CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-265

MEDICAL REVIEW

NDA: 21,265 Dates submitted: 4/20/00 & 11/27/00
Drug:Multi-12/K$_I$ Pediatric(multiple vitamins for infusion)
Dates received: 4/20/00 and 11/28/00
Sponsor: Sabex Inc. Date reviewed: January 5, 2001

MEDICAL OFFICER'S REVIEW

Executive Summary:

I: Recommendations:

Approval is recommended for Multi-12/K$_I$ Pediatric from the clinical perspective.

II: Summary:

Multi-12/K$_I$ Pediatric is safe and effective for multivitamin maintenance in infants and in children up to 11 years of age receiving parenteral nutrition. The active ingredients are quantitatively and qualitatively identical to that of MVI Pediatric which was fully approved by FDA on September 21, 2000 for the above indication. Therefore, the NDA was submitted as a 505(b)(2) application.

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/S/
Jean Temeck, M.D.

/S/ 1-10-01
No Div. Director memo required as I concur - Dr. Temeck
/S/
2/2/01

I. Introduction and Background:

Sabex is submitting this NDA as a 505(b)(2) application with the following indication: daily multivitamin maintenance dosage for infants and children up to 11 years of age receiving parenteral nutrition. The active ingredients- i.e. the vitamin composition, are in accordance with the Federal Register Notice (FRN) of January 26, 2000 as well as the 1975 AMA guideline for parenteral multivitamin preparations and Astra Zeneca's MVI Pediatric which is currently the only FDA approved product for the above indication. The January 26, 2000 FRN upgraded pediatric multivitamin preparations to effective for daily multivitamin maintenance provided they were formulated according to the 1975 AMA guideline. In addition, this FRN required Astra Zeneca to submit by March 27, 2000, revised labeling for MVI Pediatric in accordance with the Notice. The most notable revision in the label was to the Precautions section where a bolded paragraph was required regarding the potential interaction between vitamin K and warfarin-type anticoagulant therapy. AstraZeneca complied with the requirements of this Notice and was subsequently upgraded from conditional approval to full approval on September 21, 2000. In the April 2, 2000 pre-NDA meeting, FDA informed Sabex that they would have the option of submitting a 505(j) application when AstraZeneca received full approval for MVI Pediatric.

Although identical in their active (vitamin) composition, MVI Pediatric and Multi-12/K_1 Pediatric differ in their inactive ingredients as follows:

Inactive Ingredient	MVI Pediatric (AstraZeneca)	Mult-12/K_1 Pediatric (Sabex)
Polysorbate 80	50 mg	50 mg
Polysorbate 20	0.8 mg	Nil
Butylated hydroxytoluene	58 ug	Nil
Butylated hydroxyanisole	14 ug	Nil
NaOH and/or HCl	To adjust pH	To adjust pH
Water for injection	Nil	[redacted]
Mannitol	375 mg	75 mg
Citric acid and/or Na citrate	Nil	To adjust pH

In the April 2, 2000 pre-NDA meeting, FDA requested Sabex to provide information that supports the efficacy and safety of their product where differences exist between theirs and AstraZeneca's MVI Pediatric. However, as indicated by the above table, the Sabex product contains fewer inactive ingredients than AstraZeneca's.

MVI Pediatric consists of a single vial of lyophilized, sterile powder containing all the ingredients which are reconstituted by adding 5 ml of sterile water or 5% dextrose or sodium chloride. Multi-12/K_1 Pediatric is an aqueous preparation consisting of 2 vials- one of 4 ml containing vitamins A, C, D, E, K, B_1, B_2, B_6, niacin and dexpanthenol; and the other of 1 ml containing folic acid, biotin and B_{12}.

Route of administration is intravenous.

The sponsor requested a priority review due to shortage of MVI-Pediatric which is the only parenteral multivitamin product approved by the FDA for use in children. Although AstraZeneca was operating on an allocation program at the time of submission

of the Sabex NDA, Astra stated the number of unfilled orders for MVI Pediatric was zero. In addition, AstraZeneca returned to full supply of MVI Pediatric in June, 2000. Therefore, the NDA was classified as a standard review.

Sabex is in the process of receiving marketing approval for this product in Canada.

