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APPLICATION NUMBER: 020924

MEDICAL REVIEW(S)

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McCart

NDA# 20-924

Cernevit-12 IV Multivitamins

Baxter Healthcare Corp., Round Lake, IL

Date of application: March 20, 1998

Proposed indication: daily multivitamin maintenance dosage for adults and children >11 years receiving TPN and in other clinical situations, such as surgery or extensive burns, where administration by the intravenous route is required.

Team Leader Note on original NDA

Date: 11-9-98

Dr. Temeck's review dated 11-6-98 thoroughly summarizes the information submitted supporting the safety and efficacy of this product in the target population. This is a literature-based ("505(b)(2)") application. Only one small (20 patients, 3 months) study was conducted with Cernevit. Other studies of a comparable product (Protovit MM) were submitted, however. Cernevit is nearly identical to MVI-12, the current approved parenteral multivitamin product, and meets AMA-recommended standards for injectable multivitamin preparations. The excipients in Cernevit, however, are mixed micelles of glycocholic acid and lecithin. No other products approved in the U.S. contains these excipients. Their purpose is to act as vehicles for fat soluble drug products and vitamins. Valium and vitamin K formulations in mixed micelles are approved in Europe.

Dr. Temeck raises issues in three areas. Her concerns appear well-founded, and they will be summarized here.

1. Safety of preparations containing mixed micelles of glycocholic acid and lecithin

Of 13 studies in the literature submitted in support of the safety of such preparations, 3 were of 4-6 days' duration in a total of fewer than 30 adults treated daily with IV mixed micelles and raised no significant short-term safety concerns at doses comparable to the amount in the daily dose of Cernevit.

The only "long-term" study examining the safety of parenteral mixed micelles was of 6 months' duration in 22 children (aged 3 months -6 years) treated biweekly with a mixed micellar preparation of vitamin K by the intramuscular route. The treatment was well tolerated.

In studies of adults treated with [REDACTED] (similar to Cernevit), reversible elevations in hepatic transaminases were observed in patients with inflammatory bowel disease and baseline liver dysfunction. In other studies, some patients receiving Cernevit did develop elevated serum levels of bile acids, most marked in patients with underlying hepatic dysfunction, suggesting an accumulation of glycocholic acid and metabolites during chronic administration (up to 2 months).

In addition, *in vitro* studies suggest that, because glycocholic acid binds to albumin, it may significantly displace bilirubin (potentially clinically significant in the newborn) as well as drugs binding to albumin (e.g. warfarin, diazepam, ketoprofen, furosemide, and probenecid). If significant accumulation of glycocholic acid occurs over time, such displacement may have clinical significance.

Finally, the results of another *in vitro* study suggest as well a risk, particularly at higher doses of mixed micelles (and therefore in the setting of bile acid accumulation), of displacement of drugs bound to alpha-1 acid glycoprotein (e.g. propranolol, quinidine, prazosin, disopyramide), thereby increasing free fraction and the potential for toxicity.

In sum, there really are no data in children or adults adequately addressing the safety and tolerability over extended periods of daily intravenous administration of mixed micelles of glycocholic acid and lecithin in doses comparable to those in the daily dose of Cernevit. Concerns include the potential for increases in serum levels of bile acids, perhaps particularly in patients with liver disease (but potentially over the course of prolonged therapy in those with apparent normal liver function) and the impact of such accumulation on free levels of bilirubin as well as of drugs bound predominantly to serum albumin and on free levels of drugs bound predominantly to alpha-1 acid glycoprotein. Longer term studies are needed to address these safety issues.

2. Efficacy of Cernevit

In one 3-month study in 20 patients, levels of fat-soluble vitamins were followed. No patient developed signs of vitamin deficiency, and in 4 patients, existing signs of deficiency resolved. Of concern, though, were the significant incidences of below-normal levels of vitamin D (in 45%) and of vitamin E (in 65%).

In sum, the efficacy of Cernevit as a source of fat-soluble vitamins requires further investigation in longer-term studies.

3. Cernevit in children under 11 years

Finally, Dr. Temeck points out that Cernevit is not an appropriate parenteral vitamin formulation for pediatric patients under 11 years of age inasmuch as it is devoid of vitamin K and contains only 25-50% of the daily dose of vitamin D recommended by the AMA.

