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APPLICATION NUMBER:

21-265

PHARMACOLOGY REVIEW

NDA 21-265 **Review Completed: May 5, 2000**

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

Date Submitted: April 21, 2000

Date Received: April 21, 2000

DRUG: Multi-12/K1 Pediatric (multiple vitamins for infusion)

CATEGORY: Vitamins/pediatric use

PHARMACOLOGY REVIEW OF NDA
NDA 21-265 Initial NDA (April 21, 2000)

DRUG: multivitamins (fat and water-soluble vitamins as a dual vial preparation) (this formulation includes vitamin K).

CATEGORY: Parenteral vitamins for pediatric use.

INDICATION: Daily IV administration as maintenance supplement for infants and children < 11 years old receiving parenteral nutrition.

DOSAGE: Ready for immediate use when added to IV infusion fluid.

a. For infants and children ≥3kg up to age 11: One vial each Vial 1 and Vial 2 added directly to not less than 100 ml of IV dextrose (5%), saline (0.9%) or similar infusion solution.
b. For infants and children ≥1kg and < 3kg: 65% of the contents of one vial each Vial 1 and Vial 2 added directly to not less than 100 ml of IV dextrose (5%), saline (0.9%) or similar infusion solution.
c. For infants and children <1kg: 30% of the contents of one vial each Vial 1 and Vial 2 added directly to not less than 100 ml of IV dextrose (5%), saline (0.9%) or similar infusion solution.

RELATED IND: Sponsor is relying on the FDA finding of safety of NDA 21-163 (Multi 12, the adult formulation) as previously agreed with the division. Additional data are supplied as necessary to support changes in formulation (e.g., data on Vitamin K). Also, reference is made to the Federal Register notices 65FR4253 and 44FR40933, 49FR36446)

PREVIOUS MARKETING EXPERIENCE: Current product is similar to MVI Pediatric which received condtional approval in 1983

BACKGROUND: The sponsor is relying on the FDA finding of safety of NDA 21-163 (Multi 12, the adult formulation) as previously agreed with the division. Additional data are supplied as necessary to support changes in formulation (e.g., data on Vitamin K). Also, reference is made to the Federal Register notices 65FR4253 and 44FR40933, 49FR36446).
The cited product is of similar composition to the presently conditionally approved MV pediatric product with minor changes in the levels of some inactive ingredients, 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 as specified in 65FR4263	TOXIC LEVEL
ACTIVE COMPONENTS of VIAL 1			
Retinol palmitate (Vitamin A)	2300 IU	70 mcg	Acute Tox detected at 1-30X10^6 in adults Chronic tox at 50-1000x 10^3 IU
Cholecalciferol (Vitamin D_3)	400 IU	10 mcg	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)	7 IU	7 mcg	LD_{50} rats>2000 mg/kg In humans, doses of 3200 IU/day are relatively well tolerated.
Ascorbic acid (Vitamin C)	80 mg	80 mg	Relatively non-toxic: 10 g/day does not constitute a serious health risk.
Nicotinamide (Vitamin B_3)	17 mg	17 mg	No data
Dexpanthenol	5 mg	5 mg	No data
Pyridoxine HCl (Vitamin B_6)	1 mg	1 mg	No data
Riboflavin sodium phosphate (corresponding to riboflavin/Vitamin B_2)	1.4 mg	1.4 mg	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)	1.2 mg	1.2 mg	No data
Vitamin K_1	0.2 mg	0.2 mg	
ACTIVE INGREDIENTS OF VIAL 2			
Folic acid	140 mcg	140 mcg	10 mg/day for 5 years was not toxic to humans
D-Biotin	20 mcg	20mcg	IV LD50 in rabbits = 0.41 mcmol/day in 30 days In dogs = 6.15 mcmol/day in 10 days
Cyanocobalamin (Vitamin B_{12})	1 mcg	1 mcg	GRAS
OTHER INGREDIENTS/vial 1			
polysorbate 80		50 mg	
Sodium Hydroxide and/or hydrochloric acid		to adjust pH	
Water for injection		q.s.	
OTHER INGREDIENTS/vial 2			
Mannitol		75 mg	
Citric acid and/or sodium citrate		To adjust pH	
Water for injection		q.s.	

