HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLOPERBA® safely and effectively. See full prescribing information for GLOPERBA®.

GLOPERBA® (colchicine USP) Oral Solution
Initial U.S. Approval: 1961

----------INDICATIONS AND USAGE----------

- GLOPERBA is indicated for prophylaxis of gout flares in adults (1).

Limitations of use:

The safety and effectiveness of GLOPERBA for acute treatment of gout flares during prophylaxis has not been studied. GLOPERBA is not an analgesic medication and should not be used to treat pain from other causes.

----------DOSAGE AND ADMINISTRATION----------

0.6 mg (5 mL) once or twice daily. Maximum dose 1.2 mg/day. (2.1)

GLOPERBA is administered orally, without regard to meals.

----------DOSAGE FORMS AND STRENGTHS----------

0.12 mg/mL oral solution (3)

----------CONTRAINDICATIONS----------

- Patients with renal or hepatic impairment should not be given GLOPERBA in conjunction with both P-glycoprotein (P-gp) and CYP3A4 inhibitors (4).
- Patients with both renal and hepatic impairment should not be given GLOPERBA (4).

----------WARNINGS AND PRECAUTIONS----------

- *Fatal overdoses* have been reported with colchicine in adults and children. Keep GLOPERBA 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).
- *Drug interaction CYP3A4 and/or P-gp inhibitors:* Coadministration of colchicine with strong CYP3A4 and/or P-gp inhibitors has resulted in life-threatening interactions and death (5.3, 7).
- *Neuromuscular toxicity:* Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. If neuromuscular toxicity or rhabdomyolysis, consider temporary interruption or discontinuation of GLOPERBA (5.4, 6).

----------ADVERSE REACTIONS----------

- Gastrointestinal disorders are the most common adverse reactions with colchicine (6).

To report SUSPECTED ADVERSE REACTIONS, contact Customer Complaints Manager at (1-888-612-8466) or FDA at 1-800-FDA-1088 (*www.fda.gov/medwatch*).

----------DRUG INTERACTIONS----------

- Coadministration of CYP3A4 and/or P-gp 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 (7).
- Concomitant use of GLOPERBA and inhibitors of both CYP3A4 and P-gp should be avoided if possible. If treatment with a strong CYP3A4 and P-gp inhibitor is required in patients with normal renal and hepatic function, the patients' dose of colchicine may need to be reduced or interrupted (7).
- Four drug-drug interaction studies were conducted with GLOPERBA; one with a P-gp inhibitor and three with CYP3A4 inhibitors (7).

----------USE IN SPECIFIC POPULATIONS----------

- In the presence of renal or hepatic impairment, patients should be monitored closely and dose adjustment should be considered as necessary (8.6, 8.7).
- Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe renal impairment (8.6).
- Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment (8.7).
- 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; nursing mothers should be advised to monitor the infant for gastrointestinal side effects (8.2).
- Geriatric Use: Dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease or other drug therapy (8.5, 12.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2019

FULL PRESCRIBING INFORMATION: CONTENTS

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLOPERBA® (colchicine USP) Oral Solution is indicated for prophylaxis of gout flares in adults.

Limitations of use: The safety and effectiveness of GLOPERBA for acute treatment of gout flares during prophylaxis has not been studied. GLOPERBA is not an analgesic medication and should not be used to treat pain from other causes.

2 DOSAGE AND ADMINISTRATION

2.1 Gout Prophylaxis

The recommended dosage of GLOPERBA for adults and adolescents older than 16 years of age is 0.6 mg once or twice daily. The maximum recommended dose is 1.2 mg/day.

GLOPERBA is administered orally, without regard to meals.

Prophylactic therapy may be beneficial for at least the first six months of uric acid-lowering therapy.

2.2 Recommended Pediatric Dosage

GLOPERBA is not recommended for pediatric use in prophylaxis of gout flares.