Recommendation

I concur with Dr. Temeck that Cernevit should be approved for administration to adults and children > 11 years of age receiving TPN. There is, however, a need for further information on the long-term (6-month) safety and efficacy of the product in daily administration. These issues should be discussed with the sponsor prior to any regulatory action and agreement reached on how best to address them.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

cc:
NDA Arch 20-924
HFD-510
HFD-510: Sobel/Temeck/McCort

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APPEARS THIS WAY ON ORIGINAL

NDA: 20924
 Drug: Cernevit-12 IV Multivitamins
 Sponsor: Baxter Healthcare Corp.

Date submitted: 3/20/98
 Date received: 3/23/98
 Date reviewed: 11/6/98

Proposed indication: Daily multivitamin maintenance dosage for adults and children aged 11 yrs. and above receiving parenteral nutrition and in other clinical situations, such as surgery or extensive burns, where administration by the IV route is required.

Dosage form: Intravenous (IV) Dosage: 1 vial/day

Pertinent background information:

Cernevit-12 IV Multivitamins is a lyophilisate for parenteral use. It contains both water soluble and fat soluble vitamins.

Cernevit-12 IV Multivitamins has been marketed in Europe by Baxter since 1990. In 1982, Hoffmann-La Roche Inc. (Switzerland), developed a product, Ro 12-3764/004 (brand name: Protovit MM). The vitamin composition of Protovit MM was based on the 1975 recommendations of the Nutrition Advisory Committee (NAG) of the AMA for injectable multivitamin preparations. The Agency adopted the AMA recommendations as a requirement for injectable multivitamin products in a Federal Register Notice in 1979, reaffirmed in a 1984 FR notice. Hoffmann-La Roche began marketing the product in Switzerland in 1982 under the brand name Protovit MM. The vitamin composition of Protovit MM was quantitatively the same as M.V.I.-12 which is currently the only FDA approved parenteral multivitamin product for use in adults and children ages ≥ 11 yrs. However, the excipients in M.V.I.-12 are polysorbate-20 and 80 and propylene glycol while in Protovit MM and Cernevit, it is a mixed micelles. Due to a shortage of parenteral multivitamins in the US since December, 1996, Cernevit has been imported into the US since June, 1997.

Cernevit is similar to the currently marketed M.V.I.-12 which is Astra's parenteral multivitamin product. The following table compares these 2 products and to the AMA recommendation:

	<u>Cernevit-12 IV</u>	<u>MVI-12</u>	<u>AMA</u>
Vitamin A (Retinol palmitate)	3500 IU	3300 IU*	3300 IU
Vitamin D ₃ (Cholecalciferol)	200 IU	200 IU*	200 IU
Vitamin E (tocopherol)	11.2 IU	10 IU	10 IU
Vitamin C (ascorbic acid)	125 mg	100 mg	100 mg
Niacin	46 mg	40 mg	40 mg
Pantothenic acid	17.25 mg	15 mg	15 mg
Pyridoxine (B ₆)	4.53 mg	4 mg	4 mg
Riboflavin (B ₂)	4.14 mg	3.6 mg	3.6 mg
Thiamine (B ₁)	3.51 mg	3 mg	3 mg
Folic acid	414 mcg	400 mcg	400 mcg
Biotin	60 mcg	60 mcg	60 mcg
Cyanocobalamin (B ₁₂)	5.5 mcg	5 mcg	5 mcg
Vitamin K	0	0	0
Excipients:	Glycocholic acid and lecithin (mixed micelles) and glycine	Propylene glycol, polysorbate 80, polysorbate 20, gentisic acid ethanolamide, butylated hydroxytoluene and butylated hydroxyanisole	

* MVI-12 uses retinol, ergocholecalciferol and thiamine hydrochloride

Note: Cernevit was formulated slightly in excess of the AMA recommendations in anticipation that some loss would occur during manufacturing. The % excess of the following vitamins in Cernevit compared to the AMA recommendations are:

Vitamin A: 106% of AMA; 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%.

