

**Baxter**

April 1, 1999

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Metabolic and Endocrine  
Drug Products  
Central Document Room 14B-19  
5600 Fishers Lane - HFD-510  
Rockville, MD 20857-1706

Re: NDA 20-924: **Cernevit™-12 IV Multivitamins**

**Response to March 19, 1999 Comments  
Regarding Phase 4 Clinical Studies**

-- MINOR AMENDMENT --

Dear Sir or Madam:

Baxter Healthcare Corporation is responding to the Agency's March 19, 1999 comments regarding Phase 4 clinical studies of the referenced drug product. The Agency's comments are restated in bold and are followed by Baxter's response.

1. **Determine the ability of Cernevit™-12 IV Multivitamins to maintain/normalize blood levels of the water and fat soluble vitamins over at least 4 months, but preferably, 6 months in patients aged 11 years and above, receiving chronic TPN and whose only source of vitamins is Cernevit™-12.**

The vitamin profile of Cernevit™-12 IV Multivitamins is qualitatively the same and quantitatively very similar to the currently marketed parenteral multivitamin preparation, M.V.I.®-12 approved August 8, 1985 under Astra's NDA 8-809/S-004. Baxter relied on the Agency's prior finding of safety and effectiveness in Astra's NDA 8-809 to establish the safety and efficacy of Cernevit™-12 IV Multivitamins.



Like M.V.I.®-12, Cernevit™ -12 IV Multivitamins was formulated to meet the 1975 requirements of Nutrition Advisory Group (NAG) of the American Medical Association (AMA) for injectable multivitamin preparations.<sup>1</sup> A comparison of Cernevit™-12 IV Multivitamins to M.V.I.®-12 and AMA recommendations is presented here for reviewer convenience.

**Comparison of Cernevit™-12 IV Multivitamins to  
 M.V.I.®-12 and AMA Recommendations**

	Cernevit™-12 IV Multivitamins Baxter (5 mL)	M.V.I.®-12 Astra (5 mL)	AMA 100%
Retinol palmitate corresponding to retinol (Vitamin A)	3500 IU	3300 IU*	3300 IU
Cholecalciferol (Vitamin D <sub>3</sub> )	200 IU	200 IU*	200 IU
DL α-tocopherol corresponding to α-tocopherol (Vitamin E)	10.2 mg 11.2 IU	10 IU	10.0 IU
Ascorbic acid (Vitamin C)	125 mg	100 mg	100.0 mg
Nicotinamide (Vitamin B <sub>3</sub> )	46 mg	40 mg	40.0 mg
Dexpanthenol corresponding to pantothenic acid (Vitamin B <sub>5</sub> )	16.15 mg 17.25 mg	15 mg	15.0 mg
Pyridoxine hydrochloride corresponding to pyridoxine (Vitamin B <sub>6</sub> )	5.5 mg 4.53 mg	4 mg	4.0 mg
Riboflavin sodium phosphate corresponding to riboflavin (Vitamin B <sub>2</sub> )	5.67 mg 4.14 mg	3.6 mg	3.6 mg
Coccarboxylase tetrahydrate corresponding to thiamine (Vitamin B <sub>1</sub> )	5.8 mg 3.51 mg	3 mg*	3.0 mg
Folic acid	414 mcg	0.400 mg	0.400 mg
D-Biotin	60 mcg	0.060 mg	0.060 mg
Cyanocobalamin (Vitamin B <sub>12</sub> )	5.5 mcg	0.005 mg	0.005 mg
Phylloquinone (K <sub>1</sub> )	0	0	0
Excipients	Glycocholic acid and lecithin (mixed micelles) and glycine	Propylene glycol, polysorbate 80 and polysorbate 20	

\* Instead of raw materials noted, M.V.I.®-12 uses the following: retinol, ergocholecalciferol and thiamine hydrochloride.

<sup>1</sup> American Medical Association Department of Foods and Nutrition. Multivitamin preparations for parenteral use: a statement by the Nutrition Advisory Group. J Parenter Enteral Nutr. 1975:258-62. A copy of this publication is provided in Attachment 1 of this communication.

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There are two published reports which summarize the clinical efficacy of multivitamin solutions complying with AMA recommendations.<sup>2,3</sup> These reports were submitted to the Agency in the July 15, 1997 pre-NDA package for Cernevit™-12 IV Multivitamins but were omitted from the March 20, 1998 original NDA. The first study by Davis et.al.<sup>2</sup> monitored serum concentrations of vitamin A, 1,25-OH<sub>2</sub> vitamin D, and vitamin E over a 12 month period in eight adult patients receiving home parenteral nutrition due to extensive small bowel resection. Each patient received daily parenteral supplements corresponding to the AMA recommendations for those vitamins. The serum concentration for each of the three fat soluble vitamins were within the normal range at each monthly test interval throughout the study.

Shils et.al.<sup>3</sup> measured serum concentrations of thirteen vitamins in sixteen adults patients (n=8 male, n=8 female) aged 21-70 years over a 28-35 week study period. Patients received one vial of M.V.I.®-12 once daily and 5 mg AquaMEPHYTON® (vitamin K<sub>1</sub>, Merck & Co., Inc.) once weekly to meet the AMA vitamin recommendations. The study demonstrated that over many months, M.V.I.®-12 was capable of maintaining plasma and whole blood levels of eleven of its constituent vitamins and of the vitamin D metabolites consistently above the lower limits of normal in all but a few patients who had low plasma levels of vitamin C and E. The mean value for vitamin A levels was near or above the upper limit of normal. There were no symptoms suggestive of vitamin A toxicity in any patients.

Joyeux measured plasma concentrations of vitamin D, E, and A in twenty patients, aged 32 to 70 years, requiring home parenteral nutrition over a three month period [refer to Item 8, Attachment 7, (Study R4) on page 0361 of original NDA 20-924, as submitted March 20, 1998]. The elevated vitamin A serum concentrations observed by Shils et.al.<sup>3</sup> were similar to those observed by Joyeux. Joyeux also observed low levels of vitamin E similar to the findings by Shils et.al.<sup>3</sup> These parallel findings

<sup>2</sup> Davis AT, Franz FP, Courtney DA, Ullrey DE, Scholten DJ, Dean RE. Plasma vitamin and mineral status in home parenteral nutrition patients. *J Parenter Enteral Nutr.* 1987;11:480-485. A copy of this publication is provided in Attachment 2 of this communication.

<sup>3</sup> Shils ME, Baker H, Frank O. Blood vitamin levels of long-term adult home total parenteral nutrition patients: the efficacy of the AMA-FDA parenteral multivitamin formulation. *J Parenter Enteral Nutr.* 1985;9:179-188. A copy of this publication is provided in Attachment 3 of this communication.