CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-163

MEDICAL REVIEW

NDA # 21,163
Multi-12 (Multiple Vitamins for Infusion)
Sabex Inc.
Proposed indications for use: for daily multivitamin maintenance supplement for adults and children aged 11 and older receiving parenteral nutrition or in other situations in which administration by intravenous route is required

Date of submission: July 20, 1999
Date of review: May 2, 2000

Medical Team Leader comments on NDA

The following brief comments are based upon review of Volume 1 of 16 of the NDA and upon review of Dr. Jean Temeck's medical officer review dated 4-5-00.

Multi-12 is a mixture of vitamins contained in two vials that are diluted in dextrose or saline solution for immediate infusion. This product has been marketed since 1994 in Canada (among other countries) and was imported to the U.S. from Canada from 4-97 to 6-99 as a result of a parenteral multivitamin shortage in the U.S. during that interval. Multi-12 is virtually identical to another product currently marketed in the U.S., MVI-12 (Astra), save for minor differences in inactive ingredients. The product formulations are compared in the table on page 1 of Dr. Temeck's review.

This is a literature-based NDA, and includes textbook as well as literature references. Points regarding adverse reactions, drug-vitamin interactions, drug-laboratory test interactions, and solution incompatibility issues are covered in Dr. Temeck's review. I concur with her labeling comments. Based upon the identity between the Sabex product and the Astra product and after review of the application, Dr. Temeck concludes that Multi-12 is safe and effective and recommends approval of the current NDA.

Regulatory issues
Multi-12 is formulated according to 49 FR 36446 (September 17, 1984), in which FDA announced conditions for marketing an effective parenteral multivitamin preparation. This guidance was based upon the clinical evaluation of a formulation recommended in a 1975 guideline by the American Medical Association (AMA). Of note, the 1984 notice stated that future adjustments to the formulation might be necessary.

In August 1985, DMEDP and AMA co-sponsored a workshop on parenteral multivitamins which reviewed additional data relating to the safety and effectiveness of the formulation recommended in the 1975 AMA guideline (and in the 1984 FR notice), and recommended that changes be made to the formulation. Specifically, the committee recommended that the dosages of vitamins B_1, B_6, C, and folate be increased and that vitamin K be added to the formulation.

The recommendations of the working group have now been incorporated into a Federal Register notice that issued April 20, 2000 (65 FR 21200), in the form of a DESI

amendment. The notice informs manufacturers of adult parenteral multivitamin preparations of modifications in the formulation as detailed in the preceding paragraph. The notice states that "supplements to approved new drug applications (NDA's) and abbreviated new drug applications (ANDA's) are due on or before June 19, 2000." In discussion with Mr. David Read (Regulatory Counsel, CDER), and in light of the fact that supplemental applications modifying the formulation will need to include stability studies that will require more than 60 days to complete, we have been informed that the June 19, 2000 deadline is for submission of plans for submission of supplemental applications. Though not stated in the notice, sponsors failing to comply by that date are subject to enforcement action, likely initiated in the form of a Notice of Opportunity for a Hearing (NOOH).

The Sabex product that is the subject of the current NDA meets the old standard for an effective adult parenteral multivitamin preparation and is approvable as such. The issuance of the current FR notice poses some obstacles, however. Again, in discussion with David Read, who subsequently reviewed the matter with Jane Axelrad (CDER, Associate Director for Policy), it was decided that the Sabex product could be approved (before June 19, 2000) with the clear communication that the sponsor must commit, by June 19, 2000 to modifying the product in accordance with the April 20, 2000 FR notice.

Recommendation
Therefore, the recommended action is approval. The approval letter should contain language referencing the April 20, 2000 FR notice, requiring that the sponsor submit a plan for an sNDA modifying the formulation in accordance with the notice by June 19, 2000.

David G. Orloff, M.D.
Deputy Director/Medical Team Ldr
DMEDP/ODE-II/CDER/FDA

/S/

Recommendation code: AP

CC:
HFD-510
NDA 21,163 Arch

NDA: 21.163
Drug: Multi-12
Sponsor: Sabex, Inc.
Date: 4/26/2000

ADDENDUM TO MEDICAL OFFICER'S REVIEW

Today, 4/24/2000, in a follow-up to the t-con of 4/4, Mr. David Read informed Drs. Orloff, Lewis and myself and Mr. McCort, that the Division could issue an approval letter to Sabex for Multi-12 with the provision that the firm reformulate the product to meet the requirements of the Federal Register Notice dated April 20, 2000. Sabex would submit their proposed plan in the form of a supplement to the NDA within the next 60 days.

Regulatory Action:

Based on the above follow-up t-con, Multi-12 can be approved with the provision stated above.

/S/

Jean Temeck, M.D.

/S/

cc. NDA Arch 21,163
NDA Division file
HFD-510: Mr. McCort