15mL: NDC 35781-0400-2
30mL (15mL x 2): NDC 35781-0400-4

COLCIGEL®

For Gout Flares

READ THIS INFORMATION BEFORE PRESCRIBING THIS PRODUCT

INDICATIONS AND USAGE

ColciGel® (colchicinum 4X) transdermal gel is an alkaloid indicated for: Treatment and Prophylaxis of Gout Flares in adults (1.1). ColciGel® is not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION

1-4 pumps = 1 dose (0.25 mL-1.0 mL)

Gout Flares: ***Treatment of Gout Flares:*** Apply 1-4 pumps of ColciGel® (0.25 mL-1.0 mL) up to four times per day (2.1).

Prophylaxis of Gout Flares: Apply 1-3 pumps (0.25 mL-0.75 mL) of ColciGel® to the affected area twice daily in adults and adolescents older than 16 years of age (2.1). Maximum dose 6 pumps (1.5 mL) in a 24 hour period.

DOSAGE FORMS AND STRENGTHS

ColciGel® (Colchicinum 4X) is a Transdermal Gel. Each gram of ColciGel® contains Colchicinum 4X in a transdermal gel.

CONTRAINDICATIONS

Traumatized skin, secondary bacterial infection of the area of proposed application and known hypersensitivity to any of the components.

WARNINGS AND PRECAUTIONS

For External Use Only. Avoid Contact with Eyes. If irritation or sensitivity occurs or infection appears, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Prophylaxis and Treatment of Gout Flares: The most commonly reported adverse reaction in clinical trials for the prophylaxis and treatment of gout was mild skin irritation at the site of application. To report SUSPECTED ADVERSE REACTIONS, contact Gensco Laboratories at 866-608-6284 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Animal testing data and limited human data (pharmacokinetic analysis) indicate limited (sub clinical) systemic absorption after repeated applications of transdermal ColciGel®. This data supports the conclusion that drug-drug interactions with ColciGel® are not clinically significant.

This may not be a complete list of all interactions that may occur. ***This may not be a complete list of all interactions that may occur. Ask your health care provider if LiDORx® 3% may interact with other medicines that you take.***

USE IN SPECIFIC POPULATIONS

For patients undergoing dialysis, no dose adjustment is required, however, close monitoring of the patient is suggested. **Pregnancy:** Use only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Caution should be exercised when administered to a nursing woman.

FULL PRESCRIBING INFORMATION: CONTENTS

1. Indications and Usage: ***1.1 Gout Flares:*** ColciGel® transdermal gel is indicated for prophylaxis and the treatment of acute gout flares. *Treatment of Gout Flares:* ColciGel® gel is indicated for treatment of acute gout flares when used at the first sign of a flare. *Prophylaxis of Gout Flares:* ColciGel® is indicated for prophylaxis of gout flares.