II. Description of clinical data and sources:

As a 505(b)(2) application, the sponsor submitted 6 articles from the published literature pertaining to the efficacy of intravenous multivitamin administration in meeting the vitamin requirements of pediatric patients receiving parenteral nutrition with special emphasis on the needs of low-birth-weight infants.

In addition, the sponsor submitted a report on the safety of polysorbates administered intravenously to low-birth-weight infants. This report was prompted by the deaths that occurred in low-birth-weight infants receiving E-Ferol, an intravenous preparation containing vitamin E and polysorbates. As noted above, Multi-12/K_1 Pediatric is a multivitamin preparation containing polysorbate-80 which is administered intravenously to low-birth-weight infants and to children up to 11 years of age who are receiving parenteral nutrition.

III. Review of Efficacy:

Highlights from the 6 articles pertaining to the efficacy of parenteral multivitamins will be presented here.

1. Baeckert et al: Vitamin concentrations in very low birth weight infants given vitamins intravenously in a lipid emulsion: Measurement of vitamins A, D, and E and riboflavin (J Pediatr 113(6):1057-1065, 1988):

Administration of 40% of a unit dose vial of MVI Pediatric/kg body weight/day in Intralipid to 7 VLBW (very low birth-weight: mean 900 grams with range of 450-1360 gm.) infants for 19-28 days, resulted in adequate plasma concentrations of vitamins D and E. However, although vitamin A levels significantly increased, the 40% dose/kg/day was insufficient to raise the blood levels of all infants into the normal range. Vitamin A losses were minimized by adding the multivitamin preparation to Intralipid rather than to the glucose-amino acid solution. Plasma riboflavin levels increased 20-100 fold their initial values. The authors conclude that the current dose of riboflavin is excessive. Since in 5 infants, plasma riboflavin levels decreased as urinary excretion increased, the authors postulate that the marked increase in riboflavin may be related to renal immaturity. Despite the marked elevation in plasma riboflavin levels, erythrocyte riboflavin levels increased only three-to-fourfold. Although renal damage was not observed in these patients, excess riboflavin has been associated with deposition of riboflavin crystals in rats (LD_{50} in rats is 560 mg/kg) and the authors recommend periodic monitoring of renal function in preterm infants receiving this amount of riboflavin. The authors also postulate that excessive riboflavin may pose a risk of perioxidative or photosensitizing injury by increasing the formation of reactive oxygen species. Although the current recommended dose of riboflavin

is too high (40% of the full daily dose/kg), the authors state that "...an effective and safe dose remains speculative."

2. Neu et al: Scientifically-based strategies for nutrition of the high-risk low birth weight infant (Eur J Pediatr 1990;150:2-13):
The nutritional needs of the VLBW infant differ substantially from those of the healthy term infant due to immaturites in many organ systems. Regarding vitamin A, use of the palmitate form will minimize adsorption losses by the plastic tubing. The authors state that the latest available recommendations are that neonates and infants need ~420 ug/day retinol, 160 IU/kg/day vitamin D and 2-3 IU/kg/day vitamin E.

3. Levy et al: Thiamine, Riboflavin, Folate, and Vitamin B_{12} Status of Low Birth Weight Infants Receiving Parenteral and Enteral Nutrition (J Parenteral and Enteral Nutrition 1992;16(3):241-247):
The authors state that the paucity of data on the vitamin requirements of LBW infants receiving parenteral nutrition was the impetus for this study. They refer to the 1979 guidelines established by the Nutrition Advisory Group of the AMA which stated that LBW infants receive 65% of the amount of vitamins recommended for full-term infants (J Parenter and Enteral Nutr 1979;3(4):258-262). The authors also refer to the 1988 guidelines established by the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition (Am J Clin Nutr 1988;48:1324-42) which suggested that a 65% daily dose was too high and that a 40% daily dose was more appropriate. Practically, this equates to 2 ml (40%) rather than 3 ml (60%) of MVI Pediatric administered daily. The purpose of this study was to determine the adequacy of a 40% daily dose and a 60% daily dose of MVI Pediatric to achieve and maintain normal levels of thiamine, riboflavin, folate and B_{12} in LBW infants.
30 LBW infants (birth weight $\leq$1750g with mean birth weight of ~1130g) were randomized to receive either 40% or 60% of a full daily dose of MVI Pediatric. (Note: the group randomized to the 40% dose actually received slightly less than this dose for riboflavin, folate and B_{12}, receiving 0.43-0.47 mg/kg/day, 38-41 ug/kg/day and 0.21-0.24 ug/kg/day, respectively). Although 100% of the infants received TPN for the first week of the study, the % decreased to 50% by the second week and to less than 33% by the third. Thiamine, riboflavin, folate and B_{12} levels were measured weekly and compared to a control group of 18 enterally fed infants.
Results: The highest values for EGR (erythrocyte glutathione reductase activity as a measure of riboflavin status) and for plasma folate and B_{12} occurred in the group receiving 60% of a full daily dose, suggesting the administered doses of these vitamins were too high. Mean plasma folate levels were significantly higher in the 60% dose group at week 2 compared to the 40% dose group. However, mean baseline folate levels were significantly higher in the 60% dose group compared to the other 2 groups. Plasma B_{12} levels were significantly higher in the 60% dose group at week 2 compared to

