NATIONAL PBM BULLETIN

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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPE), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

NEW CONSIDERATIONS FOR THE SAFE AND EFFECTIVE USE OF COLCHICINE

I. ISSUE

In 2009, the U.S. Food and Drug Administration (FDA) approved the first colchicine product (Colcrys®) for the prevention and treatment of acute gout flares and for the management of Familial Mediterranean Fever (FMF). Recently, the FDA sent out information on two issues with colchicine; one related to dosing for acute gout and the other regarding safety.[1]

II. BACKGROUND

Colchicine has been available for treating gout in the United States since before 1938. Prior to the approval of Colcrys® in 2009, colchicine was classified as a pre-DESI (Drug Efficacy Study Implementation) drug since it had never been formally reviewed for approval by the FDA. Over the past few years, the FDA has identified older "unapproved" drugs, such as colchicine, that have been widely utilized and available since before the modern FDA approval process was in place. The current FDA approval process ensures that drugs are safe, effective, of a suitable quality and purity and are properly labeled. The FDA is encouraging manufacturers of older "unapproved" products to submit data for formal review/approval.

Colcrys® was approved in 2009, based upon a review of existing literature and of FDA and World Health Organization (WHO) sponsored adverse event databases as well as one clinical trial in treating acute gout flares and several drug-drug interaction and pharmacokinetic studies.[2-4,6] The FDA review of colchicine highlighted two issues: 1. Lower doses of colchicine could be used for treating acute gout flares; and 2. Colchicine-related toxicity (and fatalities), even at therapeutic doses, could be increased by certain factors including drug-drug interactions, renal and hepatic function and age.[1,5]

III. DISCUSSION

a. Evidence for New Lower Dose of Colchicine for Treating Acute Gout Flares

In the single published, randomized, double-blind, placebo-controlled clinical trial of the FDA approved colchicine product, Colcrys®, 185 patients with an acute gout flare were randomized to receive either low dose colchicine (1.2 mg, followed by 0.6 mg 1 hr later), high dose colchicine (1.2 mg, followed by 0.6 mg every hr for 6 hrs) or placebo.[6] The primary endpoint of a $\geq$ 50% reduction in pain at 24 hrs without rescue medication was achieved in about 38% of low dose, 33% of high dose, and 16% of placebo recipients (p=0.005, p=0.034, respectively vs. placebo).[6] The difference between the low and high dose colchicine groups was not analyzed. The most common adverse events were gastrointestinal (GI) in nature with diarrhea, nausea and vomiting being the most common. The rate of GI adverse events was higher in the high dose colchicine group versus either the low dose colchicine or placebo group (77% vs. 26% and 20%, respectively). In addition, 19% of the high dose group reported their adverse events as severe vs. none of those in the low dose or placebo groups (diarrhea was the most common severe adverse event in the high dose group).

Based upon the results of this trial, the FDA recommends that healthcare professionals use the lower dose of colchicine for treating acute gout flares (1.2 mg [2 tablets], followed by 0.6 mg [1 tablet] 1 hr later).

b. Colchicine Safety

Using data derived from drug-drug interaction and pharmacokinetic studies as well as the data from the FDA's Adverse Event Reporting System (AERS) database, the FDA also determined that certain patients have a higher risk for serious colchicine-related adverse events, including death, even in some patients taking colchicine at usual therapeutic doses. Individuals at increased risk include those taking colchicine concurrently with moderate or strong inhibitors of cytochrome P450 3A4 (CYP 3A4) or inhibitors of P-glycoprotein (P-gp), and/or in patients with impaired renal or hepatic function. In response to the potential for serious adverse events occurring with therapeutic doses of colchicine, the FDA has instituted a Risk Evaluation and Mitigation Strategy (REMS) recommending that a medication guide be dispensed to patients with each colchicine prescription to ensure its safe and effective use.[7-8]

IV. PROVIDER RECOMMENDATIONS[1,5]

These recommendations are intended to reduce the risk of serious colchicine-related adverse events, including death, occurring at usual doses of colchicine in certain patients.

1. Colchicine should not be used in patients with renal or hepatic impairment who are also receiving inhibitors of P-gp (e.g., ranolazine, cyclosporine) or strong inhibitors of CYP3A4 (e.g., clarithromycin, intraconazole, ketoconazole, atazanavir, indinavir, ritonavir, nelfinavir, saquinavir, nafazodone, telithromycin, etc.)
2. Treatment of acute gout flares with colchicine is not recommended in patients receiving long-term prophylaxis with colchicine and who are also receiving inhibitors of P-gp, moderate or strong inhibitors of CYP3A4 or in those patients with renal or hepatic impairment.
3. The dose of colchicine should be reduced or colchicine should be avoided or interrupted in patients requiring treatment with inhibitors of P-gp or moderate or strong inhibitors of CYP3A4. Examples of moderate CYP3A4 inhibitors include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil, etc. Providers should consult FDA approved labeling for dosing recommendations.
4. Since there are a number of potential interactions with colchicine, providers should refer to FDA approved labeling for specific dose recommendations and information on additional drug interactions.
5. Although colchicine has not been adequately studied in patients 65 years and older, the choice of dose should take into account the potential for a greater incidence of reduced renal function, co-existing diseases, multiple medications, etc.
6. The dose of colchicine used for treating acute gout flares should be (1.2 mg [2 tablets], followed by 0.6 mg [1 tablet] one hr later).
7. Patients receiving colchicine should be instructed to inform their providers before taking any new medications including herbal or natural products or over the counter medications.

V. REFERENCES

1. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174315.htm (accessed 6-14-10)
2. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022351s000_MedR.pdf (Accessed 5-12-10)
3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022352s000_MedR.pdf (Accessed 5-17-10)
4. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022353s000_MedR.pdf (Accessed 5-17-10)
5. **http://www.colcrys.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf** (Accessed 5-3-10)
6. Terkeltaub RA, Furst DE, Bennett K, et al. High Versus Low Dosing of Oral Colchicine for Early Acute Gout Flare. Arthritis and Rheum 2010;62:1060-1068.
7. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022353REMS.pdf (Accessed 6-14-10)
8. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176363.pdf (Accessed 6-14-10)
9. Kesselheim AS, Solomon DH. Incentives for Drug Development-The Curious Case of Colchicine. New Engl J Med 2010;362:2045-2047.

ACTIONS

- ***Facility COS:*** *Forward this document to all appropriate providers who prescribe these medications (e.g., **primary care providers and specialists in rheumatology and gastroenterology**, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*