CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-265

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-265 / N-000	**SUBMISSION DATE:**	**21-APR-00, 19 DEC-00**
BRAND NAME:	**Multi-12®/K$_1$ Pediatric**	
GENERIC NAME:	**Multiple vitamin for infusion**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Sabex Inc., Boucherville, Quebec (Canada)**	
TYPE OF SUBMISSION:	**Original Application**	

REVIEW:

This NDA seeks approval for Multi-12®/K$_1$ Pediatric, a formulation of multiple vitamins for infusion (MVI) for use in pediatric patients. MVI products are added to intravenous infusion fluids before administration. The sponsor has requested a waiver from the requirements to submit bioavailability studies as set out in 21 CFR 320.21. Currently there are approved injectable MVI products but they are approved for adult use. One MVI product, MVI Pediatric® [Astra], has received conditional approval for use in pediatric patients. The Federal Register (FR) notice of 26-JAN-00 (65 CFR 4253) specifies the acceptable pediatric formulation for MVI products; Multi-12®/K$_1$ Pediatric follows these specifications.

Table 1 presents the formulation of the conditionally approved MVI Pediatric® and Multi-12®/K$_1$ Pediatric products as well as the acceptable pediatric formulation as per the FR notice.

Criteria for granting a bioavailability waiver are set forth in 21 CFR 320.22. The sponsor cites 21 CFR 320.22(b)(1) as the basis of the waiver. This section indicates that a waiver will be granted if the drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

As shown in Table 1, the active ingredients are the same for MVI Pediatric® and Multi-12®/K$_1$ Pediatric. The inactive ingredients do differ. Unlike MVI® Pediatric, Multi-12®/K$_1$ Pediatric does not contain polysorbate 20, BHT or BHA. In terms of mannitol, Multi-12®/K$_1$ Pediatric contains 50mg whereas MVI® Pediatric contains 375mg. BHT and BHA are preservatives and will not have an effect on the bioavailability of the vitamins. Since Multi-12®/K$_1$ Pediatric is already a solution, unlike MVI® Pediatric, the lack of another solubilizing agent besides polysorbate 80 is unlikely to change the bioavailability of this new product. A discussion with the Chemist indicated that there are quality controls on the solution so the vitamins will not precipitate out of the product. The change in mannitol is also unlikely to have any impact on bioavailability of the drug substance. In addition it is necessary to keep in mind that this product is administered after further dilution in at least 100mL of intravenous infusion fluid, making these differences even less likely to impact on any aspect of bioavailability.

The waiver ingredients being gran requiremen protection o

again no need to redact

granted, based on 21 CFR 320.22(b)(1) since the inactive on as the approved MVI® Pediatric product. So, the waiver is (e) which indicates 'FDA, for good cause, may waive a e of in vivo bioavailability if waiver is compatible with the

Table 1. Formulations

	MVI® Pediatric (Astra) (1 vial of lyophilized powder for reconstitution to 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	—	
		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	-	—	

Ditto for both

The Multi-12®/K_1 labeling should be altered to reflect changes that have been made to other MVI products submitted after this NDA for Multi-12®/K_1. This issue was discussed with the MO and she is pursuing consistent labeling between MVI products.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II

(OCPB/DPE-2) has reviewed NDA 21-265/N-000 submitted 21-APR-00 and 19-DEC-00. The overall Human Pharmacokinetic Section is acceptable to OCPB. A waiver for evidence demonstrating the *in vivo* bioavailability of the drug product is granted based on 21 CFR 320.22 (e), 'good cause.'

Robert M. Shore, Pharm.D. /S/ 10-JAN-01
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader_

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 1/10/01

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