2.3 Dose Modification for Coadministration of Interacting Drugs

Significant increase in colchicine plasma levels have been observed when colchicine is coadministered with strong CYP3A4 and/or P-glycoprotein (P-gp) inhibitors (e.g., clarithromycin, cyclosporine). Toxicities have also been reported when colchicine is administered with inhibitors of CYP3A4 that may not be potent inhibitors of P-gp (e.g., grapefruit juice), or inhibitors of P-gp that may not be potent inhibitors of CYP3A4 (e.g., cyclosporine [*see Drug Interactions (7)*]. If treatment with a strong CYP3A4 and P-gp inhibitor is required in patients with normal renal and hepatic function, the patients' dose of colchicine may need to be reduced or interrupted.

2.4 Dose Modification in Renal and Hepatic Impairment

Patients with renal or hepatic impairment should not be given GLOPERBA with drugs that inhibit both CYP3A4 and P-gp inhibitors. Combining these dual inhibitors with colchicine in patients with renal or hepatic impairment has resulted in life threatening or fatal colchicine toxicity [*see Use in Specific Populations (8.6 and 8.7)*].

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

3 DOSAGE FORMS AND STRENGTHS

Ready-to-use solution for oral administration containing 0.12 mg/mL of colchicine

4 CONTRAINDICATIONS

Patients with renal or hepatic impairment should not be given GLOPERBA in conjunction with both CYP3A4 inhibitors and P-gp [*see Drug Interactions (7)*]. 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 colchicine [*see Overdosage (10)*]. GLOPERBA 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 colchicine used in therapeutic doses.

5.3 Drug Interactions

Because colchicine is a substrate for both the CYP3A4 metabolizing enzyme and the P-gp efflux transporter, inhibition of either of these pathways may lead to colchicine-related toxicity. Inhibition of both CYP3A4 and P-gp by dual inhibitors (i.e., clarithromycin) has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of GLOPERBA with CYP3A4 and P-gp inhibitors should be avoided. If treatment with colchicine is necessary, a reduced daily dose should be considered and the patient should be closely monitored for colchicine toxicity [*see Drug Interactions (7)*].

Use of GLOPERBA in conjunction with both CYP3A4 and P-gp inhibitors is contraindicated in patients with renal or hepatic impairment [*see Contraindications (*4*)*].

5.4 Neuromuscular Toxicity

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Once colchicine is stopped, the symptoms generally resolve within one week to several months.

6 ADVERSE REACTIONS

Gastrointestinal disorders are the most common adverse reactions with colchicine. These disorders are often the first signs of toxicity and may indicate that the colchicine dose needs to be reduced or therapy stopped. These disorders include diarrhea, nausea, vomiting, and abdominal pain.

Colchicine has been reported to cause neuromuscular toxicity, which may present as muscle pain or weakness.

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 toxicities most often occur with excessive accumulation or overdosage [*see Overdosage (10)*].

The following adverse reactions have been reported with colchicine. These adverse reactions have been generally reversible upon temporarily interrupting treatment or lowering the dose of colchicine.

Neurological: peripheral neuritis.

Dermatological: alopecia, maculopapular rash, purpura, rash

Digestive: abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting

Hematological: aplastic anemia, agranulocytosis.

Hepatobiliary: elevated AST, elevated ALT

Musculoskeletal: myopathy, elevated CPK, myotonia, muscle weakness, muscle pain, rhabdomyolysis

Reproductive: azoospermia, oligospermia

7 DRUG INTERACTIONS

Fatal drug interactions have been reported when colchicine is administered with clarithromycin, a dual inhibitor of CYP3A4 and P-gp. Toxicities have also been reported when colchicine is administered with inhibitors of CYP3A4 that may not be potent inhibitors of P-gp (e.g., grapefruit juice), or inhibitors of P-gp that may not be potent inhibitors of CYP3A4 (e.g., cyclosporine). If treatment with a strong CYP3A4 inhibitor and P-gp inhibitor is required in patients with normal renal and hepatic function, the patients' dose of colchicine may need to be reduced or interrupted.

Because colchicine is a substrate of the CYP3A4 metabolizing enzyme and the efflux transporter P-gp, the pharmacokinetics of GLOPERBA were evaluated following coadministration with posaconazole (a strong CYP3A4 inhibitor), ciprofloxacin hydrochloride (a moderate CYP3A4 inhibitor), amlodipine besylate (a weak CYP3A4 inhibitor) and carvedilol phosphate (a P-gp inhibitor).

