Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Nutritional Supplements in Hematology: *Cyanocobalamin (B_{12}) and Thiamine*

-February 2016-

Background:
The NPTC discussed the roles of cyanocobalamin (B_{12}) and thiamine as part of the nutritional supplements in hematology review at the February 2016 meeting. Currently neither cyanocobalamin nor thiamine are listed on the Indian Health Service (IHS) National Core Formulary (NCF). Following delivery of both clinical and pharmacoeconomic reviews including IHS procurement and utilization data trends, the **NPTC added oral cyanocobalamin** to the NCF.

Discussion:
Cyanocobalamin is an essential water-soluble vitamin that is required for DNA synthesis and cellular division. Cyanocobalamin deficiency can cause both anemia and neurological complications and is traditionally defined as a serum level less than 200 ng/L. Measurement of methylmalonic acid and homocysteine are however more sensitive in the diagnosis of cyanocobalamin deficiency than a serum cyanocobalamin level alone[1]. The evolution of cyanocobalamin deficiency is slow due to an approximate half-life of 30 hours and liver stores[2]. It often presents as macrocytosis, which may later progress to macrocytic anemia[3]. Macrocytic anemia predominantly affects older adults due to physiologic changes associated with aging, such as the decreased secretion of hydrochloric acid in the stomach and subsequent reduction of cyanocobalamin absorption[4]. Other less defined symptoms of cyanocobalamin deficiency can include peripheral neuropathies and memory impairment.

The Recommended Dietary Allowance (RDA) for adults is 2.4 micrograms (mcg) daily. Cyanocobalamin can be obtained from animal products and fortified foods or through supplementation with oral, parenteral, or topical cyanocobalamin[5]. Adverse effects of cyanocobalamin supplements are minimal, with the most worrisome being hypersensitivity reactions[6].

Conclusions from a 2005 Cochrane review (2 RCTs) indicate high doses of oral cyanocobalamin (i.e., 2000mcg PO daily or 1000mcg PO for 10 days, then once weekly for 4 weeks, then monthly) are as effective as monthly 1000mcg intramuscular injections for the treatment of cyanocobalamin deficiency[2]. Additionally, oral cyanocobalamin may benefit patients in terms of fewer health care visits and reduced discomfort associated with injections. In January 2012, the British Columbia Guidelines and Protocols Advisory Committee released guidelines on the diagnosis and management of cyanocobalamin deficiency. The Committee recommended oral vitamin B12 supplementation because it determined it was as effective as parenteral cyanocobalamin[7]. A 2013 Canadian analysis (3 RCTs) evaluating cyanocobalamin and cognitive function concluded that, despite finding no appreciable changes in cognitive function, that oral cyanocobalamin was as effective as parenteral cyanocobalamin in restoring normal serum levels of patients with confirmed cyanocobalamin deficiency[8].

Thiamine is an essential water-soluble vitamin that is required for energy metabolism and cellular function. Thiamine deficiency may be determined by several possible mechanisms; however, measurement of erythrocyte thiamine pyrophosphate (TPP) concentrations (<70 nmol/L is indicative of deficiency) is among the more sensitive indices[9]. The evolution of thiamine deficiency is quick due to an approximate half-life of 9.5 to 18.5 days and no appreciable storage[9,10]. The initial presentation includes weight loss, confusion, and muscle weakness. Later, the deficiency may result in peripheral neuropathy or Wernicke-Korsakoff syndrome[9,11].

In the United States, thiamine deficiency is most prevalent among people with chronic alcoholism due to malnutrition. The RDA for thiamine is 1.2 milligrams daily and 1.1 milligrams daily for male and female adults, respectively. Thiamine can be obtained from both animal and plants products or through supplementation with oral or parenteral thiamine[11]. Adverse effects of thiamine are minimal, with the most worrisome being hypersensitivity reactions and precipitation of acute symptoms of thiamine deficiency

subsequent to dextrose administration[12]. A 2011 National Institute for Health and Care Excellence (NICE) Guideline emphasizes the importance of thiamine supplementation, oral or parenteral, in people at high risk of developing or with suspected Wernicke's encephalopathy[13]. Additional review of literature regarding the role of cyanocobalamin and thiamine supplementation in celiac disease and cardiovascular disease or cancer is dissuading and inconclusive[8,14-16].

Findings:
The **NPTC added oral cyanocobalamin** to the IHS National Core Formulary based on the conclusions derived from aforementioned literature reviews, which declared high dose oral cyanocobalamin to be as effective as the intramuscular injection. At this time, the NPTC decided against adding thiamine to the NCF due to the limited role of thiamine for the prevention of Wernicke's encephalopathy in alcohol-use disorders, as highlighted in the 2011 NICE Guideline[12].

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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