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 ≥ 19 years of age is 2000 IU/day.[1,2] Cases of vitamin D toxicity have occurred at doses of > 40,000 IU *per day*.[3] 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.[4,5] 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.[4,6] In general, doses equivalent to vitamin D 100 IU daily should be expected to increase 25(OH)D levels 1 ng/ml.[6]

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/vitamind/vitad.pdf .[7]

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., ≥50,000 IU every week). No deaths or hospitalizations were reported for cholecalciferol or ergocalciferol ≥ 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;[4] 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.[7,8-9] It has been suggested that doses of 800 IU to 1000 IU per day are necessary for those individuals with inadequate sun exposure,[4] 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_2 is as effective as vitamin D_3 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 D3 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).*