

**Colchicine in the Management of Gout  
Clinical Guidance  
October 2010**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Abbreviated Colchicine Drug Monograph at <http://vaww.pbm.va.gov> for further information.*

In 2009, the U.S. Food and Drug Administration (FDA) approved the first single ingredient colchicine product (Colcrys®) for the prevention and treatment of acute gout flares and for the management of Familial Mediterranean Fever (FMF). During their review of colchicine, the FDA highlighted two issues: 1) Lower doses of colchicine can be used for treating acute gout flares; and 2) Life-threatening and fatal colchicine-related toxicity can occur with usual doses of colchicine in patients with certain risk factors including drug-drug interactions, impaired renal or hepatic function and age ( $\geq 65$  years).<sup>1,2</sup>

In response to this information and the FDA approval of colchicine, the VA Pharmacy Benefits Management Services (PBM), Medical Advisory Panel (MAP) and VISN Pharmacist Executives (VPE) provide the following guidance intended to improve the prescribing of colchicine in VA and to reduce the risk of serious colchicine-related adverse events, including death, that can occur with usual doses of colchicine ( $< 2$  mg/day) in certain patients.

***Colchicine is contraindicated in patients with renal or hepatic impairment AND who are receiving inhibitors of P-glycoprotein (P-gp) or strong cytochrome P450 (CYP3A4) inhibitors since life-threatening and fatal colchicine toxicity has been reported in these patients taking usual doses of colchicine ( $< 2$  mg/day).***

**I. Treatment of Acute Gout Flares with Colchicine**

- Dose: 2 tablets (1.2 mg) at the first sign of a flare or in the earliest phase of a flare (e.g. within the first 12 hours of onset), followed by 1 tablet (0.6 mg) one hour later.<sup>2,3</sup> (*The dosing of colchicine in patients with acute gout flares of a longer duration than 12 hours is not known. Alternatives to colchicine for acute gout flares include nonsteroidal anti-inflammatory drugs [NSAIDs] and oral, intramuscular or intra-articular corticosteroids*).
- For dose adjustments and frequency of repeat treatment in patients with renal or hepatic impairment or in those receiving inhibitors of P-gp or CYP 3A4, refer to the colchicine product labeling.<sup>2</sup> (For examples of P-gp or CYP 3A4 inhibitors, and for recommended dose adjustments in patients with severe renal or hepatic impairment, refer to “**Issues for Consideration**” section).
- For recommendations on treatment of an acute gout flare with colchicine in those patients receiving prophylactic colchicine, refer to “**Treatment of an acute gout flare in patients receiving prophylactic colchicine**” below.
- Measurement of a serum urate level is not necessary in the setting of an acute gout flare since it may be normal or even low. The optimal time to measure a serum urate level is approximately 2 to 3 weeks after an attack or flare.
- Dietary changes, cessation of alcohol and weight loss may help to reduce hyperuricemia. Additionally, certain medications can reduce uric acid excretion and potentially precipitate gout attacks and may include diuretics, niacin, cyclosporine, salicylates (low dose), levodopa, tacrolimus, ethambutol, cytotoxic chemotherapy, ribavirin and interferon, etc.

**II. Prevention of Acute Gout Flares with Colchicine in Patients receiving Urate Lowering Therapy (ULT)**

- Dose: 1 or 2 tablets (0.6 or 1.2 mg) daily. Maximum daily dose is 1.2 mg.
- Refer to the product labeling<sup>2</sup> for appropriate dose adjustments in patients with renal or hepatic impairment or in those receiving inhibitors of P-gp or moderate or strong inhibitors of CYP 3A4. (For examples of P-gp or CYP 3A4 inhibitors, refer to “**Issues for Consideration**” section). *In general, no dose adjustment is required in patients with mild to moderate renal or hepatic impairment; however, patients should be monitored closely for adverse events. Dose reduction is recommended in patients with severe renal or hepatic impairment (refer to table 2 in the “Issues for Consideration” section for recommended dose adjustments).*

**III. Treatment of Acute Gout Flares with Colchicine in Patients Receiving Prophylactic Colchicine**

- The treatment dose is the same as above (2 tablets at the first sign of a gout attack, followed by 1 tablet one hour later). Wait 12 hours before resuming the prophylactic dose.
- In patients with renal or hepatic impairment who are receiving prophylactic colchicine or in those patients receiving prophylactic colchicine and inhibitors of P-gp or CYP 3A4 concurrently, treatment of an acute gout flare with colchicine is not recommended.

