

IV infusion over 12 hrs. of 30x the amount of glycocholic acid in a daily dose of Cernevit and 75x the amount of lecithin to 8 healthy adults for 6 days, resulted in GI adverse events in all (diarrhea and abdominal cramping). One patient also experienced blurred vision, and, another, headache and drowsiness. Reductions in hemoglobin and erythrocyte counts were observed as well as increases in serum iron.

The long-term safety study was of 3 months duration and was performed in children with chronic cholestasis, ages 3 months- 6 years. 22 children received vitamin K IM biweekly for 6 months, 13 received Vitamin K MM orally and 9 received Vitamin K IM. No significant changes were observed in liver function tests, including serum bile acids, before and after the long-term oral or IM administration of the MM preparation.

#### Summary of the Mixed Micelles Safety Studies:

Mixed micelles, glycocholic acid and lecithin, appear to be well tolerated when administered to children or adults. Acute toxicity of glycocholic acid and lecithin, at doses exceeding by 30 fold and 75 fold, respectively, of that contained in a daily dose of Cernevit, predominately caused diarrhea and abdominal cramping. An anaphlactoid reaction occurred in 1 patient who received MM at doses fairly comparable to that in Cernevit. At single doses exceeding that in Cernevit by 4 fold for glycocholic acid, and by 9 fold for lecithin, there is significant displacement of bilirubin from albumin. Although the acute toxicity studies in humans are reassuring, we lack safety data when mixed micelles are administered by IV infusion daily for >3 months as would be the case in some patients receiving chronic TPN, a target patient population for this product. The 3 month safety study in children is not adequate because the drug was administered by a route and frequency different from that recommended in the label and biweekly administration would permit clearance of glycocholic acid by the liver between injections.

Although data are inadequate to support the safety of mixed micelles in newborns, the sponsor is not seeking an indication for Cernevit in this age group. The newborn requiring a blood transfusion at 1 month of age after receiving a therapeutic dose of Vitamin K MM IM is worisome and the SGOT elevations bear mentioning. Among the preclinical toxicology findings in dogs were increased hemolysis, and elevations in liver function (transaminase levels, bilirubin and alkaline phosphatase), and cholestasis.

Regarding the Safety of Cernevit Administered to Adults and Children  $\geq 11$  yrs (note: the product was initially named Protovit MM. Compared to Protovit MM, Cernevit contains: Vitamin A: 106%; vitamin E: 112%; vitamin C: 125%; Niacin (B3), Pantothenic acid and Riboflavin (B2): 115%; Pyridoxine (B6): 113%; Thiamine (B1): 117%, Folic acid: 104% and Cyanocobalamin (B12): 110%):

Of the 10 such studies performed, 5 evaluated local and systemic tolerance only (i.e. laboratory safety parameters such as hematology or biochemistry profiles were not obtained). Protovit MM, 1 vial/day, was administered by IV infusion, IV injection or IM injection. 2 of these 5 studies entailed single dose administration and, in the other 3, Protovit MM was administered for 5 consecutive days by IM or IV injection, or, 10 days by IV infusion (in glucose, saline or TPN). Other than 1 patient who experienced nausea and vomiting after IV infusion, only pain at the injection site occurred in some patients.

The remaining 5 studies will be discussed briefly.

CS 021 (which differs from Cernevit in the following vitamins: CS021/Cernevit-vitamin D: 220 IU/200 IU; B12: 6 ug/5.5 ug; biotin: 69 mcg/60 mcg), was administered, 1 vial/day, by IV injection for 5 consecutive days to 40 patients (Colin et al, report R5). These patients had various GI disorders, including inflammatory bowel disease (IBD), GI malignancies, cirrhosis and hepatitis. There was no evidence of local or systemic intolerance. There were no significant variations in mean bile acid levels from baseline to day 6. Mean SGPT did further increase from an elevated baseline (46 IU/L to 61 IU/L). In a subgroup of 13 patients with IBD, mean SGPT rose from 46 to 99 IU/L. Notable rises (2.3- 3.4 x baseline value) in SGPT occurred in 3 of these patients with IBD, all of whom had elevated levels at baseline. The SGPT elevations were not accompanied by rises in other liver function tests. These elevated levels returned to normal within 1 week of treatment discontinuation in these 3 patients. The authors conclude that CS021 should be avoided in patients with IBD and liver dysfunction.