2. Dosage and Administration: The long term use of colchicine is established for the prophylaxis of gout flares but the safety and efficacy of repeat treatment for gout flares has not been evaluated. Each 0.25 mL dose (1 pump) is adequate to cover a 2 inch by 2 inch area of unbroken skin. ColciGel® gel is administered topically. ColciGel® is not an analgesic medication and should not be used to treat pain from other causes. ***2.1 Gout Flares:*** *Treatment of Gout Flares:* The recommended dose of ColciGel® for treatment of a gout flare is 0.25 mL–1.0 mL (1-4 pumps) of the gel applied to the affected area at the first sign of the flare followed by 0.25 mL–1.0 mL (1-4 pumps) of ColciGel® applied to the affected area as needed for pain relief up to every hour for a maximum of 4 doses within 24 hours. The maximum recommended dose for treatment of gout flares is 1.5 mL (6 pumps) of gel over any 1 hour period. ColciGel® may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 0.5 mL (2 pumps) at the first sign of the flare followed by 0.5 mL (2 pumps) hourly up to 3 doses, as needed. Wait 12 hours and then resume the prophylactic dose. *Prophylaxis of Gout Flares:* The recommended dosage of ColciGel® for prophylaxis of gout flares for adults and adolescents older than 16 years of age is 0.25 ml-0.75 mL (1-3 pumps) applied to the affected area twice daily. The maximum recommended dose for prophylaxis of gout flares is 1.5 mL (6 pumps)/day. ***2.2 Recommended Pediatric Dosage:*** *Treatment and Prophylaxis of Gout Flares:* ColciGel® is not recommended for pediatric use in treatment or prophylaxis of gout flares. ***2.3 Dose Modification for Co-administration of Interacting Drugs:*** *Concomitant Therapy:* Co-administration of ColciGel® with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) has the potential of colchicinum-induced toxic effects should significant systemic absorption occur. No dose adjustment or modification is necessary but monitoring of the patient for signs of colchicine toxicity. ***2.4 Dose Modification in Renal Impairment:*** ColciGel® dosing should be individualized in patients with severe renal function impairment [see Renal Impairment (8.6)]. Clcr in mL/minute may be estimated from serum creatinine (mg/dL) determination using the following formula: [140-age (years) × weight (kg)] | Clcr = ---------- × 0.85 for female patients | 72 × serum creatinine (mg/dL). *Gout Flares: Treatment of Gout Flares:* For treatment of gout flares in patients with mild (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 colchicinum. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every week. For patients with gout flares requiring repeated treatment courses consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.25 mL (1 pump) of the gel. For these patients, the treatment course should not be repeated more than once every week [see Clinical Pharmacology (12.3) and Renal Impairment (8.6)]. Treatment of gout flares with ColciGel® is not recommended in patients undergoing dialysis who are receiving ColciGel® for prophylaxis. *Prophylaxis of Gout Flares:* For prophylaxis 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 colchicinum. However, in patients with severe impairment, the starting dose should be 0.25 mL (1 pump) of gel per day and any increase in dose should be done with close monitoring. For the prophylaxis of gout flares in patients undergoing dialysis, the starting doses should be 0.25 – 0.5 mL (1-2 pumps) of gel applied twice a week with close monitoring [*see Clinical Pharmacology (12.3) and Renal Impairment (8.6)*]. ***2.5 Dose Modification in Hepatic Impairment:*** *Gout Flares: Treatment of Gout Flares:* For treatment of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicinum. However, for the treatment of gout flares in patients with severe impairment while the dose does not need to be adjusted, a treatment course should be repeated no more than once every week. For these patients, requiring repeated courses for the treatment of gout flares, consideration should be given to alternate therapy [*see Hepatic Impairment (8.7)*]. Treatment of gout flares with ColciGel® is not recommended in patients with severe hepatic impairment who are receiving ColciGel® for prophylaxis. *Prophylaxis of Gout Flares:* For prophylaxis of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicinum. Dose reduction should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment [*see Hepatic Impairment (8.7)*].

3. Dosage Form and Strength: ColciGel® is Colchicinum 4X in a transdermal gel base. The gel is viscous and amber in color. ColciGel® is available in 15 mL sealed dispensing containers that produce 0.25 mL of gel per each manual depression of the plunger top (pump).

4. Contraindications: Patients with severe renal or severe hepatic impairment should not be given ColciGel® in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors, except fosamprenavir). In these patients, life-threatening and fatal colchicine toxicity has been reported with ORAL 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 colchicinum [*see OVERDOSAGE (10)*]. ColciGel® should be kept out of the reach of children. ***5.2 Blood Dyscrasias:*** Myelosuppression, leukopenia, granulocytopenia, throm- bocytopenia, pancytopenia, and aplastic anemia have been reported with ORAL colchicine used in therapeutic doses. ***5.3 Drug Interactions:*** Colchicinum is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with ORAL 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, no dose adjustment is required, however, the patient should be monitored for signs of colchicine toxicity. [*see DRUG INTERACTIONS (7)*]. Use of ColciGel® in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors, except fosamprenavir) is contraindicated in patients with severe renal or severe hepatic impairment [*see CONTRAINDICATIONS (4)*]. ***5.4 Neuromuscular Toxicity:*** Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic ORAL treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine with ColciGel® may potentiate the development of myopathy [*see DRUG INTERACTIONS (7)*]. Once colchicinum is stopped, the symptoms generally resolve within 1 week to several months.

6. Adverse Reactions: *Treatment of Gout Flares:* The most common adverse reactions reported in the clinical trial with ColciGel® for treatment of gout flares was skin irritation at the site of application. *Prophylaxis of Gout Flares:* The most commonly reported adverse reaction in clinical trials of colchicine for the prophylaxis of gout was skin irritation at the site of application. ***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. Reported adverse reactions to ColciGel® are rare and are limited to skin irritation at the site of application. The following adverse reactions have been reported with ORAL colchicine and, though, are not associated with ColciGel®, may be encountered in cases of over dosage or ingestion with significant systemic absorption. These have been generally reversible upon temporarily interrupting treatment or lowering the dose of ORAL 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: ColciGel® (Colchicinum 4X) 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 colchicinum. If ORAL colchicine is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicinum are likely. Fatal drug interactions have been reported. Topical application of ColciGel® has demonstrated insignificant systemic absorption in animal testing and confirmed in limited human pharmacokinetic evaluations and, therefore, poses a limited risk of clinically significant drug interactions. Physicians should, however, ensure that patients are suitable candidates for treatment with ColciGel® and remain alert for signs and symptoms of toxicities related to increased colchicinum exposure as a result of a drug interaction. Signs and symptoms of ColciGel® toxicity should be evaluated promptly and, if toxicity is suspected, ColciGel® should be discontinued immediately.