the control group. LBW infants who received 40% or less (as little as 20-25% for B_{12}) of the full daily dose, maintained adequate levels of these four vitamins during short-term parenteral nutrition.
The study is flawed in that the MVI Pediatric administered to the patients was not the only source of vitamins- a significant percentage of the infants were weaned to enteral feedings after the first week of the study. It is also flawed in that while the vitamin assays used to measure thiamine and riboflavin could detect deficiencies, they could not detect excesses of these vitamins.

4. Inder et al: Vitamin A and E status in very low birth weight infants: Development of an improved parenteral delivery system (J Pediatr 1995; 126(1):128-131):
68 VLBW infants (mean gestational age: 29.1 weeks and birth weight: 1,084g) received 30% of a full daily dose of MVI Pediatric/kg body weight/day in the conventional manner: as a continuous infusion in dextrose-amino acid solution. 61 of these infants received TPN for a mean period of 14 days. 20 other VLBW infants (mean gestational age: 27.6 weeks and birth weight: 1,020g) received 40% of the daily dose of MVI Pediatric/kg body weight/day in a new delivery system. This new delivery system infused the multivitamins over 6 hours by a syringe pump which was placed in a black bag and connected by minimal tubing to the lowest entry point into the IV line infusing parenteral nutrition. Plasma vitamin A and E levels were measured in both groups in cord blood and at 1 and 4 weeks of age. With the conventional delivery system, there was significant loss of vitamin A with mean plasma levels being 70% below recommended levels. The loss was attributed to tubal adherence and photodegradation. With the new delivery system, vitamin A levels were significantly increased compared to the conventional method of delivery. This was attributed to minimizing surface contact and light exposure and increasing the administered dose. Although with the new system, the mean vitamin A level was above the minimal recommended level, individual infants still had low levels. Vitamin E levels were comparable between the two groups with mean levels above the minimal cut-off but with low levels in some infants.

5. Greene et al: Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorous in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition (Am J Clin Nutr 1988;48:1324-42):
This article makes the following points:
   - The 1975 AMA guidelines identified the need for separation of the water-soluble vitamins from the lipid-soluble vitamins although both could be dispensed in a single package. (Note: the 1975 guideline recommended a full multivitamin dose daily in children weighing $\geq$10 kg and 10% of a full dose/kg body weight/day in those weighing <10 kg).