Colchicine plasma levels (C_{max} and $AUC_{0\text{-}inf}$) were markedly elevated (2.3 to 3.1 fold) when GLOPERBA was coadministered with a strong CYP3A4 inhibitor (i.e., posaconazole) (*see Table 2*). There were no significant effects when GLOPERBA was coadministered with a moderate CYP3A4 inhibitor (i.e., ciprofloxacin hydrochloride) a weak CYP3A4 inhibitor (i.e., amlodipine besylate) or a P-gp inhibitor (i.e., carvedilol phosphate) [*see Clinical Pharmacology (12.3)*]. However, the results should not be extrapolated to other moderate/weak CYP3A4 and P-gp inhibitors.

GLOPERBA provides flexibility in adjusting colchicine doses without requiring alterations to dose frequency.

Some drugs such as HMG-CoA reductase inhibitors and fibrates may increase the risk of myopathy when combined with GLOPERBA. Complaints of muscle pain or weakness could be an indication to check serum creatinine kinase levels for signs of myopathy.

Physicians should ensure that patients are suitable candidates for treatment with GLOPERBA 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, GLOPERBA should be discontinued immediately.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of GLOPERBA in pregnant women. Colchicine crosses the human placenta. Animal reproduction and development studies were not conducted with GLOPERBA. GLOPERBA should only be used during pregnancy if the expected benefit to the patient outweighs the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Women should be advised to contact their physician if they become pregnant while taking GLOPERBA.

The potential effect of GLOPERBA on labor and delivery is unknown.

Data

A potential teratogenic effect of colchicine may occur due to colchicine's ability to interfere with microtubule formation, thereby affecting mitosis and other microtubule-dependent functions. Colchicine induced low frequencies of micronuclei in male rats which were centromere positive suggesting detached chromosomes.

Colchicine does not appear to be a major human teratogen. Colchicine is relatively safe when used in appropriate doses in patients with normal kidney and liver function. The results from published meta-analysis suggest that colchicine therapy did not significantly increase the incidence of fetal malformations or miscarriages when taken for treatment of Familial Mediterranean fever (FMF) during pregnancy.

There is limited data from published observational cohort registries and meta-analyses indicating no apparent increased rate of congenital malformations or miscarriages in babies born to women with rheumatic diseases, such as rheumatoid arthritis, Behcet's disease or FMF, who continued colchicine at therapeutic doses throughout pregnancy. In a systematic review and meta-analysis publication, colchicine use in pregnant women with and without FMF was associated with a relatively lower birthweight and gestational age compared with a control group including healthy women who did not take colchicine. Whether these findings are applicable to patients receiving colchicine for gout prophylaxis is unknown.

8.2 Lactation

Risk Summary

Colchicine is excreted into human milk. Limited data suggest no or minimal adverse effects to breastfed infants; however, colchicine may affect gastrointestinal cell turnover and function which can result in gastrointestinal or other unknown adverse effects.

No increase in adverse long-term outcomes was found in colchicine-exposed breastfed infants supporting continuation of breastfeeding in women treated with colchicine. Breastfeeding while taking colchicine is safe.

Clinical Considerations

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GLOPERBA and any potential adverse effects on the breastfed infant from GLOPERBA or from the underlying maternal condition.

Data

Limited published data exist to suggest that breast-fed infants receive < 10% of the maternal weight-adjusted dose, although one report estimated breast-fed infants may receive up to 31.5% of the maternal dose. One rheumatology task force publication reported no adverse effects in 149 breastfed children and advised to reconsider breastfeeding if the infant has diarrhea. In a prospective observational cohort study, no gastrointestinal or other symptoms were reported in 38 colchicine-exposed breastfed infants.

8.3 Females and Males of Reproductive Potential

Risk Summary

There are no adequate and well controlled studies of the effect of colchicine on reproductive fertility.

Clinical Considerations

Women and men of reproductive potential who are taking GLOPERBA who intend to have children should be advised to contact their physician before attempting to become pregnant.

Women of reproductive potential who are taking GLOPERBA and do not want to become pregnant should be advised to use effective contraception. Males taking GLOPERBA with female sexual partners of reproductive potential who do not want to become pregnant should be advised to use effective contraception.