Cernevit was compared to another multivitamin preparation, Soluvit/Vitalipid (which does not contain mixed micelles), to determine the safety of a mixed micelle preparation administered to patients with and without liver disease (Bischoff et al). Although study duration was 4-57 days, only 11% (7/63), were treated  $\geq 1$  month. 32 patients (15 of who had liver disease) received Cernevit and 31 patients received the other preparation (16 of whom had liver disease). There were no significant

differences in liver function between patients with liver disease who received Cernevit vs. those receiving the other preparation except for biliary acids. Biliary acids were elevated in the group with liver disease who received Cernevit compared to those who received Soluvit/Vitalipid. The authors state that while glycocholic acid is rapidly cleared by the liver after IV administration to healthy subjects, hepatic extraction of bile acids is reduced in patients with chronic liver disease, resulting in rising serum concentrations. However, it should be noted that serum biliary acids were elevated in the patients who received Cernevit, with or without liver disease, compared to those who received the other preparation.

The third study (Colin et al, report R6) was a retrospective analysis of a subgroup of 22 patients who participated in a trial comparing 2 lipid emulsions to each other. Cernevit 1 vial/day, had been added to the binary portion of the TPN (glucose, amino acid, electrolyte portion of the TPN) for at least 15 days. The notable findings were: an increase in serum bile acids from 5.81  $\mu\text{mol/l}$  at baseline to 9.24  $\mu\text{mol/L}$  at study end (normal:  $<6 \mu\text{mol/L}$ ,  $p= 0.01$ ). Biliary acids increased during the study in 7/22 patients (32%), in one of whom, the rise was transient. The only other notable findings were a 2 fold increase in SGPT from baseline to study end in 1 patient and hepatomegaly in 3 patients, one of whom also developed sludge.

The change in mean liver function tests (transaminases, alkaline phosphatase, total bilirubin, and gamma GT) from baseline to week 6 were not significantly different in 15 patients who received Cernevit 1 vial/day added to TPN compared to a group of 6 patients who received another multivitamin preparation that did not contain mixed micelles (Colin et al, report: R7). (note: this was a retrospective study).

The final study to be addressed was a 3 month efficacy and safety study. Only the safety portion will be summarized here (Joyeaux, report: R4). 20 patients received Cernevit 1 vial/day added to TPN for 3 months. Safety monitoring included hematology and biochemistry parameters (Ca, phosphorous, magnesium, SGOT/SGPT, bilirubin, albumin, retinol binding protein, triglycerides and total cholesterol). There was no evidence of toxicity based on mean changes in any of these parameters except for an elevation in serum transaminase levels in 1 patient with a normal baseline (SGPT increased 2.6x normal by study end and SGOT, 1.1 x normal).

#### Summary of Cernevit Safety Studies in Patients $\geq 11$ yrs.:

During Cernevit administration by daily IV infusion, serum bile acids became elevated in patients who had liver disease and those who did not. The only other notable finding was a sporadic increase in SGPT in some patients.

Two in vitro studies were conducted by Guentert et al and they will be summarized briefly. Because glycocholic acid binds to albumin, Guentert examined the effect of different concentrations of glycocholic acid on displacement of bilirubin from albumin using a ligand for bilirubin, monoacetyldiaminodiphenylsulfone or MADDs. The displacement of bilirubin is potentially very significant in the newborn, where, if significant displacement occurs, the newborn is then at risk for development of kernicterus. Cord serum was obtained from 6 neonates. When 117  $\mu\text{mol/L}$  glycocholic acid was added to neonatal serum (corresponding to a 100  $\mu\text{l}$  dose of Vitamin K MM), there was an 8-15% decrease in reserve albumin for binding MADDs in 5/6 neonates and 23% in the sixth. The reduction in adult serum was also modest. However, when higher concentrations were used: 351  $\mu\text{mol/L}$  to 1 ml of serum, there was a 31% and 35% decrease in reserve albumin for binding MADDs in adults and newborns, respectively.

