CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-163

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-163 / N-000	**SUBMISSION DATE:**	**19-JUL-99**
BRAND NAME:	**Multi-12®**	
GENERIC NAME:	**Multiple vitamins for infusion**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Sabex, Inc, Boucherville, Quebec, Canada**	
TYPE OF SUBMISSION:	**Original NDA**	

SUBMISSION:

The sponsor has submitted an original NDA as a 505(b)(2) for Multi-12, an injectable preparation of multiple vitamins for infusion. The sponsor indicates that this product is pharmaceutically equivalent to the approved M.V.I.-12 (Astra, NDA 08-809) in that they differ in the inactive ingredients only (see Tables 1A and 1B). Multi-12 is to be marketed as 2x5 ml vials to be diluted in 500-1000mL of infusion solution. The indication, as per the proposed labeling, is as a daily multivitamin maintenance supplement for adults and children aged 11 and older receiving parenteral nutrition (Note: The Orange Book lists three injectable multivitamin preparations with this indication, two are rated 'AP' and are also RLD; see Appendix 1).

The submission indicates that Multi-12 has been available in the US from April 1997 to June 30, 1999 under a special request from the FDA to alleviate a multivitamin shortage. Multi-12 was approved in Canada in 1994.

The labeling for Multi-12 is almost identical to M.V.I.-12.

According to minutes from a Pre-NDA meeting between Sabex and the FDA (15-SEP-98), the FDA waived the 21CFR 320.21 requirement for submission of *in vivo* bioavailability and bioequivalent data (Note: no OCPB representative was at this meeting).

DISCUSSION:

Under 21CFR 320.22 (1), a drug product's *in vivo* bioavailability may be considered self-evident if the product meets the following criteria: (i) it is a pareneral solution intended solely for administration by injection..., and (ii) contains the same active and inactive ingredients in the same concentrations as a drug product that is the subject of an approved full new drug application. Multi-12 meets (i) but strictly speaking, not (ii), since there are inactive ingredients in Multi-12 that are not in M.V.I.-12. However, the differences in inactive ingredients should not cause any difference in systemic bioavailability, especially since these products are significantly diluted before administration. As such, a waiver of the requirement to submit evidence of *in vivo* bioavailability for Multi-12 can be granted under 21CFR 320.22(e), for good cause.

Table 1A: Comparison of Multi-12® with MVI®-12 .

VIAL 1

	MVI-12 (Astra) (2-vial set of 5 mL each)	Multi-12 (Sabex) (2-vial set of 5 mL each)
	5 mL vial	5 mL vial
Vitamin A	3 300 IU	3 300 IU
Vitamin D	200 IU	200 IU
Vitamin E	10 IU	10 IU
Vitamin C	100 mg	100 mg
Vitamin B_1 (Thiamine)	3 mg	3 mg
Vitamin B_2 (Riboflavin)	3.6 mg	3.6 mg
Vitamin B_6 (Pyridoxine)	4 mg	4 mg
Niacinamide	40 mg	40 mg
Dexpanthenol	15 mg	15 mg
Polysorbate 80	1.6%	1.4%
Polysorbate 20	0.028%	nil
Propylene Glycol	1.5 g (30%)	nil
Gentisic Acid Ethanolamide	2%	nil
Butylated Hydroxytoluene	0.002%	nil
Butylated Hydroxyanisole	0.0005%	nil
Sodium Hydroxide	to adjust pH	to adjust pH
Water for injection	q.s. 5 mL	q.s. 5 mL

Table 1B: Comparison of Multi-12® with MVI®-12 .