Data

Limited published data suggest that colchicine may rarely result in low or absent sperm counts in men, which could result in male infertility.

8.4 Pediatric Use

Gout is rare in pediatric patients; safety and effectiveness of GLOPERBA in pediatric patients has not been established.

8.5 Geriatric Use

Clinical studies with colchicine did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient with gout should be cautious, reflecting the greater frequency of decreased renal function, concomitant disease or other drug therapy [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

No dedicated pharmacokinetic study has been conducted using GLOPERBA in patients with varying degrees of renal impairment. Colchicine is known to be excreted in urine in humans and the presence of severe 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 GLOPERBA 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.

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 four-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.

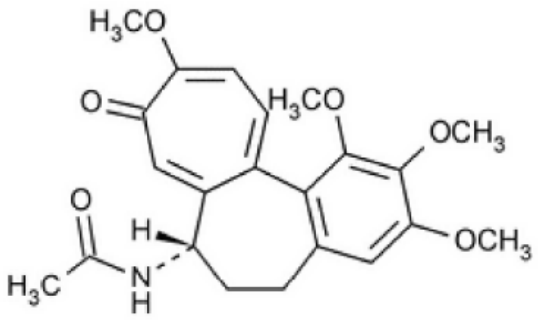
The first stage of acute colchicine toxicity typically begins within 24 hours of ingestion and includes gastrointestinal symptoms such as abdominal pain, nausea, vomiting, diarrhea and significant fluid loss, leading to volume depletion. Peripheral leukocytosis may also be seen. Life-threatening complications occur during the second stage, which occurs 24 to 72 hours after drug administration, attributed to multiorgan failure and its consequences. Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery of multiorgan injury may be accompanied by rebound leukocytosis and alopecia starting about one 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 Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Colchicine is an alkaloid obtained from various species of *Colchicum*. The chemical name for colchicine is (*S*)-*N*-(5,6,7,9- tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]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 provided in Figure 1.

Figure 1: Colchicine Structural Formula



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.

GLOPERBA is supplied for oral administration as a slightly hazy, red liquid with a cherry odor, containing 0.12 mg/mL of the active ingredient colchicine USP. Inactive ingredients: benzyl alcohol, FD&C Red No. 40, artificial cherry flavor, anhydrous citric acid, dibasic sodium phosphate, glycerin, propylene glycol, sucralose, xanthan gum and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mode of action of colchicine in gout is unknown. It is not an analgesic, though it relieves pain in acute attacks of gout. It is not a uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel. Colchicine's effectiveness as a prophylactic 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 β-tubulin into microtubules, thereby preventing the activation, degranulation and migration of neutrophils to sites of inflammation. Colchicine also interferes with the inflammasome complex found in neutrophils and monocytes that mediates interleukin-1β (IL-1β) activation.

In man and certain other animals, colchicine can produce a temporary leukopenia that is followed by leukocytosis.

Colchicine has other pharmacologic actions in animals: It alters neuromuscular function, intensifies gastrointestinal activity by neurogenic stimulation, increases sensitivity to central depressants, heightens response to sympathomimetic compounds, depresses the respiratory center, constricts blood vessels, causes hypertension by central vasomotor stimulation, and lowers body temperature.

12.3 Pharmacokinetics

Absorption

In healthy adults, GLOPERBA reached a mean C_{max} of 2.16 ± 0.87 ng/mL in 1 hour (range 0.5 to 2 hours) after a single dose administered under fasting conditions. A minimal food effect was observed when GLOPERBA was administered following a high fat, high calorie meal. A slight decrease in C_{max} was observed; however, the overall extent of absorption based on $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, was similar in the fed and fasted states. The absolute bioavailability of colchicine is reported to be approximately 45%. Mean pharmacokinetic parameter values for GLOPERBA in healthy adults are shown in Table 1.