In the second in vitro study, Guentert et al demonstrated, that at therapeutic concentrations of mixed micelles (0.177 mg glycocholate/ml serum), mixed micelles have minimal to no effect on the protein binding of drugs known to bind exclusively to albumin (such as warfarin, diazepam, ketoprofen, furosemide and probenecid) or transcortin (prednisolone). However, at 5x the therapeutic dose of mixed micelles, there is a significant increase (up to 45%) in the free fraction of drugs with a high affinity for albumin. At therapeutic concentrations of glycocholic acid, Guentert found a 50-80% increase in the free fraction of drugs known to bind to alpha-1 acid glycoprotein (propranolol, quinidine, prazosin or diisopyramide). At 5x the therapeutic dose of mixed micelles, the unbound fraction of these drugs increased 2- to 3-fold.

#### Comment:

Guentert demonstrated in vitro that at therapeutic concentrations of glycocholic acid, the unbound fraction of drugs that bind to alpha 1- acid glycoprotein, such as inderal, significantly increases (by 50-80%). Since bile acid levels have been shown to increase when Cernevit is administered

by daily IV infusion to patients with and without liver disease, there is the potential for a significant increase in the free fraction of these drugs which bind to alpha 1- acid glycoprotein, such as inderal. Since bile acids are cleared less efficiently in patients with liver disease, patients with liver dysfunction are at a greater risk for this drug interaction. This is an important safety issue which will require further investigation such as an in vivo study.

#### Summary of the 1 efficacy study performed with Cernevit:

The ability of Cernevit to normalize/maintain normal serum levels of the fat soluble vitamins, A, D and E, was examined in a 3 month study in 20 patients (Joyeux et al, report: R4). Cernevit, 1 vial/day, was added to TPN. 4 patients had symptoms of vitamin deficiency at baseline: smooth tongue in all, and, in 2, it was associated with desquamation of the skin. B and C vitamin deficiencies were suspected but not measured. Vitamin A deficiency was also suspected in 2 of these patients and was confirmed by low vitamin A levels. No patient had signs of vitamin deficiency after 60 days of supplementing TPN with Cernevit.

Although mean plasma 1,25-OH vitamin D and vitamin E levels were low at baseline but normal at study end (3 months), these vitamin levels remained low in a significant number of patients- 45% (9/20) for 1,25-OH vitamin D and 65% (13/20) for vitamin E. Mean 25-OH vitamin D and A levels were normal at baseline and remained normal. However, vitamin A levels were high at the end of the study in 40% (8/20) of the patients.

#### Comments regarding the above study:

Vitamin A levels were high at baseline in only 3/20 patients (15%), but were high after 3 months of Cernevit administration in 8/20 patients (45%). It is important to determine if, with a longer period of Cernevit administration in TPN, vitamin A levels will continue to rise or if they will plateau.

The high incidence of low 1,25-OH vitamin D levels at study end requires confirmation.

Furthermore, per Ben Hariz (Clinical Nutrition 1993, 12:147-152), vitamin C, a water soluble vitamin, is unstable in binary solutions (amino acid, glucose, electrolyte portion of TPN). Therefore, it is important to determine the status of the water soluble vitamins in patients receiving Cernevit in TPN. These vitamins were not measured in the Joyeux study. Long-term studies (up to 12 months) in patients on chronic TPN supplemented with MVI-12 indicated that vitamin C levels were low throughout the study in a significant number of patients (42%). It, therefore, appears that the amount of vitamin C in parenteral multivitamin products may need to be increased if this is confirmed with Cernevit.