**IV. Issues for Consideration**

- **The recommended dose of colchicine is dependent upon a patient’s age, renal and hepatic function and use of other medications. The product labeling should be consulted for dose selection [http://www.colcrvs.com/assets/pdf/COLCRYS\\_Full\\_Prescribing\\_Information.pdf](http://www.colcrvs.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf).**
- **There are a number of drug-drug interactions involving colchicine necessitating either avoidance of colchicine (if an acceptable alternative exists) or a reduction in the dose of colchicine (See product labeling for recommended dose adjustments<sup>2</sup>), see table 1 as follows:**

**Table 1**

Interacting Drug(s)	Recommendations for Avoidance of Colchicine Combinations or Use of Reduced Doses of Colchicine (if no alternative to colchicine exists)	Recommended Adjusted dose for Treatment of Acute Gout Flares	Recommended Adjusted dose for Prophylaxis of Acute Gout Flares
<b>Inhibitors of P-gp:</b> ranolazine, cyclosporine*	If possible, avoid combining with colchicine. Otherwise, a reduction in the dose of colchicine is necessary. ** <i>Significant increases in colchicine plasma concentrations and fatal colchicine toxicity has been reported with cyclosporine. It can be anticipated that P-gp inhibitors may similarly increase colchicine plasma concentrations.</i>	0.6 mg (1 tablet) once. Dose should not be repeated sooner than 3 days.	Range***: 0.3 mg (1/2 tablet) once daily or 0.3 mg every other day.
<b>Strong CYP 3A4 Inhibitors:</b> atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin*	If possible, avoid combining with colchicine. Otherwise, a reduction in the dose of colchicine is necessary. ** <i>Significant increases in colchicine plasma concentrations and fatal colchicine toxicity has been reported with clarithromycin. (If a macrolide is necessary, azithromycin can be used.<sup>4</sup>) It can be anticipated that</i>	0.6 mg (1 tablet) once followed by 0.3 mg (1/2 tablet) 1 hr later. Dose should not be repeated sooner than 3 days.	Range***: 0.3 mg (1/2 tablet) once daily or 0.3 mg every other day.

	<i>other strong CYP 3A4 inhibitors may similarly increase colchicine plasma concentrations.</i>		
<b>Moderate CYP 3A4 Inhibitors:</b> amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil*	If possible, avoid combining with colchicine. Otherwise, a reduction in the dose of colchicine is necessary. **	1.2 mg (2 tablets) once. Dose should not be repeated sooner than 3 days.	Range***: 0.3 mg (1/2 tablet) once daily, 0.3 mg (1/2 tablet) twice daily or 0.6 mg once daily.
<b>Other potentially significant drug-drug interactions:</b> statins, fibrates, or digoxin, a substrate for P-gp. * Combining colchicine with these agents may increase the risk for muscle toxicity.	Weigh the potential risks and benefits of these agents in combination with colchicine. During initial therapy, patients should be monitored for any signs or symptoms of muscle pain, tenderness or weakness.	During initial therapy, patients should be monitored for any signs or symptoms of muscle pain, tenderness or weakness.	During initial therapy, patients should be monitored for any signs or symptoms of muscle pain, tenderness or weakness.

\*List may not be all-inclusive; these examples were listed in the Colcris® product labeling.

\*\* For the recommended colchicine dose reductions, refer to the Colcris® product labeling. [http://www.colcris.com/assets/pdf/COLCRYS\\_Full\\_Prescribing\\_Information.pdf](http://www.colcris.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf).

\*\*\*The adjusted dose range is dependent upon the “original intended dose”; refer to the prescribing information for details.