Table 1: Mean Pharmacokinetic Parameter Estimates for GLOPERBA in Healthy Adults

Parameter	GLOPERBA, 0.6 mg (0.12 mg/mL, 5 mL) Fasted (N=34)	GLOPERBA, 0.6 mg (0.12 mg/mL, 5 mL) Fed (N=34)
C_{max} (ng/mL)	2.16 (0.87)	1.68 (0.39)
$AUC_{0\text{-}t}$ (h·ng/mL)	18.59 (4.63)	17.20 (4.23)
$AUC_{0\text{-}inf}$ (h·ng/mL)	19.90 (4.74)	18.47 (4.29)
T_{max} (h) (Min-Max)	1.00 (0.50: 2.00)	2.00 (1.00: 4.00)
$t_{1/2}$ (h)	31.04 (5.99)	30.54 (5.22)

Distribution

The mean apparent volume of distribution(V_z/F) of GLOPERBA in healthy adults was approximately 1420 L. Colchicine binding to serum protein is reported to be low (39 ± 5%) primarily due to albumin regardless of concentration.

Colchicine crosses the placenta (plasma levels in the fetus are reported to be approximately 15% of the maternal concentration) [s*ee Use in Specific Populations (8.1)*]. Colchicine also distributes into breast milk at concentrations similar to those found in the maternal serum [s*ee Use in Specific Populations (8.2)*].

Metabolism

Colchicine is demethylated to two primary metabolites [2-*O*-demethylcolchicine (2-DMC) and 3-*O*-demethylcolchicine (3-DMC)] and one minor metabolite [10-*O*-demethylcolchicine (colchiceine)]. *In vitro* studies using human liver microsomes have shown that CYP3A4 is involved in the metabolism of colchicine to 2-DMC and 3-DMC. Plasma levels of these metabolites are minimal (less than 5% of parent drug). Glucuronidation is also believed to be a metabolic pathway for colchicine.

Elimination/Excretion

The mean elimination half-life of GLOPERBA in healthy adults is 31 hours (± 6 hours). In a published study in healthy adults approximately 40 to 65% of a single 1-mg oral dose of colchicine was reported to be recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are postulated to play a role in colchicine elimination. Colchicine is also a substrate of P-gp, and P-gp efflux is postulated to play an important role in colchicine disposition. 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 were not evaluated in pediatric patients.

Elderly: Pharmacokinetics of GLOPERBA have not been determined in elderly patients. A published report described the pharmacokinetics of a 1-mg oral colchicine tablet dose in four elderly women compared to six young healthy males. The mean age of the four elderly women was 83 years (range 75 to 93), mean weight was 47 kg (38 to 61 kg) and mean creatinine clearance was 46 mL/minute (range 25 to 75 mL/minute). 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 (0.17 vs. 0.73 L/hr/kg) and prolonged plasma elimination half-life (18.8 hours vs. 4.4 hours) as compared to subjects with normal renal function [s*ee Use in Specific Populations (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 [s*ee Use in Specific Populations (8.7)*]. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

Drug Interactions

Fatal: Patients with renal or hepatic impairment should not be given GLOPERBA with drugs that inhibit both CYP3A4 and P-gp. Combining these dual inhibitors with GLOPERBA in patients with renal and hepatic impairment has resulted in life-threatening or fatal colchicine toxicity.

The pharmacokinetics of GLOPERBA were evaluated following coadministration with posaconazole (a strong CYP3A4 inhibitor), ciprofloxacin hydrochloride (a moderate CYP3A4 inhibitor), amlodipine besylate (a weak CYP3A4 inhibitor) and carvedilol phosphate (a P-gp inhibitor) (Table 2).

Table 2: Drug Interactions: Pharmacokinetic Parameters for GLOPERBA in the Presence of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug (mg)	Dose of GLOPERBA* (mg)	N	% Colchicine GMR Ratio (90% CI)	
				C_{max}	$AUC_{0\text{-}inf}$
Posaconazole†	300	0.6	20 to 22	227 (202 to 256)	309 (281 to 339)
Ciprofloxacin‡	500	0.6	19 to 20	88 (74 to 104)	88 (79 to 98)
Amlodipine§	5-10	0.6	20 to 21	109 (94 to 128)	122 (109 to 136)
Carvedilol¶	20-40	0.6	19 to 21	96 (90 to 102)	118 (112 to 124)