VIAL 2

	MVI-12 (Astra) (2-vial set of 5 mL each)	Multi-12 (Sabex) (2-vial set of 5 mL each)
	5 mL vial	5 mL vial
Biotin	60 µg	60 µg
Folic Acid	400 µg	400 µg
Vitamin B_{12} (Cyanocobalamin)	5 µg	5 µg
Propylene Glycol	30%	30%
Citric acid and Sodium Citrate	to adjust pH	to adjust pH
Sodium Hydroxide	to adjust pH	nil
Water for injection	q.s. 5 mL	q.s. 5 mL

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-163/N-000 submitted 19-JUL-99 and concludes that a waiver of the requirement to submit evidence of *in vivo* bioavailability for Multi-12 can be granted under 21CFR 320.22(e), for good cause. The application is approvable pending labeling changes.

LABELING COMMENTS TO BE SENT TO THE SPONSOR:

As per the submitted draft labeling included in Volume 1/ pages 124-127:

1) Page 125: '**Indications and Usage**...Multi-12 (administered in intravenous fluids...vitamins, execpt vitamin K...'

Please correct the spelling of execpt to except.

2) Page 126: **Overdosage**

The labeling for the currently marketed M.V.I.-12 product contains the following wording in this section: 'Clinical manifestations of hypervitaminosis A have been reported in patients with renal failure receiving 1.5mg/day retinol. Therefore, vitamin A supplementation of renal failure patients should be undertaken with caution.' Please include this statement in the **Overdosage** section of your labeling after the sentence 'The possibility of hypervitaminosis A or D should be borne in mind'.

Robert M. Shore, Pharm.D. /S/ 28-OCT-99
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 28-OCT-99

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 10/28/99

CC: NDA 21-163/N-000 (orig.,1 copy), HFD-510(McCort, Lewis, Steigerwalt), HFD-870(Ahn, ChenME), CDR (Barbara Murphy).

Code: AE

Appendix 1. Orange Book listing of injectable multivitamin products with similar indication, as of 27-OCT-99.

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020924		Yes	ALPHA-TOCOPHEROL; ASCORBIC ACID; BIOTIN, D-; CHOLECALCIFEROL; CYANOCOBALAMIN; FOLIC ACID; NIACINAMIDE; PANTOTHENIC ACID; PYRIDOXINE; RIBOFLAVIN; THIAMINE; VITAMIN A	Injectable; Injection	11.2 IU/VIAL; 125MG/VIAL; 60 UGM/VIAL; 200 IU/VIAL; 5.5MG/VIAL; 414 UGM/VIAL; 46MG/VIAL; 17.25MG/VIAL; 4.53MG/VIAL; 4.14MG/VIAL; 3.51MG/VIAL; 3,500 IU/VIAL	CERNEVIT-12	BAXTER HLTHCARE
008809	AP	Yes	ASCORBIC ACID; BIOTIN; CYANOCOBALAMIN; DEXPANTHENOL; ERGOCALCIFEROL; FOLIC ACID; NIACINAMIDE; PYRIDOXINE HYDROCHLORIDE; RIBOFLAVIN PHOSPHATE SODIUM; THIAMINE HYDROCHLORIDE; VITAMIN A; VITAMIN E	Injectable; Injection	10MG/ML; 0.006MG/ML; 0.5 UGM/ML; 1.5MG/ML; 20 IU/ML; 0.04MG/ML; 4MG/ML; 0.4MG/ML; 0.36MG/ML; 0.3MG/ML; 330 UNITS/ML; 1 IU/ML	M.V.I.-12	ASTRA PHARMS
018439	AP	Yes	ASCORBIC ACID; BIOTIN; CYANOCOBALAMIN; DEXPANTHENOL; ERGOCALCIFEROL; FOLIC ACID; NIACINAMIDE; PYRIDOXINE HYDROCHLORIDE; RIBOFLAVIN PHOSPHATE SODIUM; THIAMINE HYDROCHLORIDE; VITAMIN A; VITAMIN E	Injectable; Injection	10MG/ML; 0.006MG/ML; 0.5 UGM/ML; 1.5MG/ML; 20 IU/ML; 0.04MG/ML; 4MG/ML; 0.4MG/ML; 0.36MG/ML; 0.3MG/ML; 330 UNITS/ML; 1 IU/ML	MVC PLUS	STERIS