRYS, published animal reproduction and development studies indicate that colchicine causes embryofetal toxicity, teratogenicity, and altered postnatal development at exposures within or above the clinical therapeutic range. Colchicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of colchicine on labor and delivery is unknown.

8.3 Nursing Mothers

Colchicine is excreted into human milk. Limited information suggests that exclusively breastfed infants receive less than 10 percent of the maternal weight-adjusted dose. While there are no published reports of adverse effects in breast-feeding infants of mothers taking colchicine, colchicine can affect gastrointestinal cell renewal and permeability. Caution should be exercised and breastfeeding infants should be observed for adverse effects when colchicine is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of colchicine in children of all ages with FMF has been evaluated in uncontrolled studies. There does not appear to be an adverse effect on growth in children with FMF treated long-term with colchicine. Gout is rare in pediatric patients, safety and effectiveness of colchicine in pediatric patients has not been established.

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8.5 Geriatric Use
Clinical studies with colchicine for 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 from 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 *Dose Modification for Co-administration of Interacting Drugs (2.4)*].

8.6 Renal Impairment
Colchicine is significantly excreted in urine in healthy subjects. Clearance of colchicine is decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis.

Gout Flares
For patients with mild (Clcr 50 – 80 mL/min) and moderate (Clcr 30 – 50 mL/min) renal impairment, adjustment of the dose recommended for treatment of gout flares is not required. However, in patients with severe renal failure dose reduction should be considered with careful monitoring as necessary and the treatment course should be repeated no more than once every 2 weeks. Colchicine is not removed by hemodialysis. For patients undergoing dialysis, the total recommended dose for gout flares should be reduced to a single dose of 0.6 mg (1 tablet). A treatment course should not be repeated more than once every 2 weeks with no increase in dosage. [*See Pharmacokinetics (12.3) and Dose Modification in Renal Impairment (2.5)*].

FMF
Although, pharmacokinetics of colchicine in patients with mild (Clcr 50 – 80 mL/min) and moderate (Clcr 30 – 50 mL/min) renal impairment is not known, these patients should be monitored closely for adverse effects of colchicine. Dose reduction may be necessary. In patients with severe renal failure (Clcr less than 30 mL/minute) and end-stage renal disease requiring dialysis, colchicine may be started at the dose of 0.3 mg/day. Any increase in dose should be done with adequate monitoring of the patient for adverse effects of colchicine. [*See Pharmacokinetics (12.3) and Dose Modification in Renal Impairment (2.5)*].

8.7 Hepatic Impairment
The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment, compared to healthy subjects [*See Pharmacokinetics (12.3)*]. Nonetheless, colchicine (0.6 mg twice daily) administered long-term to patients with Stage 3 cirrhosis (fibrosis) has been well tolerated.

In patients with mild to moderate hepatic impairment, adjustment of the dose recommended for treatment of gout flares or FMF is not required, but patients should be monitored closely for adverse effects of colchicine [*See Pharmacokinetics (12.3) and Dose Modification in Hepatic Impairment (2.6)*].

Gout Flares
In patients with severe hepatic disease, dose reduction should be considered with careful monitoring as necessary and the treatment course should be repeated no more than once every 2 weeks. [*See Pharmacokinetics (12.3) and Dose Modification in Hepatic Impairment (2.6)*].

FMF
In patients with severe hepatic disease, dose reduction should be considered with careful monitoring as necessary. [*See Pharmacokinetics (12.3) and Dose Modification in Hepatic Impairment (2.6)*].

9 DRUG ABUSE AND DEPENDENCE
Tolerance, abuse, or dependence with colchicine has not been reported.

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10 OVERDOSAGE

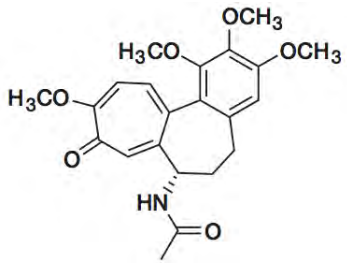
The exact dose of colchicine that produces significant toxicity is unknown. Fatalities have occurred after ingestion of a dose as low as 7 mg over a 4-day period, while other patients have survived after ingesting more than 60 mg. A review of 150 patients who overdosed on colchicine found that those 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.