GMR: Geometric Mean Ratio (Test/Reference)
CI: Confidence Interval
* Single dose 0.6 mg GLOPERBA (0.12 mg/mL, 5 mL) administered alone (Reference) or following a CYP3A4/P-glycoprotein inhibitor (Test) dosed to steady state.
† Posaconazole: Strong CYP3A4 & P-glycoprotein inhibitor; 300 mg Noxafil® (posaconazole) (100 mg×3) delayed-release tablets (a.m./p.m. Day 11) and then a.m. on Days 12 to 17 to steady state prior to a second dose of GLOPERBA (0.6 mg) on Day 17
‡ Ciprofloxacin Hydrochloride: Moderate CYP3A4 inhibitor; 500 mg Cipro® (ciprofloxacin hydrochloride) administered a.m/p.m on Days 11 to 17 to steady state prior to a second dose of GLOPERBA (0.6 mg) on Day 17
§ Amlodipine Besylate: Weak CYP3A4 inhibitor; 5 mg Norvasc® (amlodipine besylate) a.m. on Days 11 to 13 then 10 mg a.m. on Days 14 to 20 to steady state prior to a second dose of GLOPERBA (0.6 mg) on Day 20
¶ Carvedilol Phosphate: P-glycoprotein inhibitor; each subject received 20 mg Coreg CR® extended-release capsules on Days 11 to 12 a.m. followed by 40 mg a.m. on Days 13 to 17 to steady state prior to a second dose of GLOPERBA (0.6 mg) on Day 17

Strong CYP3A4 Inhibitor: Mean colchicine C_{max} values were elevated by approximately 2.3-fold from 2.053 ng/mL (alone) to 4.670 ng/mL (with posaconazole) and mean $AUC_{0\text{-}last}$ values were elevated approximately 3.1-fold from 15.28 h·mg/mL (alone) to 47.14 h·ng/mL (with posaconazole). The terminal half-life remained unchanged when GLOPERBA was administered alone (32.86 hours) or with posaconazole (32.51 hours). Although the combination of colchicine + posaconazole was generally well tolerated in healthy adults, a dose adjustment from 5 mL (0.6 mg) to 2 mL (0.24 mg) is recommended when coadministering colchicine with posaconazole due to a significant increase in C_{max}.

Moderate CYP3A4 Inhibitor: Ciprofloxacin hydrochloride had no marked effects on the mean C_{max}, $AUC_{0\text{-}last}$ and terminal half-life of GLOPERBA. These results indicate that significant interactions with the moderate CYP3A inhibitor ciprofloxacin hydrochloride are unlikely.

Weak CYP3A4 Inhibitor: Amlodipine besylate had a modest effect on the mean C_{max} (approximately a 1.17-fold increase) and $AUC_{0\text{-}last}$ (approximately a 1.15-fold increase) of GLOPERBA. These results indicate that significant interactions with the weak CYP3A4 inhibitor amlodipine besylate are unlikely.

P-gp Inhibitor: Carvedilol phosphate had no effect on the C_{max} of colchicine. The geometric mean percent ratio of $AUC_{0\text{-}last}$ (coadministration with carvedilol phosphate /colchicine alone) was 117.9% and its 90% CI was in the range of 112.0% to 124.1%. The 90% CIs for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were contained within the 80.00 to 125.00% limits. These results indicate that an interaction with carvedilol phosphate is unlikely. 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 coadministration of P-gp inhibitors (i.e., cyclosporine) have been published.

Fatal drug interactions have been reported when colchicine is administered with clarithromycin, a dual inhibitor of CYP3A4 and P-gp. Toxicities have also been reported when colchicine is administered with inhibitors of CYP3A4 that may not be potent inhibitors of P-gp (e.g., grapefruit juice), or inhibitors of P-gp that may not be potent inhibitors of CYP3A4 (e.g., cyclosporine). If treatment with a P-gp and/or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patients' dose of colchicine may need to be reduced or interrupted.

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), colchicine presents a theoretical 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

There were no studies conducted of the effects of GLOPERBA on fertility. Published nonclinical studies have demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Published colchicine reproductive studies have reported abnormal sperm morphology and reduced sperm counts in males and interference with sperm penetration, second meiotic division and normal cleavage in females.