The NDA submitted for this product is a 505(b)(2). Baxter will rely on the Agency's prior finding of the safety and effectiveness of Astra's MVI-12. Baxter has submitted data from published clinical studies on mixed micelles to support the excipient used in Cernevit. The sponsor has also provided published literature which describes the use of IV multivitamin preparations in pediatric patients from 1-11 yrs. of age to support the pediatric use subsection of the product labeling.

Clinical Studies submitted:

Clinical Studies on Mixed Micelles:

Mixed micelles of glycocholic acid and lecithin are excipients for 2 other parenteral preparations: Valium-MM and Konakion-MM (i.e. a mixed micelle formulation of vitamin K). Neither are marketed in the US. The sponsor searched the published literature for human studies conducted with any of these 3 preparations in addition to human studies on mixed micelles alone. Selected for analysis, were 15 published studies and 1 unpublished describing clinical trials using mixed micelles in human subjects.

In the 16 studies, a total of 409 evaluable patients (311 adults, 98 infants/children) received a parenteral mixed micelle preparation either IM (n= 48), IV injection (n= 332) or IV infusion (n= 29). The amount of glycocholic acid and lecithin in the mixed micelle preparations studied varied, but the quantities in a typical adult dose of Cernevit-12 IV Multivitamins is within the clinical ranges studied. Since the purpose of the mixed micelles is to act as a vehicle for fat soluble drug products, the ability to deliver the desired drug was considered a measure of the acceptability of the mixed micelles. Safety was evaluated through standard laboratory screening including hematology, serum chemistry and UA as well as symptomatic reporting.

There appeared to be no significant differences in mixed micelle formulations as compared to conventional diluents. 1 patient experienced an anaphylactoid reaction following IV injection of a mixed micelle vitamin K preparation.

The following is a summary of these 16 human studies performed with mixed micelles:

1. Title: Tolerance to Valium Mixed Micelles Vehicle Following Daily Infusion for 6 Days, in Healthy Male Volunteers

Investigator: Dr. Darragh, Dublin, Ireland

Date of study: 1982

Valium mixed micelles formulation contains 88.5 mg/ml glycocholic acid in aqueous solution. Thus a daily dose of 250 mg valium IV is accompanied by administration of 4.425 g glycocholic acid. The total pool of cholic acids in the body is <3.5 g with simultaneous excretion and reuptake of 0.3-0.8 g/day. when administered 4.425 g glycocholic acid. The purpose of this study was to investigate the tolerance of repeated administration of large amounts of a valium mixed micelles formulation in healthy male volunteers.

This was a single blind cross-over study in 2 groups of 4 healthy male volunteers (i.e. total of 8 subjects), ages 18-40 yrs. The protocol was as follows:

Period 1:

Study day 1: baseline (medical hx., PE, ECG, hematology and biochemistry screen, serum iron, lipid profile, UA and complement)

Study days 2-7: either valium mixed micelles, 50 ml diluted in 1,000 ml 5% glucose, or placebo, 1000 ml 5% glucose was infused over a 12 hour period/day for 6 consecutive days. 50 ml Valium mixed micelles contains: 4.425 g glycocholic acid, 40% NaOH 0.950 ml, 8.465 g lecithin, 0.750 ml benzyl alcohol, 0.050 g sodium pyrosulfite and HCl in pH 6.0 (Note: this amount of glycocholic acid is ~30 x and, lecithin, 75 x that contained in Cernevit). Blood was collected for hematology, biochemistry and complement prior to each infusion and 3 hours after the start of each infusion. VS were measured periodically during the infusion.

Study days 8-13: washout. Lipid profile was taken on day 8.

Period 2: identical to period 1 except subjects were crossed-over to the other infusion. Also, on study day 21, subjects received 1 additional ml of placebo or undiluted valium mixed micelles injected by slow bolus. VS were monitored periodically for up to 6 hours after injection.

Each subject received a PE, ECG and laboratory tests (hematology, biochemistry and complement), within 7 days of study completion.

Results:

GI side effects occurred in all 8 subjects during the period of mixed micelle administration. Subjects experienced abdominal cramps, accompanied by bouts of diarrhea, ranging in