

## For Gout Flares

### READ THIS INFORMATION BEFORE PRESCRIBING THIS PRODUCT

#### INDICATIONS AND USAGE

ColciGel® (colchicine 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® (Colchicine 4X) is a Transdermal Gel. Each gram of ColciGel® contains Colchicine 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.

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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 colchicine-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:  $140 - \text{age (years)} \times \text{weight (kg)}$  | Clcr = -----  $\times 0.85$  for female patients |  $72 \times \text{serum creatinine (mg/dL)}$ . *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 colchicine. However, in patients with severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should be repeated no more than once every 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 colchicine. 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 colchicine. However, for the treatment of gout flares in patients with severe impairment while the dose does not need to be adjusted, a treatment course should be repeated no more than once every 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 colchicine. 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 Colchicine 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 colchicine [see OVERDOSAGE (10)]. ColciGel® should be kept out of the reach of children. **5.2 Blood Dyscrasias:** Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported with ORAL colchicine used in therapeutic doses. **5.3 Drug Interactions:** Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with 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 colchicine 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® (Colchicine 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 colchicine. If ORAL colchicine 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. 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 colchicine 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 colchicine 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 colchicine 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 colchicine 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 colchicine, colchicine 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 colchicine. 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 colchicine 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 colchicine. 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 colchicine. 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 colchicine 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 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 (12.2)].

**11. Description:** Colchicine is an alkaloid chemically described as (S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[alpha]heptalen-7-yl)acetamide with a molecular formula of C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> and a molecular weight of 399.4. Colchicine occurs as a pale yellow powder that is soluble in water. ColciGel® is Colchicine 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 colchicine exerts its beneficial effect in patients has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-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 cm<sup>2</sup> 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 colchicine 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**