The following table is scanned directly from the sponsor's submission to compare composition of Astra product and FR recommendations:

Table I. Comparative Formulations of Multivitamin Preparations

	MVI® Pediatric (Astra) (1 vial of lyophilized powder for reconstitution in 5 mL)	Multi-12®/K$_1$ Pediatric (Sabex) (2-vial set for a total of 5 mL)	Effective formulation as specified in Federal Register 65CFR 4263
	5 mL vial	4 mL vial (Vial 1)	
Vitamin A	0.7 mg	0.7 mg	0.7 mg
Vitamin D	10 µg	10 µg	10 µg
Vitamin E	7 mg	7 mg	7 mg
Vitamin C	80 mg	80 mg	80 mg
Vitamin B$_1$ (Thiamine)	1.2 mg	1.2 mg	1.2 mg
Vitamin B$_2$ (Riboflavin)	1.4 mg	1.4 mg	1.4 mg
Vitamin B$_6$ (Pyridoxine)	1 mg	1 mg	1 mg
Niacinamide	17 mg	17 mg	17 mg
Dexpanthenol	5 mg	5 mg	5 mg
Vitamin K$_1$	0.2 mg	0.2 mg	0.2 mg
Polysorbate 80	50 mg	50 mg	
Polysorbate 20	0.8 mg	nil	
Butylated Hydroxytoluene	58 µg	nil	
Butylated Hydroxyanisole	14 µg	nil	
Sodium Hydroxide and/or Hydrochloric acid	see below	to adjust pH	
Water for injection	nil	q.s. 4 mL	
		1 mL vial (Vial 2)	
Biotin	20 µg	20 µg	20 µg
Folic Acid	140 µg	140 µg	140 µg
Vitamin B$_{12}$ (Cyanocobalamin)	1 µg	1 µg	1 µg
Mannitol	375 mg	75 mg	
Citric acid and/or Sodium Citrate	nil	to adjust pH	
Sodium Hydroxide	to adjust pH	nil	
Water for injection	-	—	

The proposed formulation of vitamin contents reflects identical composition to the conditionally approved Astra product and the FR notice recommendations. 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 any of these compounds. No further preclinical data were presented. However, there were supportive literature references provided for the levels of Vitamin K_1. Based on the above table the composition of this product would appear to be within reasonable safety levels and accordance with 65FR 4263.

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OVERALL SUMMARY AND EVALUATION

The sponsor is relying on the FDA finding of safety of Astra's M.V.I® Pediatric Federal Register notice 65CFR 4263 for composition of active ingredients. The c of identical composition to the current product and the CFR recommendations changes in the levels of some inactive ingredients which would not appear to be tox important. There were no formulation issues for pharmacology/toxicology consi Appropriate literature references for vitamin K_1 were provided by the sponsor as was ag the February 2, 2000 meeting with the sponsor [redacted] No fu preclinical data were provided and none are necessary since the composition of this produc is identical to the recommendations proposed in 65FR 4263 and there are no formulation issues.

CONCLUSION: Based on the relative lack of toxicity, the considerable human experience with similar products, and the fact that the proposed formulation complies with the recommendations of 65CFR 4263 pharmacology, recommends approval of this NDA.

LABELING COMMENTS TO BE COMMUNICATED TO SPONSOR: This formulation is for pediatric use. Therefore, no pregnancy category is necessary. The labeling proposed by the sponsor is adequate for the pharmacology/toxicology sections. No further action is necessary from pharmacology.

/S/

Ronald W. Steigerwalt, Ph.D.
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cc: NDA Arch
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