HIGHLIGHTS OF PRESCRIBING INFORMATION
Rx Only
These highlights do not include all the information needed to use MITIGARE™.
MITIGARE™ (colchicine) capsules
Initial U.S. Approval: 1961

INDICATIONS AND USAGE
• MITIGARE™ is indicated for prophylaxis of gout flares in adults (1).

 Limitations of use: The safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied.

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

DOSE AND ADMINISTRATION
• 0.6 mg (one capsule) once or twice daily (2). Maximum dose 1.2 mg/day.

 MITIGARE™ is administered orally, without regard to meals (2).

DOSE FORMS AND STRENGTHS
• 0.6 mg Capsules (3).

CONTRAINDICATIONS
• Patients with renal or hepatic impairment should not be given MITIGARE™ in conjunction with drugs that inhibit both P-gp and CYP3A4 (4).

• Patients with both renal and hepatic impairment should not be given MITIGARE™ (4).

WARNINGS AND PRECAUTIONS
• Fetal overdoses have been reported with colchicine in adults and children. Keep MITIGARE™ 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).

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FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
MITIGARE™ (colchicine) capsules are indicated for prophylaxis of gout flares in adults.

 Limitations of use: The safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied.

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

2 DOSAGE AND ADMINISTRATION
2.1 Gout Prophylaxis
For prophylaxis of gout flares, the recommended dosage of MITIGARE™ is 0.6 mg once or twice daily. The maximum dose is 1.2 mg per day. MITIGARE™ is administered orally, without regard to meals.

2.2 Blood Dyscrasias
Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported with colchicine use in therapeutic doses.

2.3 Interactions with CYP3A4 and P-gp Inhibitors
Because colchicine is a substrate for both the CYP3A4 metabolism enzyme and the P-gp proton pump transporter, inhibition of either of these pathways may lead to colchicine-related toxicity. Inhibition of both CYP3A4 and P-gp by dual inhibitors such as clarithromycin has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-gp should be avoided (See Drug Interactions (7)). If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity. Use of MITIGARE™ in conjunction with drugs that inhibit both CYP3A4 and P-gp is contraindicated in patients with renal or hepatic impairment (See Contraindications (4)).

4 CONTRAINDICATIONS
Patients with renal or hepatic impairment should not be given MITIGARE™ with drugs that inhibit both P-gp and CYP3A4 inhibitors (See Drug Interactions (7)). Combining these dual inhibitors with colchicine in patients with renal or hepatic impairment has resulted in life-threatening or fatal colchicine toxicity.

Patients with both renal and hepatic impairment should not be given MITIGARE™.

6 WARNINGS AND PRECAUTIONS
6.1 Fatal Overdose
Fatal overdoses, both accidental and intentional, have been reported in adults and children (See Overdosage (10)). MITIGARE™ should be kept out of the reach of children.

6.2 Blood Dyscrasias
Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported with colchicine use in therapeutic doses.

6.3 Interactions with CYP3A4 and P-gp Inhibitors
Because colchicine is a substrate for both the CYP3A4 metabolism enzyme and the P-gp proton pump transporter, inhibition of either of these pathways may lead to colchicine-related toxicity. Inhibition of both CYP3A4 and P-gp by dual inhibitors such as clarithromycin has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-gp should be avoided (See Drug Interactions (7)). If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity. Use of MITIGARE™ in conjunction with drugs that inhibit both CYP3A4 and P-gp is contraindicated in patients with renal or hepatic impairment (See Contraindications (4)).

7 DRUG INTERACTIONS
Colchicine is a substrate of the efflux transporter P-glycoprotein (P-gp), and the CYP3A4 and P-gp pathways. Drug interactions have been reported when colchicine is administered with inhibitors of CYP3A4 (4). Combining these dual inhibitors with MITIGARE™ should be avoided (See Drug Interactions (7)).

8 USE IN SPECIFIC POPULATIONS
8.1 Use in Pregnancy
Pregnancy Category: C
There are no adequate and well-controlled studies with MITIGARE™ in pregnant women. Colchicine crosses the human placenta. Developmental studies in animals were not conducted with MITIGARE™. However published animal reproduction and development studies with colchicine demonstrated 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 to the mother justifies the potential risk to the fetus.

8.2 Labor and Delivery
The effect of colchicine on labor and delivery is unknown.

8.3 Use in Nursing Mothers
Colchicine is excreted into human milk. Limited information suggests that infants exclusively breastfed 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 and biliary motor functions. Caution should be exercised and breastfeeding infants should be observed for adverse effects when MITIGARE™ is administered to a nursing woman.