**Table 2: Dosing of Colchicine in Patients with Severe Renal or Hepatic Impairment**

	<b>Treatment of Acute Gout Flares*</b>	<b>Prophylaxis of Acute Gout Flares</b>
<b>Severe Renal Impairment (CrCl &lt;30 mL/min)</b>	No dose adjustment required; repeat treatment should be no more frequent than once every 2 weeks	0.3 mg/day (1/2 tablet) once daily
<b>Dialysis</b>	Single 0.6 mg tablet; repeat treatment should be no more frequent than once every 2 weeks	0.3 mg (1/2 tablet) twice a week
<b>Severe Hepatic Impairment</b>	No dose adjustment required; repeat treatment should be no more frequent than once every 2 weeks	Reduced dose is recommended, no clear guidance is provided in product labeling for reduced colchicine dose

\*Treatment of acute gout flares with colchicine is not recommended in patients with renal or hepatic impairment who are receiving colchicine for prophylaxis. Patients should be monitored closely for colchicine-related adverse events.

- **Considerations for urate-lowering therapy (ULT) (e.g. allopurinol, probenecid, febuxostat):**
  - Urate-lowering therapy (ULT) is indicated in patients with: recurrent gout flares (>2 per year), tophi (diagnosed clinically or radiographically), persistent gouty arthritis, multiple joint involvement, combined gout and uric acid nephrolithiasis or urolithiasis.
  - Urate-lowering therapy (ULT) should not be initiated in the setting of an acute gout attack. However, if a patient experiences an acute gout attack while receiving ULT, the ULT should be continued.
  - Urate-Lowering Therapy:<sup>5</sup> (For more detailed information relating to the use of urate-lowering therapy in the management of gout, refer to references 6-12)
    - Allopurinol (Treat to target approach): In patients with normal renal function, the initial dose of allopurinol is 100 mg daily; then increase by 100 mg increments on a weekly basis or every 2-4 weeks until uric acid levels are <6 mg/dL or a maximum dose of 800 mg/day is reached. Lower maximum doses are recommended in patients with renal impairment. The manufacturer recommends doses >300 mg daily be given in divided doses.

- **Probenecid:** If probenecid is selected for lowering serum urate concentrations (*in patients with adequate renal function [CrCl>50 ml/min] and underexcretion of uric acid*), the initial dose is 250 mg twice daily for the first week, followed by 500 mg twice daily. Depending upon the uric acid response, the dose can be further titrated by 500 mg increments every 4 weeks up to 2-3 grams per day. Alkalinization of the urine is beneficial. It may be possible to slowly reduce the probenecid dose after acute gout flares have subsided and serum urate levels are controlled.
  - **Febuxostat:**<sup>13</sup> Febuxostat 40 mg daily can be considered in the following circumstances (*Febuxostat Criteria For Use are available on the PBM Website, refer to reference 13*)
    - Intolerance to allopurinol, OR
    - Inadequate serum urate lowering despite adequate titration of allopurinol to maximum doses, AND
    - Inadequate serum urate lowering with probenecid in appropriate candidates (underexcretors of uric acid and adequate renal function [e.g. CrCl >50 ml/min]), OR
    - Not an appropriate candidate for probenecid (CrCl<50 ml/min, urolithiasis)
  - The dose of febuxostat should be increased to 80 mg daily if the serum uric acid goal (<6mg/dL) is not achieved after 2 weeks.
- **Duration of colchicine prophylaxis:**
    - Although the duration of prophylaxis with colchicine is unclear, most evidence supports colchicine for the first 6 months of urate-lowering therapy and potentially for a longer duration in selected patients with continued gout flares or significant/large tophi.
    - Prolonged use of colchicine may be appropriate in the following circumstances:
      - The patient's serum urate level continues to be >6 mg/dL despite appropriate selection and use of urate-lowering therapy at therapeutic doses and the patient continues to experience frequent flares on urate-lowering therapy and/or has significant tophi.

## V. References

1. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm174315.htm> (accessed 8-2-10)
2. [http://www.colcryst.com/assets/pdf/COLCRYS\\_Full\\_Prescribing\\_Information.pdf](http://www.colcryst.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf) (Accessed 8-2-10)
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13. <http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Criteria%20For%20Use/Febuxostat,%20Criteria%20for%20Non-Formulary%20Use.doc>