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 is indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF) (1).

DOSAGE AND ADMINISTRATION

- Give total daily dose in one or two divided doses (2.1).
- Recommended Dosing (2.2) (2.3)

Age	Daily Dose	
	Usual	Maximum
Adults and children older than 12 years	1.2 mg	2.4 mg
Children 6 to 12 years	0.9 mg	1.8 mg
Children 4 to 6 years	0.3 mg	1.8 mg

- 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 colchicine 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

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 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 (5.3, 7).

USE IN SPECIFIC POPULATIONS

- A dose adjustment is recommended for patients with impaired renal function, based on the patient's estimated creatinine clearance (2.5).
- Close monitoring is recommended for patients with impaired renal (8.6) or hepatic function (8.7) or a change in medications or medical conditions that may increase exposure to COLCRYS (7).
- 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).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 7/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Information

Review of concomitant medications and assessment of renal and hepatic function should be performed prior to initiating COLCRYS.

COLCRYS is administered orally, without regard to meals.

The total daily COLCRYS dose may be administered in one or two divided doses.

2.2 Recommended Adult Dosage

The recommended dosage of COLCRYS for adults is 1.2 mg to 2.4 mg daily.

2.3 Recommended Pediatric Dosage

The recommended dosage of COLCRYS for 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

2.4 Dose Modification Guidelines

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.

2.5 Dose Modification in Renal Impairment

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

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

[*See Renal Impairment (8.6).*]

2.6 Dose Modification in Hepatic Impairment

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.

5 WARNINGS AND PRECAUTIONS

5.1 Fatal Overdose

Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested COLCRYS [*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

COLCRYS 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)*]. In patients with renal or hepatic impairment, P-gp or strong CYP3A4 inhibitors should not be given in conjunction with colchicine [*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

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.

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, ABCB1). 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 colchicine toxicity should be evaluated promptly and, if toxicity is suspected, COLCRYS should be discontinued immediately.

Table 1 provides recommendations as a result of established drug interactions with colchicine, based on drug interaction studies or reported cases.

Table 1
Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class or Food	Noted or Anticipated Outcome	Clinical Comment
Strong CYP3A4 Inhibitors: atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, ketoconazole, liponavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir/ritonavir, 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.	Use COLCRYS with caution at reduced maximum dose of 0.3mg twice daily with increased monitoring for adverse effects. In patients with renal or hepatic impairment, use of colchicine in conjunction with these drugs is contraindicated.
Moderate CYP3A4 Inhibitors: 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.	Use COLCRYS with caution at reduced starting doses and lower maximum doses with increased monitoring for adverse effects.
P-gp Inhibitors: *e.g.*, 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.	Use COLCRYS with caution at reduced starting doses and lower maximum doses with increased monitoring for adverse effects.

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	

[1] For magnitude of effect on colchicine plasma concentrations [*See Pharmacokinetics (12.3)*]

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. 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.

8.5 Geriatric Use

Clinical studies of colchicine in patients with FMF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic or renal function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Colchicine is significantly excreted in urine in healthy subjects. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis. Although, pharmacokinetics of colchicine in patients with mild and moderate 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 (estimated creatinine clearance [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 Dosage and*

Administration (2.5)]. In patients with mild or moderate renal impairment, especially those whose medications or medical condition changes, frequent monitoring may be warranted.

8.7 Hepatic Impairment

The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with hepatic impairment, compared to healthy subjects [*See Pharmacokinetics (12.3)*]. In patients with hepatic impairment, especially those whose medications or medical condition changes, frequent monitoring may be warranted.

9 DRUG ABUSE AND DEPENDENCE

Tolerance, abuse, or dependence with colchicine has not been reported.

10 OVERDOSAGE

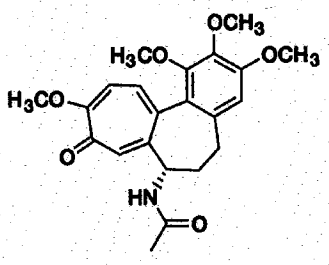
The exact dose of colchicine that produces significant toxicity is unknown. Fatalities have occurred after ingestion of a dose as low as 7 mg over a 4-day period, while other patients have survived after ingesting more than 60 mg. A review of 150 patients who overdosed on colchicine found that those 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 a beta-tubulin interactor 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 (colchicine) exerts its beneficial effect in patients with FMF has not been fully elucidated; however, recent data 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.