In addition, the duration of the Joyeux study was shorter than that recommended in the Federal Register Notice which states that multivitamin formulations intended for intravenous use, be studied for at least 4 months, preferably 6 months.

In summary, another study of at least 4 months duration, but preferably, 6 months, is needed in patients  $\geq$  11 yrs. old on chronic TPN, supplemented with Cernevit. All 12 vitamins should be measured and a quantitative assay used to detect overages as well as deficiencies.

Cernevit is not an appropriate parenteral multivitamin preparation for pediatric patients <11 yrs. of age. It lacks vitamin K and contains only 25-50% (depending on the dose of Cernevit administered: 1/2 vial/day or 1 vial/day, respectively) of the AMA recommended vitamin D dose for children in this age group receiving total parenteral nutrition. FDA permitted the use of Cernevit in this age group in the US because there was a shortage of MVI Pediatric (MVI Pediatric meets by 100%, the AMA vitamin requirements for patients <11 yrs. old receiving TPN). Cernevit was to be supplemented with vitamins D and K if used in children <11 yrs. old.

The 1 study (by Ben Hariz, see page 11 of this review) that was performed with Cernevit in children <11 years of age was inadequate for the following reasons:

1. The 3 month study duration was inadequate (the FRN recommends at least 4 months, preferably, 6 months)
2. Storage conditions differed from those recommended in the label
3. The lipid emulsion was supplemented with vitamin E. The FRN requires that the multivitamin preparation to be tested be the sole source of vitamins administered.

4. Water soluble vitamins were measured only in children >3 years of age; 1,25-OH vitamin D was measured in only 7 children.
5. The adequacy of dosing children <2 yrs. of age with 1/2 vial Cernevit/day was limited to 6 patients because only 6 patients in this study were <2yrs. old. Furthermore, only fat soluble vitamins data were obtained on this dose and, in only 2 patients, were 1,25-OH vitamin D levels measured on this dose.

Labeling Review:

Description section:

Omit the column whose heading reads: **DRAFT LABELING**

Indications and Usage:

**DRAFT LABELING**

Precautions:

**DRAFT LABELING**

Nursing Mothers:

**DRAFT LABELING**

Pediatric Use:

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Adverse Reactions:

**DRAFT LABELING**

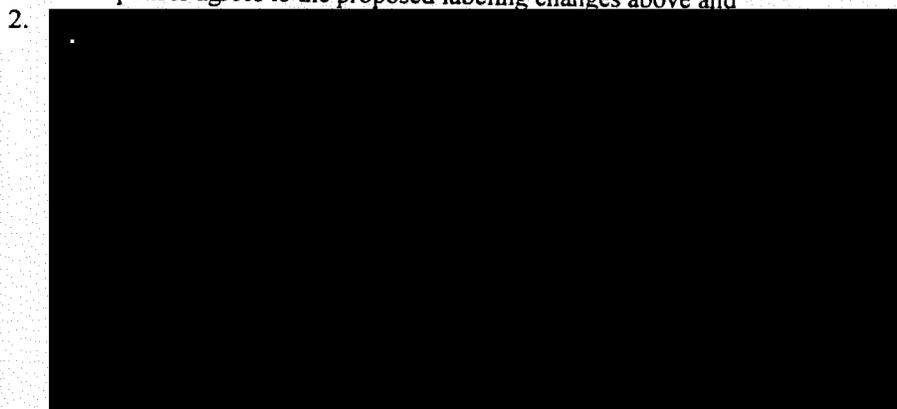
DRAFT LABELING



**Regulatory Action:**

Cernevit is approved as a daily multivitamin maintenance preparation for intravenous infusion in adults and children  $\geq$  11 years of age receiving parenteral nutrition provided the following conditions are met:

1. The sponsor agrees to the proposed labeling changes above and



cc. NDA Arch 20.924  
HFD-510 Division file  
HFD-510 Dr. Sobel, Dr. Orloff and Mr. McCort

/s/

Jean Temeck, M.D.

/s/

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APPEARS THIS WAY ON ORIGINAL