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 of colchicine poisoning should begin with gastric lavage and measures to prevent shock. Otherwise, treatment is symptomatic and supportive. No specific antidote is known. Colchicine is not effectively removed by dialysis [*See Pharmacokinetics (12.3)*].

11 DESCRIPTION

Colchicine is an alkaloid chemically described as (S)N- (5,6,7,9-tetrahydro- 1,2,3, 10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide with a molecular formula of $C_{22}H_{25}NO_6$ and a molecular weight of 399.4. The structural formula of colchicine is given below.



Colchicine occurs as a pale yellow powder that is soluble in water.

COLCRYS™ (colchicine USP) tablets is supplied for oral administration as purple, film-coated, capsule-shaped tablets (0.1575” × 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 COLCRYS exerts its 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-1β. 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.

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12.3 Pharmacokinetics

Absorption

In healthy adults, COLCRYS is absorbed when given orally, reaching a mean C_{max} of 2.5 ng/mL (range 1.1 to 4.4 ng/mL) in 1 to 2 hours (range 0.5 to 3 hours) after a single dose administered under fasting conditions.

Following oral administration of COLCRYS given as 1.8 mg colchicine over 1 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 non-recommended high-dose regimen (4.8 mg over 6 hours), mean maximal 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 post-dose (range 0.5 to 3.0 hours). Mean pharmacokinetic parameter values in healthy adults are shown in Table 4 below.

Table 4
Mean (%CV) Pharmacokinetic Parameters in Healthy Adults Given COLCRYS

C_{max} (colchicine ng/mL)	T_{max}[1] (h)	Vd/F (L)	CL/F (L/hr)	$t_{1/2}$ (h)
COLCRYS 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)	--
COLCRYS 0.6 mg b.i.d. 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)

[1] T_{max} mean (range)
CL= Dose/AUC_{0-t} (Calculated from mean values)
Vd = CL/Ke (Calculated from mean values)

In some subjects, secondary colchicine peaks are seen, occurring between 3 and 36 hours post-dose 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 COLCRYS with food has no effect on the rate of colchicine absorption, but did decrease the extent of colchicine by approximately 15%. This is without clinical significance.

Distribution

The mean apparent volume of distribution in healthy young volunteers was 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 Pregnancy (8.1) and Nursing Mothers (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 colchiceine). *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).

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Elimination/Excretion
In healthy volunteers (n=12) 40 – 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-glycoprotein (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: Pharmacokinetics of colchicine has not been determined in elderly patients. 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 – 93), mean weight was 47 kg (38 – 61 kg) and mean creatinine clearance was 46 mL/min (range 25 – 75 mL/min). Mean peak plasma levels and AUC of colchicine were two times higher in elderly subjects compared to young healthy males. However, it is possible that the higher exposure in the elderly subjects was due to decreased renal function.

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 Dose Modification in Renal Impairment (2.5) and Renal Impairment (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 inter-patient 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 Dose Modification in Hepatic Impairment (2.6) and Hepatic Impairment (8.7)*]. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

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 co-administration of other drugs with COLCRYS on C_{max}, AUC, and C_{min} are summarized in Table 5 (effect of other drugs on colchicine) and Table 6 (effect of colchicine on other drugs). For information regarding clinical recommendations, see Table 1 in Dose Modification for Co-administration of Interacting Drugs (2.4)].

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Table 5
Drug Interactions: Pharmacokinetic Parameters for Colchicine in the Presence of the Co-Administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of COLCRYS (mg)	N	% Change in Colchicine Concentrations from Baseline (Range: Min - Max)	
				C_{max}	AUC_{0-t}
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 BID, 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 BID, 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 BID, 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 × 1 day, then 250 mg × 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 BID, 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) co administered with COLCRYS (0.6 mg b.i.d. × 14 days), hormone concentrations are not affected.

In healthy volunteers given theophylline coadministered with COLCRYS (0.6 mg b.i.d. x 14 days), theophylline concentrations were not affected.