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 1.0 to 2 hours (range 0.5 to 3 hours) after a single dose administered under fasting conditions. 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 2 below.

Table 2
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)

One to two secondary colchicine peaks were evident in 5 subjects, occurring between 3 to 6 hours in 2 subjects and between 12 to 36 hours in 3 subjects. 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 absorption 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) & 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).

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 Dosage and Administration (2.5) & 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 Dosage and Administration (2.6)*]. 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:

Clarithromycin (strong CYP3A4 and P-gp inhibitor): Following administration of 250 mg b.i.d. × 7 days, there was a significant increase in exposure to a single oral dose of COLCRYS 0.6 mg: increases of 200% and 240% were observed for C_{max} and AUC, respectively. Total apparent oral clearance (CL/F) of colchicine was

decreased by 75% compared to the reported total apparent oral clearance when colchicine was administered alone (12.0 L/hr *versus* 46.8 L/hr) [*See DRUG INTERACTIONS (7)*].

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.

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 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 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 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 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 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.

Open-label experience with colchicine in adults and children 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 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 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 every day 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, patients should take the dose as soon as possible and then 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 colchicine treatment.

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:
AR SCIENTIFIC, INC.
Philadelphia, PA 19124 USA
by:
MUTUAL PHARMACEUTICAL COMPANY, INC.
Philadelphia, PA 19124 USA

Rev July, 2009

MEDICATION GUIDE

COLCRYS™
(KOL-kris)

(Colchicine Tablets, USP)

Read the Medication Guide that comes with COLCRYS 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 COLCRYS when you start taking it and at regular checkups.

What is the most important information I should know about COLCRYS?

COLCRYS can cause serious side effects or even death if COLCRYS levels are too high in your body. Keep COLCRYS out of the reach of children.

Tell your healthcare provider about all your medical conditions, including if you have kidney or liver problems. Your dose of COLCRYS may need to be changed.

Certain medicines when taken with COLCRYS can cause the levels of COLCRYS to be too high in your body. It is important for you to tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. COLCRYS and other medicines may affect each other causing serious side effects or even death. Do not start taking a new medicine without telling your healthcare provider or pharmacist.

Even medications that you might take for a short period of time, such as antibiotics, can interact with COLCRYS and cause serious side effects or death.

Especially tell your healthcare provider if you take:

- clarithromycin (Biaxin®)
- telithromycin (Ketek®)
- cyclosporine (Neoral®, Gengraf®, Sandimmune®)
- ketoconazole (Nizoral®)
- itraconazole (Sporanox®)
- HIV protease inhibitors
- nefazodone (Serzone®)

This is not a complete list of all the medicines that can interact with COLCRYS. Talk to your healthcare provider or pharmacist to find out if taking COLCRYS with the other medicines you are taking could be dangerous.

Talk to your healthcare provider before taking any new medicine.

COLCRYS is not a pain medicine and it should not be taken to treat pain related to other conditions unless specifically prescribed for those conditions.

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.

What is COLCRYS?

COLCRYS is a prescription medicine used to treat familial Mediterranean fever (FMF).

COLCRYS is only for adults and children age four or older.

Who should not take COLCRYS?

Do not take COLCRYS 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 I should know about COLCRYS?"

What should I tell my healthcare provider before starting COLCRYS?

See "What is the most important information I should know about COLCRYS?"

Before you take COLCRYS 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 COLCRYS will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. COLCRYS passes into your breast milk. You and your healthcare provider should decide if you will take COLCRYS or breast-feed. If you take COLCRYS and breast-feed, 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 I should know about COLCRYS?" Do not start a new medicine without talking to your healthcare provider.

Using COLCRYS 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 COLCRYS. Talk to your healthcare provider about whether the medications you are taking might interact with COLCRYS, and what side effects to look for.

How should I take COLCRYS?