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

GLOPERBA (colchicine) Oral Solution is a slightly hazy, red liquid with a cherry odor.

150 mL: NDC 75854-801-01

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

Patients should be advised to take GLOPERBA 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 GLOPERBA is missed, 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

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

Blood Dyscrasias

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

Drug and Food Interactions

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

Neuromuscular Toxicity

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

Other Signs of Early Toxicity

Patients should be advised to report to their healthcare provider if they experience persistent moderate or severe abdominal pain, nausea, vomiting or diarrhea, either when taking GLOPERBA or when a new medication is taken with GLOPERBA, as this may be a sign of acute or early colchicine toxicity.

MEDICATION GUIDE

GLOPERBA® (colchicine USP) Oral Solution

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

What is the most important information that I should know about GLOPERBA**?**

GLOPERBA can cause serious side effects or death if levels of colchicine are too high in your body.

- Taking certain medicines with GLOPERBA can cause your level of colchicine to be too high, especially if you have kidney or liver problems.
- Tell your healthcare provider about all your medical conditions, including if you have kidney or liver problems. Your dose of GLOPERBA may need to be changed.
- Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.
- Even medicines that you take for a short period of time, such as antibiotics, can interact with GLOPERBA and cause serious side effects or death.
- Talk to your healthcare provider or pharmacist before taking any new medicine.

What is GLOPERBA?

GLOPERBA is a prescription medicine used to prevent gout flares in adults

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

It is not known if GLOPERBA is safe and effective in children. Keep GLOPERBA out of the reach of children.

Who should not take GLOPERBA?

Do not take GLOPERBA 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 that I should know about GLOPERBA?"**

What should I tell my healthcare provider before starting GLOPERBA?

See **"What is the most important information that I should know about GLOPERBA?"**

Before you take GLOPERBA, 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 GLOPERBA will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. GLOPERBA passes into your breast milk. You and your healthcare provider should decide if you will take GLOPERBA or breastfeed. If you take GLOPERBA and breastfeed, 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 prescription, over-the-counter medicines, vitamins, or herbal supplements.

- Using GLOPERBA with certain other medicines can affect each other, causing serious side effects and/or death.
- Do not take GLOPERBA with other medicines unless your healthcare provider tells you to.
- Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.
- Especially tell your healthcare provider if you take:
    - medicines that may affect how your liver works (CYP3A4 inhibitors);
    - cyclosporine ;
    - cholesterol lowering medicines; or
    - antibiotics.

Ask your healthcare provider or pharmacist if you are not sure if you take any of the medicines listed above. This is not a complete list of all the medicines that can affect GLOPERBA.

How should I take GLOPERBA?

- Take GLOPERBA exactly as your healthcare provider tells you to take it. **If you are not sure about your dosing**, call your healthcare provider.
- GLOPERBA can be taken with or without food.
- If you take too much GLOPERBA, go to the nearest hospital emergency room right away.
- Do not stop taking GLOPERBA even if you start to feel better, unless your healthcare provider tells you.
- If you take GLOPERBA daily and you miss a dose, then take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time.
- If you have a gout flare while taking GLOPERBA daily, report this to your healthcare provider.

What should I avoid while taking GLOPERBA?

Avoid eating grapefruit or drinking grapefruit juice while taking GLOPERBA. It can increase your chances of having serious side effects.

What are the possible side effects of GLOPERBA?

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

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

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 GLOPERBA. 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 GLOPERBA?

- Store GLOPERBA at room temperature between 68°F and 77°F (20°C and 25°C).

- **Keep GLOPERBA and all medicines out of the reach of children.**

General Information about the safe and effective use of GLOPERBA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use GLOPERBA for a condition for which it was not prescribed. Do not give GLOPERBA 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 GLOPERBA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about GLOPERBA that is written for healthcare professionals.

What are the ingredients in GLOPERBA?

Active Ingredient: colchicine

Inactive Ingredients: benzyl alcohol, FD&C Red No. 40, artificial cherry flavor, anhydrous citric acid, dibasic sodium phosphate, glycerin, propylene glycol, sucralose, xanthan gum and purified water.

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

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