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# NATIONAL PBM BULLETIN

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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM),  
MEDICAL ADVISORY PANEL (MAP), & CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

## HIGH DOSE VITAMIN D USE AND SAFETY

### I. ISSUE

In an effort to reduce medication errors resulting in potential toxicity, vitamin D, high dose (cholecalciferol or ergocalciferol 50,000 IU, oral) is listed on the VA National Formulary (VANF), **noting that this formulation is not to be used as a vitamin supplement and is restricted to 9 doses per 30 day supply** (dose determined to be at the upper end of required therapy for the majority of patients). Vitamin D (cholecalciferol or ergocalciferol 400 to 2000 IU, oral) is also listed on the VANF, designated for use as a vitamin supplement. VAMedSAFE has conducted a database review of prescription data and found a case of potential inappropriate dosing.

### II. BACKGROUND

The Institute of Medicine (IOM) recommends an Adequate Intake (AI) of vitamin D for normal bone health and calcium in healthy men and women:

- 200 IU/day (available in combination dietary supplements) for ages 19 to 50 years;
- 400 IU/day for ages 51 to 70 years;
- 600 IU/day for ages > 70 years.

The UL or Tolerable Upper Intake Level (above which long term use may result in increased adverse events) for individuals  $\geq 19$  years of age is 2000 IU/day.<sup>1,2</sup> Cases of vitamin D toxicity have occurred at doses of > 40,000 IU *per day*.<sup>3</sup> High dose vitamin D (i.e., 50,000 IU) can be used *weekly* for 4 to 12 weeks to address mild to severe vitamin D deficiency states, typically when the 25-hydroxyvitamin D (25(OH)D) level is less than 20 ng/mL [50 nmol/L]. Patients can then proceed to lower dosing (e.g., 800 to 1000 IU daily, or 50,000 IU *monthly* for 6 months), unless a follow-up 25(OH)D level again suggests that another high dose course is required for repletion, as above.<sup>4,5</sup> In patients with 25(OH)D level 20 to 30 ng/ml (i.e., vitamin D insufficiency), a dose of 800 to 1000 IU daily should provide adequate repletion after a couple months.<sup>4,6</sup> In general, doses equivalent to vitamin D 100 IU daily should be expected to increase 25(OH)D levels 1 ng/ml.<sup>6</sup>

Certain malabsorptive states or primary hypoparathyroidism may require longer term and/or more frequent high dose vitamin D use but this should be determined only by those with specific knowledge and expertise (e.g., endocrinology).

A technology assessment/evidence report from the Agency for Healthcare Research and Quality (AHRQ) reviews effectiveness and safety of vitamin D on bone health and can be accessed at: <http://www.ahrq.gov/downloads/pub/evidence/pdf/vitamin/vitad.pdf>.<sup>7</sup>

Within the VA, from March 1, 2007 to September 8, 2009, 30 adverse event reports associated with Vitamin D use (all formulations) were submitted to the VA Adverse Drug Event Reporting System (VA ADERS). Of the 30 reports, 14 were associated with ergocalciferol or cholecalciferol use, out of which 7 occurred with a high dose (i.e.,  $\geq 50,000$  IU every week). No deaths or hospitalizations were reported for cholecalciferol or ergocalciferol  $\geq 50,000$  IU oral.

### III. PROVIDER RECOMMENDATIONS

Daily supplementation of 400 IU to 2000 IU of vitamin D has been recommended for the prevention of vitamin D deficiency in those at high risk;<sup>4</sup> and doses of 700 IU to 1000 IU per day combined with calcium have been shown to reduce the risk of fractures in older patients.<sup>7,8,9</sup> It has been suggested that doses of 800 IU to 1000 IU per day are necessary for those individuals with inadequate sun exposure,<sup>4</sup> or who have vitamin D insufficiency. **Short courses of high dose therapy (e.g., 50,000 IU *weekly* for 4 to 12 weeks) are reserved for those with more severe vitamin D deficiency. Daily doses of high dose vitamin D (50,000 IU) should NOT be prescribed unless required under rare conditions as determined by clinical experts.**

#### **IV. REFERENCES**

1. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. National Academy Press, Washington, DC, 1999.
2. National Institutes of Health Office of Dietary Supplements. Dietary Supplement Fact Sheet: Vitamin D. URL: <http://ods.od.nih.gov/factsheets/vitamind.asp>. Available from internet. Accessed 2009 Sept 2.
3. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety. Am J Clin Nutr 1999;69:842-56.
4. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
5. National Kidney Foundation. KDOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(suppl 3):S84-S89.
6. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D<sub>3</sub> is as effective as vitamin D<sub>2</sub> in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrin Metab 2007;doi:10.1210/jc.2007-2308.
7. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and Safety of Vitamin D in Relation to Bone Health. Evidence Report/Technology Assessment No. 158 (Prepared by the University of Ottawa Evidence-based Practice Center (UO-EPC) under Contract No. 290-02-0021. AHRQ Publication No. 07-E013. Rockville, MD: Agency for Healthcare Research and Quality. August 2007.
8. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670-6.
9. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D<sub>3</sub> and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.

#### **ACTIONS:**

- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g., **primary care providers and specialists in endocrinology, nephrology, and rheumatology**, 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).