- Take COLCRYS exactly as your healthcare provider tells you to take it. **If you are not sure about your dosing**, call your healthcare provider.
- COLCRYS can be taken with or without food.
- If you take too much COLCRYS go to the nearest hospital emergency room right away.
- If you miss a dose of COLCRYS, take it as soon as you remember. Do not take 2 doses at the same time.
- Do not stop taking COLCRYS even if you start to feel better, unless your healthcare provider tells you.
- Your healthcare provider may do blood tests while you take COLCRYS.

What should I avoid while taking COLCRYS?

- Avoid eating grapefruit or drinking grapefruit juice while taking COLCRYS. It can increase your chances of getting serious side effects.

What are the possible side effects of COLCRYS?

COLCRYS can cause serious side effects or even cause death. See "What is the most important information I should know about COLCRYS?"

Get medical help right away, if you have:

- Muscle weakness or pain
- Numbness or tingling in your fingers or toes
- Unusual bleeding or bruising

- Increased infections
- Feel weak or tired
- Pale or gray color to your lips, tongue, or palms of your hands
- Severe diarrhea or vomiting

The most common side effects of COLCRYS include:

- Diarrhea
- Stomach pain or cramping

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of COLCRYS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COLCRYS?

- Store COLCRYS at room temperature between 68° and 77° F (20°C to 25°C).
- Keep COLCRYS in a tightly closed container.
- Keep COLCRYS out of the light.

Keep COLCRYS and all medicines out of the reach of children.

General information about COLCRYS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COLCRYS for a condition for which it was not prescribed. Do not give COLCRYS to other people, even if they have the same symptoms that you have. It may harm them. This Medication Guide summarizes the most important information about COLCRYS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about COLCRYS that is written for healthcare professionals.

For more information, go to www.COLCRYS.com or call 1-888-351-3786.

What are the ingredients in COLCRYS?

Active Ingredient: Colchicine

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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
AR SCIENTIFIC, INC.
Philadelphia, PA 19124 USA
by:
MUTUAL PHARMACEUTICAL COMPANY, INC.
Philadelphia, PA 19124 USA

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NDA 22-352

COLCRYS™ (colchicine, USP) tablets

Mutual Pharmaceutical Company, Inc.
Philadelphia, PA 19124

Contact Information:
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PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goal of this REMS is to inform patients of the serious risks associated with the use of COLCRYS™ (colchicine), including the risks of increased susceptibility to colchicine toxicity in patients with renal or hepatic impairment and potential serious drug-drug interactions with colchicine.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each COLCRYS™ (colchicine, USP) tablets prescription in accordance with 21 CFR 208.24.

In accordance with 21 CFR 208.24(b), Mutual will ensure that the Medication Guide is available for distribution to patients by providing the Medication Guide in sufficient numbers to distributors, packers or authorized dispensers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription of COLCRYS™ (colchicine, USP) tablets.

Sufficient numbers of Medication Guides will be included with each COLCRYS™ (colchicine, USP) tablets bottle along with the Prescribing information. Sufficient numbers of Medication Guides will be attached to or provided with each bottle such that one Medication Guide is dispensed with each 30 day supply. Packaging the product literature with the bottles ensures that every patient receives the Medication Guide with each COLCRYS™ (colchicine, USP) tablets prescription.

Mutual will also make the Medication Guide available through use of tear pads or on our website, www.COLCRYS.com

In accordance with 21CFR 208.24 (d), Mutual will include a statement on the container labels for COLCRYS™ (colchicine, USP) tablets to alert pharmacists to dispense the Medication Guide with the product.

B. Communication Plan

This REMS for COLCRYS™ (colchicine, USP) tablets does not include a communication plan.

C. Elements To Assure Safe Use

This REMS for COLCRYS™ (colchicine, USP) tablets does not include elements to assure safe use.

D. Implementation System

Because this REMS for COLCRYS™ (colchicine, USP) tablets does not include elements to assure safe use, an implementation system is not required.

E. Timetable for Submission of Assessments

The Timetable for Assessments is as follows:

1st Assessment: 18 months post approval
2nd Assessment: 3 years post approval
3rd Assessment: 7 years post approval.

Mutual will submit the assessments within 60 days of the close of the interval as noted above.