

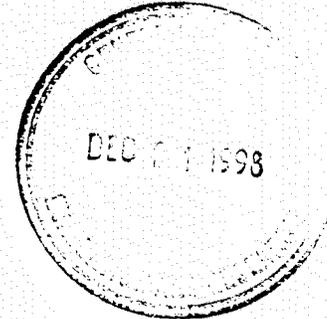
**Baxter**

**ORIG AMENDMENT**

December 18, 1998

ISL

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 December 17, 1998 Labeling Recommendations**

**-- MINOR AMENDMENT --**

Dear Sir or Madam:

Baxter Healthcare Corporation is providing a revised direction insert in response to your December 17, 1998 letter<sup>1</sup>. All changes recommended by the Agency have been incorporated into the insert with the following exceptions for the noted sections:

**Drug Reactions**

In the last sentence of paragraph 1, we have replaced the word "alpha" with the symbol, "α". We have also rearranged the order of drugs known to bind α<sub>1</sub>-acid glycoprotein so that disopyramide is listed first. Of the drugs listed, disopyramide is exclusively bound to α<sub>1</sub>-acid glycoprotein. The revised order of drugs is "e.g., disopyramide, propranolol, quinidine and prazosin".

<sup>1</sup>Letter was received via facsimile on December 16, 1998.

# **Baxter**

## **Adverse Reactions**

As recommended by the Agency, "following IV injection of Cernevit over 1-4 minutes" was incorporated into line 2 of paragraph 1. The new sentence is:

"There have been very rare reports of anaphylactic reactions following IV injection of Cernevit™ over 1-4 minutes."

The words, "one of which was fatal", however, were omitted from this sentence because they infer the noted fatality was attributable to Cernevit™. As described in Item 8.VI.E., Adverse Reactions (Case 3) of the original March 21, 1998 NDA submission, this fatality was fully investigated by the French Authorities at the time of its occurrence. This adverse event was recorded as having a doubtful association with Cernevit™.

The Agency's recommendations for paragraph 2 of the **Adverse Reactions** section have not been incorporated. Except for urticaria and rash, the listed adverse reactions have not been observed in patients receiving Cernevit™-12 IV Multivitamins. The other listed reactions are associated with other marketed parenteral multivitamin formulations, possibly because of the excipient used in the other formulations. Instead, the following statement was added to the end of paragraph 1 of this section:

"Urticaria and rash have also been associated with Cernevit™-12 IV Multivitamins."

## **References**

Baxter incorporated the Agency's recommended changes to the **Pediatric Use** section of the direction insert. Consequently, all references listed are no longer relevant because they were related to text in the former **Pediatric Use** section. These references have been deleted.

Baxter has added two references in support of FDA's recommended additions to the **Drug Reactions** section and to the **Pediatric Use** section of the direction insert. The following reference to the in vitro study information added to paragraph 1 of **Drug Reactions** has been added:

"Guentert TW, Oie S, Paalzow L, et al. Interaction of mixed micelles formed from glycocholic acid and lecithin with the protein binding of various drugs. Br. J. Clin. Pharmac. 1987; 23: 569-77."

# **Baxter**

The following reference to the recommendations of the Nutrition Advisory Group of the Department of Food and Nutrition, American Medical Association, as noted in the revised **Pediatric Use** section has been added:

“Multivitamin preparations for parenteral use a statement by the Nutrition Advisory Group. J. Paren. Enteral. Nutr. 1979; 3(4): 258-62.”

An electronic version of the revised direction insert for the Cernevit™-12 IV Multivitamins product is provided on the diskette in **Attachment 1**. The revised direction insert was saved as a Word 97 document and is entitled “dir\_ins2.doc”. A marked-up, unformatted paper copy of the revised insert is provided in **Attachment 2** and a clean, unformatted paper copy of the revised insert is provided in **Attachment 3**.

Thank you for incorporating this revised labeling into the file.  
If you have questions or comments, please contact Ms. Linda Coleman or Tamima Itani, Ph.D. at (847) 270-2577.

Sincerely,

*Marcia Marconi (Lc)*

Marcia Marconi  
Vice President, Regulatory Affairs  
(847) 270-4637  
(847) 270-4668 (FAX)

# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

BLA Number: 20924 Trade Name: CERNEVIT-12 IV MULTIVITAMINS 5ML

Supplement Number: CERNEVIT-12 IV MULTIVITAMINS 5ML

Supplement Type: INJ

Regulatory Action: PN Proposed Indication: Indicated as a daily multivitamin maintenance dosage for adults and children aged 11 years and above receiving parenteral nutrition. Indicated in other situations where administration by the intravenous route is required.

### IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

### What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days )  Children (25 Months-12 years)

Infants (1-24 Months)  Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups *children > 11 years of age.*

Formulation Status -

Stability Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

### COMMENTS:

4-2-99 - The adult preparation is approved for population >11 years of age for Cernevit-12.. The Cernevit-12 formulation is not approved and is not recommended for children < 11 years of age because it lacks vitamin K and contains an inadequate amount of vitamin D compared to that recommended by the Nutrition Advisory Group (NAG) of the Department of Food and Nutrition, American Medical Association (AMA) for children in this age group receiving total parenteral nutrition.

4-2--99 Cernevit-12 was granted a waiver of pediatric studies for children < 11years of age because the drug product lacks vitamin K and contains an inadequate amount of vitamin D compared with that recommended by the American Medical association for children in this age receiving total parenteral nutrition.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN MCCORT

[Signature]  
Signature

April 2, 1999  
Date

Cernevit™-12 IV Multivitamins  
NDA 20-924  
Patent Information

### **13. PATENT INFORMATION**

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To the best of Baxter's knowledge, there are no active, competitive patents that claim the drug substance, drug product or method of using the drug product that would affect the marketability of the proposed product.

Cernevit™-12 IV Multivitamins  
NDA 20-924  
Patent Certification

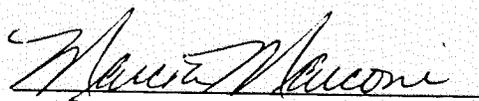
#### **14. PATENT CERTIFICATION**

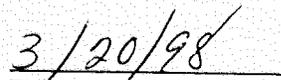
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Baxter certifies that, to the best of its knowledge, there are no active, competitive patents that claim the drug substance, drug product or method of using the drug product that would affect the marketability of the proposed product.

Certification per section 505(b)(2) of the Food, Drug and Cosmetic Act:

In the opinion, and to the best knowledge of Baxter Healthcare Corporation, there are no patents that claim the listed drugs referred to in this application or that claim a use of the listed drugs.

  
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Marcia Marconi, Vice President  
Regulatory Affairs

  
\_\_\_\_\_  
Date