8. Use in Specific Populations: ***8.1 Use in Pregnancy:*** Pregnancy Category C: There are no adequate and well-controlled studies with colchicinum in pregnant women. ORALLY administered 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 ORAL colchicine to treat familial Mediterranean fever (FMF). Although animal reproductive and developmental studies were not conducted with ColciGel®, published animal reproduction and development studies indicate that colchicinum causes embryofetal toxicity, teratogenicity, and altered postnatal development at exposures within or above the clinical therapeutic range. ColciGel® 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 colchicinum on labor and delivery is unknown. ***8.3 Nursing Mothers:*** ORALLY administered colchicine is excreted into human milk. Limited information suggests that exclusively breast-fed infants receive less than 10 percent of the maternal weight-adjusted ORAL dose. While there are no published reports of adverse effects in breast-feeding infants of mothers taking colchicinum, colchicinum can affect gastrointestinal cell renewal and permeability. Caution should be exercised and breast-feeding infants should be observed for adverse effects when ColciGel® 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. ***8.5 Geriatric use:*** Clinical studies with ORAL colchicine for prophylaxis and treatment of gout did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. ColciGel® applied topically at recommended doses does not demonstrate clinically significant systemic absorption and, therefore, limited potential for drug accumulation. In general, dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease, other drug therapy, and the potential for increased systemic absorption. [*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. *Treatment of Gout Flares:* For treatment of gout flares in patients with mild (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 ColciGel®. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every week. For patients with gout flares requiring repeated treatment courses consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.25 mL (1 pump) of the gel. For these patients, the treatment course should not be repeated more than once every week [*see Dose Modification in Renal Impairment (2.5)*]. *Prophylaxis of Gout Flares:* For prophylaxis 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 colchicinum. However, in patients with severe impairment, the starting dose should be 0.5 mL (2 pumps) of gel per day and any increase in dose should be done with close monitoring. For the prophylaxis of gout flares in patients undergoing dialysis, the starting doses should be 0.5 mL (2 pumps) given twice a week with close monitoring [*see Dose Modification in Renal Impairment (2.5)*]. ***8.7 Hepatic Impairment:*** The clearance of colchicinum may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment, compared to healthy subjects [*see Pharmacokinetics (12.3)*]. Treatment of Gout Flares: For treatment of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended ColciGel® dose is not required, but patients should be monitored closely for adverse effects of colchicinum. However, for the treatment of gout flares in patients with severe impairment while the dose does not need to be adjusted, the treatment course should be repeated no more than once every week. For these patients, requiring repeated courses for the treatment of gout flares, consideration should be given to alternate therapy [*see Dose Modification in Hepatic Impairment (2.6)*]. *Prophylaxis of Gout Flares:* For prophylaxis of gout flares in patients with mild to moderate hepatic function impairment, adjustment of the recommended dose is not required, but patients should be monitored closely for adverse effects of colchicinum. Dose reduction should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment [*see Dose Modification in Hepatic Impairment (2.6)*].

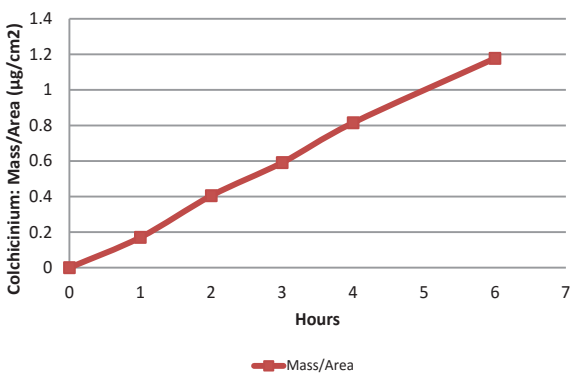
9. Drug Abuse and Dependence: Tolerance, abuse, or dependence with colchicinum has not been reported.

10. Over Dosage: The exact dose of ORAL 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 ORAL 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 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 colchicinum poisoning should begin with gastric lavage and measures to prevent shock. Otherwise, treatment is symptomatic and supportive. No specific antidote is known. Colchicinum is not effectively removed by dialysis [*see Pharmacokinetics (12.2)*].

