CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-163

PHARMACOLOGY REVIEW

NDA 21-163 Review Completed: January 6, 2000

Sponsor: Sabex, Inc; 145 Jules-Leger Street; Boucherville (QC), CANADA J4B 7K8

Date Submitted: July 19, 1999

Date Received: July 20, 1999

DRUG: Multi-12 multivitamins (water and fat soluble)

CATEGORY: Vitamins

PHARMACOLOGY REVIEW OF NDA
NDA 21-163 Initial NDA (July 20, 1999)

DRUG: multivitamins (fat and water-soluble vitamins as a dual vial preparation) (this does not include vitamin K).

CATEGORY: Parenteral vitamins

INDICATION: Daily IV administration for adults and children > 11 years old on parenteral nutrition. This is for nutritional supplementation, not treatment of vitamin deficiencies.

DOSAGE: One vial is reconstituted in 5 ml of sterile water for injection, USP and administered by intravenous infusion. For children >11 years old and adults, recommended dose is one vial (5 ml/day). To be added to intravenous infusion fluids.

RELATED IND: Sponsor is relying on the FDA finding of safety of Astra's M.V.I® -12 product, NDA 8-809/S004 (approved August 1985) no right of reference is cited.

PREVIOUS MARKETING EXPERIENCE: Currently, Cernivit™-12 (recently approved in the US and approved in Europe since 1982) and Astra's M.V.I® -12 product which are very similar to the present produced are marketed.

PHARMACOLOGY REVIEW OF ORIGINAL NDA SUBMISSION
(Original submission dated July 20, 1999)

BACKGROUND: The sponsor is relying on the FDA finding of safety of Astra's M.V.I® -12 product, NDA 8-809/S004 (approved August 1985) no right of reference is cited. The cited product is of similar composition to the present product with minor changes in the levels of some vitamin components, which would not appear to be toxicologically important. The sponsor has provided no preclinical studies to support this application. Copies of relevant literature were provided for the pharm/tox section of this NDA.

Composition of Multi-12 IV Multivitamins

COMPONENT	QUANTITY per 5 ml (vial contents)	NUTRITIONAL REQUIREMENTS	TOXIC LEVEL
ACTIVE COMPONENTS of VIAL 1			
Retinol palmitate (Vitamin A)	3300 IU	700-1000 retinol equivalents*	Acute Tox detected at 1-30X10^6 in adults Chronic tox at 50-1000x 10^3 IU
Cholecalciferol (Vitamin D_3)	200 IU	400 IU* (considered arbitrary, 100 IU is sufficient)	MLD Est. 50,000 IU for adult humans (1000-2000 IU for infants or adults with certain infections and metabolic diseases.
DL-α-Tocopherol (Vitamin E)	——	8-10 mg/dl 12-15 IU* (may be lower for some disease states)	LD_{50} rats>2000 mg/kg In humans, doses of 3200 IU/day are relatively well tolerated.
Ascorbic acid (Vitamin C)	100 mg	60 mg* (increase to 80 and 100 during pregnancy and lactation	Relatively non-toxic: 10 g/day does not constitute a serious health risk.
Nicotinamide (Vitamin B_3)	40 mg	13-20* mg (niacin equiv.)	No data
Dexpanthenol	15 mg	4-7 mg/day*	No data
Pyridoxine HCl (Vitamin B_6)	4 mg	1.4-2.0* mg	No data
Riboflavin sodium phosphate (corresponding to riboflavin Vitamin B_2)	——	1.3-1.8*mg/day for adult females and m...s	Oral doses of 10g/kg in rat and 2 g/kg produced no toxic effects. LD_{50} IP=560 mg/kg in rats.
Thiamine HCl (Vitamin B_1)	3mg	1-1.5* mg/day for adult females and males	No data
ACTIVE INGREDIENTS OF VIAL 2			
Folic acid	400 mcg	200 mcg/day*	10 mg/day for 5 years was not toxic to humans
D-Biotin	60 mcg	100-200mcg/day**	IV LD50 in rabbits = 0.41 mcmol/day in 30 days In dogs = 6.15 mcmol/day in 10 days
Cyanocobalamin (Vitamin B_{12})	5 mcg	2 mcg/day**	GRAS
OTHER INGREDIENTS vial 1			
1.4 % polysorbate 80			
Sodium hydroxide for pH adjustment and water injection			
OTHER INGREDIENTS vial 2			
30% propylene glycol			
Citric acid and/or citrate for pH adjustment and water for injection			

*Recommended Daily Allowance set by the Nutritional Research Council-US (range given for males and females aged 10-70 + years) data taken from Handbook of Vitamins, 2nd edition. Ed. L. J. Machlin 1991.

** Recommended by Food and Nutrition Board of the U.S. National Academy of Sciences

The proposed formulation of vitamin contents reflects, with the exception of Biotin, low multiples of the RDA. Vitamin E is close to the range specified by the RDA. Literature indicates that the toxic levels of vitamins listed above are considerably higher than the RDA recommendations, so it is not expected that the vitamin content would approach the toxic range for these compounds. No further preclinical data were presented. However, there were supportive literature references provided. Based on the above table, the composition of this product would appear to be within reasonable safety levels. Unlike Cernivit™-12 IV, there are no formulation issues with this product since the water soluble and fat soluble vitamins are provided separately and there is no need for a mixed micelle formulation.

OVERALL SUMMARY AND EVALUATION

The sponsor is relying on the FDA finding of safety of Astra's M.V.I® -12 product, NDA 8-809/S004 (approved August 1985) no right of reference is cited. The cited product is of similar composition to the current product with minor changes in the levels of some vitamin components which would not appear to be toxicologically important. There were no formulation issues for pharmacology/toxicology consideration. Appropriate literature references were provided by the sponsor. No further preclinical data were provided and none are necessary since the composition of this product is similar to approved products and there are no formulation issues.

CONCLUSION: Based on the relative lack of toxicity and the considerable human experience with similar products, pharmacology recommends approval of this NDA pending the resolution of minor labeling issues described below.

LABELING COMMENTS TO BE COMMUNICATED TO SPONSOR

For consistency in current labeling practices, the preclinical sections of the label should be rewritten as follows:

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity, mutagenicity and fertility studies have not been performed with Multi-12®(Multivitamins for infusion).

Pregnancy
Pregnancy Category C: Animal reproduction studies have not been conducted with Multi-12®(Multivitamins for infusion). It is also not known whether Multi-12®(Multivitamins for infusion) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Multi-12®(Multivitamins for infusion) should be given to a pregnant woman only if clearly needed. Pregnant women should follow the U.S. Recommended Daily Allowances for their condition, because their vitamin requirements may exceed those of nonpregnant women. The use of Multi-12®(Multivitamins for infusion) has not been studied in human pregnancy.

/S/

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cc: NDA Arch
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