- This article summarizes the findings of the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition which reviewed existing data on vitamin and trace minerals in pediatric patients and, if necessary, to revise the guidelines. The conclusions reached were:
    a. There is a need to develop a multivitamin preparation that specifically meets the needs of preterm infants. Based on available data, administration of 40% of the full daily dose/kg body weight to preterm infants will provide adequate amounts of vitamins E, D and K but low levels of vitamin A and excess levels of most of the B vitamins. This highlights the need for separating the lipid-soluble from the water-soluble vitamins, thus providing greater flexibility in dosing. Best estimates are provided for a multivitamin formulation tailored to the needs of the preterm infant. However, further research is needed to determine optimal blood levels of specific vitamins in preterm infants and the intravenous doses needed to achieve those blood levels. With regard to specific vitamins, Greene makes the point that preterm infants have virtually no hepatic stores of retinol and are, therefore, at particular risk for vitamin A deficiency. He mentions two reports which demonstrated a correlation between a higher incidence of bronchopulmonary dysplasia (BPD) and low plasma retinol levels. It was postulated that vitamin A deficiency could contribute to the development of BPD through its normal role in modulating epithelial cell differentiation. Greene also states that 0.56 mg riboflavin/kg (i.e. a 40% dose/kg/day) appears to be excessive for preterm infants who, unlike term infants, may not have the renal capability of excreting the excess which has been reported to induce photohemolysis.
    b. There is a need to document the safety of polysorbates in preterm infants receiving them intravenously in the first several weeks of life. Otherwise, efforts should be made to decrease or eliminate them.

    (Note: The January 26, 2000 FRN states that the pediatric parenteral multivitamin formulations do not provide adequate amounts of vitamin A to LBW infants and they contain solubilizers which may be toxic. The FRN states: "Future approval of a more appropriate formulation for low birth weight infants may restrict the labeling of the current formulation to use in infants weighing more than 3 kilograms (kg).")

6. Moore et al: Evaluation of a Pediatric Multiple Vitamin Preparation for Total Parenteral Nutrition in Infants and Children 1. Blood Levels of Water-Soluble Vitamins (Pediatrics 1986;77(4):530-538):

The purpose of this study was to evaluate the efficacy of MVI Pediatric in maintaining normal levels of water-soluble vitamins in infants and children. Group 1 comprised 18 preterm infants who received 65% of a full dose of MVI Pediatric daily in TPN. Group 2A consisted of 26 full-term infants and children on TPN for 2-4 weeks who received a full dose (1 vial = 5 ml) of MVI Pediatric daily. Group 2B comprised 8 full-term infants and children on TPN for 3-6 months who also received a full dose of MVI Pediatric daily. Blood samples for measurement of water-soluble vitamin levels were obtained after 4 days of MVI Pediatric and weekly for a maximum of one month. Normative data were established for group 2 patients from 65 well children ages 2 months to 11 years. 55 cord blood samples from healthy term infants were used as reference values for preterm infants.

Results: B_1, B_2, B_6 and niacin were maintained within the reference range in all groups. Pantothenate and B_{12} levels were elevated but baseline levels were high in all groups. Red blood cell folate levels were higher than the reference population in all groups. Vitamin C and biotin levels significantly increased during treatment in preterm infants only. The authors conclude that the level of intake of folate and B_{12} can probably be decreased in all groups but further studies are especially needed in premature infants to better define the appropriate vitamin doses they should receive.

(Note: Greene and Phillips (Pediatrics 81:173-4, 1988, letter to the editor) refer to FDA's May 1985 recommendation that 30% of a vial of MVI Pediatric should be administered to infants <1 kg body weight. This was based on the above data published by Moore et al which showed that administration of 65% of the vial to infants <1 kg, resulted in higher than expected levels of several vitamins coupled with the potential for polysorbate 80 toxicity).

IV. Special Safety Evaluation:

Multi-12/K_1 Pediatric contains polysorbate 80 which serves as a dispersing agent for the lipid-soluble vitamins in the aqueous medium. Since Multi-12/K_1 Pediatric may be administered to premature and low birth-weight infants, and deaths occurred in low birth-weight infants receiving E-Ferol, a vitamin E preparation containing polysorbate 80, a safety report on polysorbate 80 was submitted by the sponsor. This safety report was based on a review of the published literature.

On November 29, 2000, I contacted Ms. Leonore Ferreira, Director, Regulatory Affairs at Sabex, to enclose the references cited in their Polysorbate 80 Safety Report. FDA received these on December 1, 2000. The following is my summary and critique of the aforementioned references.