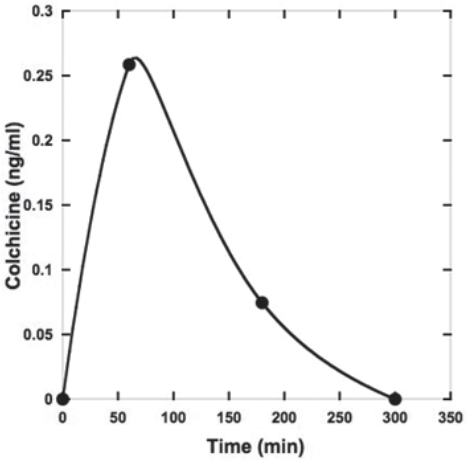
11. Description: Colchicinum is an alkaloid chemically described as (S)N- (5,6,7,9-tetrahydro- 1,2,3, 10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide with a molecular formula of C22H25NO6 and a molecular weight of 399.4. Colchicinum occurs as a pale yellow powder that is soluble in water. ColciGel® is Colchicinum 4X in a transdermal gel base. The gel is viscous and amber in color. ColciGel® is available in 15 mL sealed dispensing containers that produce 0.25 mL of gel per each manual depression of the plunger top (pump). Inactive ingredients: Purified water, Urea, Isopropyl myristate, Lecithin, Docusate sodium.

12. Clinical Pharmacology: ***12.1 Mechanism of action:*** The mechanism by which colchicinum exerts its beneficial effect in patients has not been fully elucidated; however, evidence suggests that colchicinum may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1alpha. Additionally, colchicine disrupts cytoskeletal functions through inhibition of alpha-tubulin polymerization into microtubules and consequently prevents the activation, degranulation, and migration of neutrophils thought to mediate some gout symptoms. ***12.2 Pharmacokinetics:*** *Absorption:* To assess transdermal permeation of ColciGel® an in-vitro test was conducted utilizing a vertical diffusion cell process. In this test 384 mg of ColciGel® was applied to 0.6446 cm2 surface area of a polyethersulfone membrane with a thickness of 0.45 micrometers. The permeation process was evaluated over six hours by sampling the reactor fluid hourly. The amount of colchicinium in the samples was determined by High Performance Liquid Chromatography. The results are shown in Graph 1. The results demonstrate significant transmembrane drug diffusion supporting the transdermal route of administration for ColciGel®. *Systemic absorption in healthy adults:* ColciGel® is not significantly absorbed systemically when applied topically.

Graph 1: Topical ColciGel® Colchicinium vs Time



In a Gensco sponsored study, six New Zealand White Rabbits were administered a single 375 microliter dose of ColciGel® containing, 7.5 micrograms of colchicinium, to a shaved dorsal area measuring 2.5 cm by 2.5 cm. Serum analysis demonstrated 90% of the applied dose was absorbed yielding a peak serum concentration of 0.26 nanogram / milliliter +/- 0.09 nG/mL (Tmax of 60 minutes).



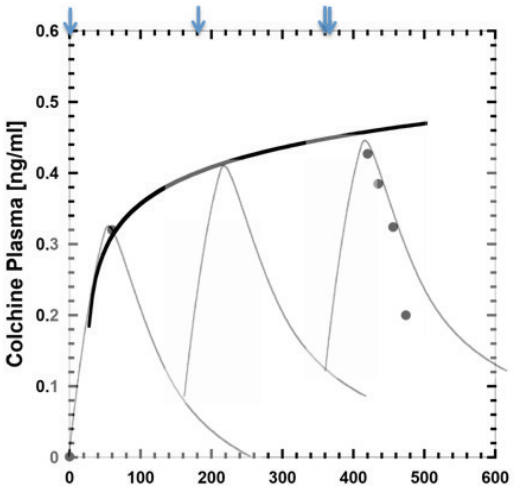
Graph 2: Single Dose ColciGel® Pharmacokinetics

The kinetics of colchicine plasma levels:
Ab- T1/2a = 30 min
sorption rate constant (ka) = .693/.5h = 1.4/h
T1/2e = 65 min
Elimination rate constant (ke) = .693/1.1h = .64/h
Total plasma absorbance = 90% (AUC)
Cmax = 0.26 ng/ml ± 0.09 ng/ml
Tmax = 60 min

In this same study four additional rabbits were administered a dose of 375mcL of ColciGel® every three hours for a total of three doses in the same manner as in the single dose experiment. Serum analysis showed a peak serum level, one hour after the third dose application, of 0.45 nG/mL. A steady state serum level of 0.5 nG/mL was cal- culated to occur after the fifth hourly dose.