Table 6
Drug Interactions: Pharmacokinetic Parameters for Co-Administration of Drug in the Presence of COLCRYS (colchicine, USP) tablets

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of COLCRYS (mg)	N	% Change in Co-Administered Drug Concentrations from Baseline (Range: Min - Max)	
				C_{max}	AUC_{0-t}
Theophylline	300 mg (elixir) single- dose	0.6 mg BID × 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 BID × 14 days	27[1]	-6.7 (-40.3 to 44.7)	-3.0[2] (-25.3 to 24.9)
Norethindrone (Ortho-Novum® 1/35)				0.94 (-37.3 to 59.4)	-1.6[2] (-32.0 to 33.7)

[1] Conducted in healthy adult females
[2] AUCτ

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of colchicine have not been conducted. Due to the potential for colchicine to produce aneuploid cells (cells with an unequal number of chromosomes), there is theoretically an increased risk of malignancy.

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 COLCRYS. However, published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Reproductive , 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 azoospermia 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 efficacy of a low dosage regimen of oral colchicine (COLCRYS total dose 1.8 mg over 1 hour) for treatment of gout flares was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1 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 × 6 hours [4.8 mg total]); low-dose colchicine (1.2 mg, then 0.6 mg in 1 hour [1.8 mg total] followed by 5 placebo doses hourly); or placebo (2 capsules, then 1 capsule hourly × 6 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 post-dose assessment relative to the pre-treatment score and did not use rescue medication prior to the actual time of 24-hour post-dose assessment.

Rates of response were similar for the recommended low-dose treatment group (38%) and the non-recommended high-dose group (33%) but were higher as compared to the placebo group (16%) as shown in Table 7.

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Table 7

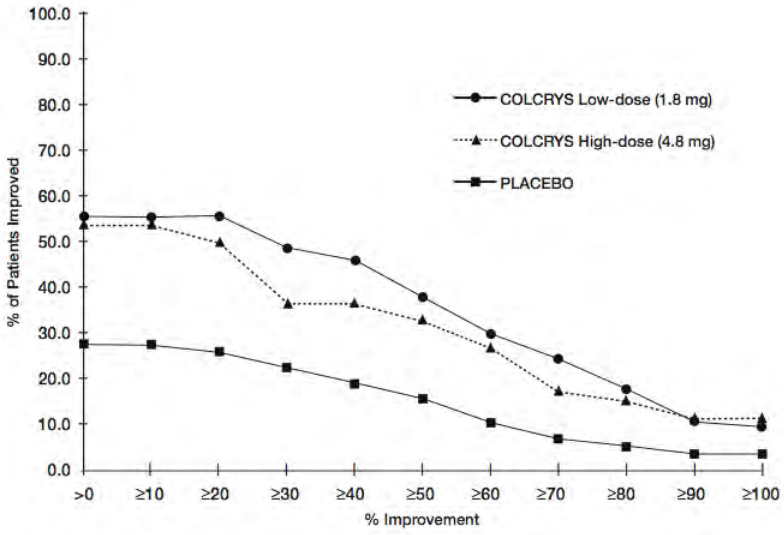
Number (%) of Responders Based on Target Joint Pain Score at 24 Hours Post First Dose

COLCRYS Dose Responders n (%)		Placebo n (%)	% Difference in Proportions	
Low-dose (n = 74)	High-dose (n=52)	(n=58)	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 below shows the percentage of patients achieving varying degrees of improvement in pain from baseline at 24 hours.

Figure 1

Pain Relief on Low and High Doses of COLCRYS and Placebo (Cumulative)



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 6-month crossover study during which 5 patients discontinued due to study non-compliance. The 10 patients completing the study experienced 5 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 4-month crossover study during which 9 patients discontinued due to lack of efficacy while receiving placebo or study non-compliance. 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 6 of the 11 patients enrolled had completed the study; results could not be confirmed.

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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

COLCRYS™ (colchicine, USP) tablets 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 13310-119-07
Bottles of 60	NDC 13310-119-06
Bottles of 100	NDC 13310-119-01
Bottles of 250	NDC 13310-119-03
Bottles of 500	NDC 13310-119-05
Bottles of 1000	NDC 13310-119-10

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

[See Medication Guide]

17.1 Dosing Instructions

Patients should be advised to take COLCRYS 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 COLCRYS is missed, then patients being treated for gout flare or FMF should take the dose as soon as possible and then patients with FMF should return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

17.2 Blood Dyscrasias

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

17.3 Drug and Food Interactions

Patients should be advised that many drugs or other substances may interact with colchicine 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 COLCRYS treatment.

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17.4 Neuromuscular Toxicity

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

17.5 Medication Guide

Manufactured for:
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