8.4 Pediatric Use
Use is rare in pediatric patients; the safety and effectiveness of MITIGARE™ in pediatric patients has not been evaluated in controlled studies.

8.5 Geriatric Use
Because of the increased incidence of decreased renal function in the elderly population, and the higher incidence of other co-morbid conditions in the elderly population requiring the use of other medications, reducing the dosage of colchicine when elderly patients are treated with colchicine should be considered carefully.

8.6 Renal Impairment
No dedicated pharmacokinetic study has been conducted using MITIGARE™ in patients with varying degrees of renal impairment.

Colchicine is known to be excreted in urine in humans and the presence of other renal impairment has been associated with colchicine toxicity. Urinary clearance of colchicine and its metabolites may be decreased in patients with impaired renal function. Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe renal impairment. Colchicine is not effectively removed by hemodialysis. Patients who are undergoing hemodialysis should be monitored carefully for colchicine toxicity.

8.7 Hepatic Impairment
No dedicated pharmacokinetic study using MITIGARE™ has been conducted in patients with varying degrees of hepatic impairment.

Colchicine is known to be metabolized in humans and the presence of severe hepatic impairment has been associated with colchicine toxicity. Hepatic clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment. Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment.

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

10 OVERDOSAGE
The dose of colchicine that would induce significant toxicity for an adult is unknown. Fatalities have been reported in patients after ingesting a dose as low as 7 mg or over a 4-day period, while other patients have reportedly 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 whereas those who ingested from
Distribution

Colchicine is not effectively removed by hemodialysis.

Absorption.

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 associated consequences. Death usually results from 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 overdose 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 hemodialysis. [See Pharmacokinetics (12.3)].

11. DESCRIPTION

Colchicine is an alkaloid obtained from the plant Cibicum autumnale. The chemical name for colchicine is (9S,9R,6S,7R,9S,10R,12S,13R)-tetramethoxy-9 oxobenz[b][a]heptalen-7-yl acetamide. The structural formula is represented below:

\[
\text{Colchicine} \quad \text{C}_{21}H_{28}O_{3} \\
\text{M.W. 399.44}
\]

Colchicine consists of pale yellow scales or powder, it darkens on exposure to light. Colchicine is soluble in water, freely soluble in alcohol, and slightly soluble in ether.

MITIGARE™ (colchicine) capsules are supplied for oral administration. Each capsule contains 0.6 mg Colchicine and the following inactive ingredients: colloidal silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell contains gelatin, purified water, titanium dioxide, erythrosine, Brilliant Blue FCF and Quinoline Yellow.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Colchicine's effectiveness as a treatment for gout has been postulated to be due to its ability to block neutrophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid. Colchicine disrupts the polymerization of polymer-2-β-glucan within microtubules, thereby preventing the activation, degranulation, and migration of neutrophils to sites of inflammation. Colchicine also interferes with the mitotic complex found in dividing neutrophils and monocytes that mediates interkinesis (IL-1β) activation.

12.3 Pharmacokinetics

Absorption

In healthy adults, MITIGARE™ when given orally reached a mean Cmax of 3 ng/mL in 1.3 h (range 0.7 to 2.5 h) after 0.6 mg single dose administration.

Absolute bioavailability is reported to be approximately 45%.

Administration with food has no effect on the rate or extent of colchicine absorption.

Colchicine is not effectively removed by hemodialysis.

Distribution

Colchicine has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding to serum protein is about 39%, primarily to albumin. Colchicine crosses the placenta and distributes into breast milk. [See Pregnancy (8.1) and Nursing Mothers (8.3)].

Metabolism

A published in vitro human liver microsome study showed that about 16% of colchicine is metabolized to 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) by CYP3A4. Glucuronidation is also believed to be a metabolic pathway for colchicine.

Excretion

In a published study in healthy volunteers, 40 to 65% of the total absorbed dose of colchicine (1 mg administered orally) was recovered unchanged in urine. Enteropllactic recirculation and biliary excretion are also believed to play a role in colchicine elimination. Colchicine is a substrate of P-gp and P-gp efflux is postulated to play an important role in colchicine disposition. Elimination half-life in humans was found to be 31 h (range 21.7 to 49.9 h).