Graph 3: Multiple Dose ColciGel® Pharmacokinetics

Arrows indicate dosing events.
Double arrow indicates final dose.
Single-dosing kinetic curves overlay the data.
Bold line is logarithmic progression prediction built to data.



In a pharmacokinetic study evaluating systemic absorption of ColciGel® in humans, six healthy volunteers were randomized into 2 groups. The first group of three subjects received a single 0.75 mg dose of ColciGel® applied topically to the base of the great toe on the right foot. Serum samples were collected from each subject every 30 minutes, post dose, for a total of 8 samples. The second group of three subjects received a dose of 0.75 mg of ColciGel® every 60 minutes for a total of four doses. ColciGel® was applied to the base of the great toe on the right foot, as in the single dose group. Serum samples were collected at 0, 120, 180, 210, 240, 270, 300, and 360 minutes after the first dose application, for a total of eight serum samples. All serum samples were analyzed by tandem HPLC/MS separation and quantification to measure colchicine down to a concentration of 0.05 ng/ml (50 pg/ml). None of the 48 serum samples analyzed measured above the 0.05 ng/ml level. This confirmed the animal testing data that predicted a human serum level of less than 50 pg/ml (estimated 8 – 16 pg/ml). A single oral 0.6 mg dose of colchicine has been shown to elicit a mean serum level of 2.5 ng/ml in healthy volunteers. ColciGel®, due to its overall low colchicinium dose, is absorbed systemically in minute quantities yielding clinically insignificant serum levels, 50 times less than oral dosing.

Distribution: The mean apparent volume of distribution in healthy young volunteers given ORAL colchicine was approximately 5 to 8 L/kg. Colchicine binding to serum protein, is low, 39 ± 5%, primarily to albumin regardless of concentration. ORALLY administered 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:* Colchicinum 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 colchicinum elimination. Following multiple oral doses of colchicine (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. Colchicinum is a substrate of P-gp. *Extracorporeal Elimination:* Colchicinum is not removed by hemodialysis. *Special Populations:* There is no difference between men and women in the pharmacokinetic disposition of colchicinum. *Pediatric Patients:* Pharmacokinetics of colchicinum was not evaluated in pediatric patients. *Elderly:* Pharmacokinetics of colchicinum has not been determined in elderly patients. *Renal impairment:* Pharmacokinetics of colchicinium in patients with mild and moderate renal impairment is not known. A published report described the disposition of ORAL 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 ColciGel® (Colchicinum 4X) on Cmax, AUC, and Cmin has not been modeled due to the extremely low systemic absorption of ColciGel®. For information regarding clinical recommendations, *see Dose Modification for Co-administration of Interacting Drugs (2.4)*. Estrogen-containing oral contraceptives: In healthy female volunteers given ethinyl estradiol and norethindrone (Ortho-Novum® 1/35) co-administered with ORAL colchicine (0.6 mg b.i.d. × 14 days), hormone concentrations are not affected. In healthy volunteers given theophylline co-administered with ORAL colchicine (0.6 mg b.i.d. × 14 days), theophylline concentrations were not affected.

13. Non Clinical Toxicity: ***13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:*** *Carcinogenesis:* Carcinogenicity studies of colchicinum have not been conducted. Due to the potential for colchicinum 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 colchicinum effects on fertility were conducted with ColciGel®. However, published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Reproductive studies also reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division, and normal cleavage in females when exposed to colchicine. Colchicine administered to pregnant animals resulted in fetal death and teratogenicity. These effects were dose dependent, with the timing of exposure critical for the effects on embryofetal development. The nonclinical doses evaluated were generally higher than an equivalent human ORAL 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 colchicinum use and female infertility. The use of colchicinum needs to be weighed against the potential risks.

14. How Supplied / Storage and Handling: ***14.1 How Supplied:*** ColciGel® is Colchicinum 4X in a transdermal gel base. The gel is viscous and amber in color. ColciGel® is available in 15 mL sealed dispensing containers that produce 0.25 mL of gel per each manual depression of the plunger top (pump): 15mL (.50 fl oz) NDC 35781-0400-2; 30 mL (1.01 fl oz) (15mL x 2 Bottles) NDC 35781-0400-4. ***14.2 Storage:*** Store at 20° to 25°C (68° to 77°F). [*See USP Controlled Room Temperature*] Protect from light. DISPENSE IN ORIGINAL CONTAINER. Manufactured for: Gensco Laboratories, 8550 NW 33rd Street, Doral, FL 33122.