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 have not been determined in elderly patients. A published report described the pharmacokinetics of 1 mg of colchicine administered orally in 116 elderly healthy males. The mean age of the group was 65 years (range 75 to 95), mean weight was 67 kg (range 58 to 71 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. 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 patients who had end-stage renal disease requiring dialysis compared to patients with normal renal function. Patients with end-stage renal disease had 75% lower colchicine clearance (1.7 L vs. 0.73 L/h/kg) and prolonged plasma elimination half-life (18.8 h vs. 4.4 h) as compared to subjects with normal renal function [See Renal impairment (8.6)].

Hepatic impairment: Published reports on the pharmacokinetics of intravenous 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 Hepatic impairment (8.7)]. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

Drug Interactions

Pharmacokinetic studies evaluating changes in systemic levels of colchicine when co-administered with CYP3A4 inhibitors in healthy volunteers have been conducted with MITIGARE™. While voriconazole 200 mg BID for 5 days (considered a strong CYP3A4 inhibitor) and cimetidine 800 mg BID for 5 days (considered a weak CYP3A4 inhibitor) did not cause any changes in colchicine systemic levels, fluconazole 200 mg BID for 4 days with a 400 mg loading dose (considered a moderate CYP3A4 inhibitor) increased colchicine AUC by 40%. As voriconazole, cimetidine, and fluconazole are known as CYP3A4 inhibitors that do not inhibit P-gp, these studies show that CYP3A4 inhibition by itself may not lead to clinically significant increases in colchicine systemic levels in humans, and P-gp inhibition in addition to CYP3A4 inhibition may be necessary for clinically meaningful interactions of colchicine. However, based on published case reports that indicate the presence of colchicine toxicity when colchicine is co-administered with strong to moderate CYP3A4 inhibitors such as clarithromycin, erythromycin, grapefruit juice, etc., as well as the 40% increase in systemic levels of colchicine observed with concomitantly administered fluconazole (a moderate CYP3A4 inhibitor that is not known to inhibit P-gp) in a drug-drug interaction study, the drug-drug interaction potential of colchicine with strong or moderate CYP3A4 inhibitors that do not inhibit P-gp cannot be ruled out completely.

Co-administration of MITIGARE™ with propafenone (a P-gp inhibitor) at 225 mg BID for 5 days, in a pharmacokinetic study in healthy volunteers, did not cause any changes in systemic levels of colchicine. This indicates that propafenone can be administered with MITIGARE™ without any dose adjustment. However, these results should not be extrapolated to other P-gp inhibitors as colchicine is known to be a substrate for P-gp and case reports of colchicine toxicity associated with the co-administration of P-gp inhibitors such as cyclosporine have been published.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Published studies demonstrated that colchicine was negative for mutagenicity in the bacterial reverse mutation assay. However, in vitro chromosomal aberration assays demonstrated the formation of micronuclei following colchicine treatment. Because published studies demonstrated that colchicine induces aneuploidy through the process of mitotic nondisjunction without structural DNA changes, colchicine is not considered clastogenic, although micronuclei are formed.

Impairment of Fertility

There were no studies of the effects of MITIGARE™ on fertility. However, published nonclinical studies have demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Published reproductive studies with colchicine reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division, and normal cleavage in females. Case reports and epidemiology studies in human male subjects on colchicine therapy indicate 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.

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.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MITIGARE™ (colchicine) capsules, 0.6 mg are No. 4. Dark Blue/ Light Blue Hard Gelatin Capsules printed “Westward 118” in white ink.

Bottles of 100 capsules

Bottles of 1000 capsules

16.2 Storage

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

17. PATIENT COUNSELING INFORMATION

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

Dosing Instructions

If a dose of MITIGARE™ is missed, advise the patient to 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

Advise the patient that fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. MITIGARE™ should be kept out of the reach of children.

Blood Dyscrasias

Advise patients that bone marrow depression with agranulocytosis, aplastic anemia, and thrombocytopenia may occur with MITIGARE™.

Drug and Food Interactions

Advise patients that many drugs or other substances may interact with MITIGARE™ 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, including short-term medications such as antibiotics. Patients should also be advised to report the use of non-prescription medication or herbal products. Grapefruit and grapefruit juice may also interact and should not be consumed during treatment with MITIGARE™.

Neuromuscular Toxicity

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

Manufactured for:

Hikma Americas, Inc.

Memphis, TN 38120

Manufactured by:

West-Ward Pharmaceuticals Corp.

Evanston, IL 60204

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