E-Ferol, an intravenous vitamin E preparation containing 25 U/ml of vitamin E (as *dl*-α-tocopherol acetate) solubilized in 9% polysorbate 80 (90 mg/ml) and 1% polysorbate 20 (10 mg/ml) was introduced to the market in late 1983. E-Ferol did not undergo premarketing tests as required for new drugs (Arrowsmith et al in Pediatrics 83:244-249, 1989) as it was viewed as a new form of an old product or as a "nutritional supplement" (Balistreri et al in Pediatrics 78:503-6, 1986). The product label recommended doses of 25-50 mg/day E-Ferol (note: 1 U vitamin E = 1 mg). The product

appeared to offer a benefit to premature infants due to reports in the literature that vitamin E administration to premature infants may have a role in preventing retrolental fibroplasia, bronchopulmonary dysplasia and hemolytic anemia. In addition, intramuscular administration of vitamin E to premature infants was ineffective due to their decreased muscle mass and poor absorption and was not uncommonly associated with local reactions. The oral route was also ineffective as absorption from the intestine was unreliable.

Subsequent to the introduction of E-Ferol to the marketplace in the fall of 1983, 38 infant deaths were reported in 11 states and 43 other infants sustained serious adverse effects. No specific cause for perinatal death could be identified on autopsy. The constellation of symptoms (subsequently called the E-Ferol syndrome) included pulmonary deterioration, hepatomegaly +/- liver failure, cholestatic jaundice, spleen enlargement, ascites, azotemia +/- renal failure, thrombocytopenia, hypotension and metabolic acidosis. Analysis of these cases by the Center for Disease Control (CDC) revealed an epidemiological association between E-Ferol and this unusual illness. All affected infants were <1,500g at birth and all had received E-Ferol.

The following table is extracted from Bove et al (JAMA 254:2422-2430, 1985):

Details of E-Ferol Therapy Among the 12 Patients From the Same Nursery Weighing < 1,200g at Birth:

Group (sample size)	Length of Rx. (days)	Vitamin E dose (mean ± S.D.)[a] Total units; U/kg/day	Polysorbate dose (mean ± S.D.)[a] Total g; mg/kg/day
Definitely affected[b] (n= 4)	28.0 ± 13.5	1,024± 584; 39.8±7.3	4.10±1.9; 147±26
Probably affected[c] (n= 4)	14.8 ± 10.2	415± 176; 34.2±6.6	1.64±0.6; 131±25
Not affected[d] (n= 4)	16.0 ± 6.0	484±195; 31.0±3.2	1.94±0.8; 124±13

a= dose range was not provided

b= definitely affected (birth weight was <1,200g in all of these infants): patients had any 3 of 4 major unexplained clinical features: thrombocytopenia, renal dysfunction, cholestasis and ascites.

c= probably affected (birth weight was <1,200g in all of these infants): patients had at least 2 of the above 4 unexplained clinical features.

d= not affected infants with birth weight <1,200g

Note that the longer duration of therapy in the definitely affected group accounted for the larger total amount of vitamin E and polysorbates received.

Infants weighing >1,200g at birth were unaffected in the Bove series. By virtue of their significantly greater body weight and shorter duration of therapy, these infants received lower per kg and total doses of vitamin E and polysorbates than either affected or unaffected infants weighing <1,200g at birth.

Bove identified the total dose, duration of therapy and body weight as the important variables in the development of this syndrome. However, he mentioned that 2 unaffected infants received E-Ferol in amounts comparable to affected infants.

would data ... be in the journal?

Bove also examined clinical data obtained from several nurser
received E-Ferol and subsequently died. 18 of these 21 infants who d
or probably affected and 3 were unaffected. The pertinent data is as follows.

Group who died (sample size)	Length of Rx. (days)	Vitamin E dose (range) Total units; U/kg/day	Polysorbate dose(range) Total g; mg/kg/day
Definitely/probably Affected[a] (n= 18)	6 – 45 days	[redacted] 21-137	[redacted] 84-548
Not affected[b] (n= 3)	1 - 3 days	[redacted] 7- 20	[redacted] 28-80

a= birth weight of definitely or probably affected infants who died was 580-1,500g;
b= birth weight of unaffected infants who died was 1,500-3,690g
As above, the total dose, duration of therapy and body weight were the key variables identified with the development of this syndrome.

In another retrospective study of low birth weight infants (≤1,250g), Martone et al (Pediatrics 78:591-600, 1986) reported that 17 affected infants received significantly higher doses of E-Ferol (37.0 ± 1.8 U/kg/day) than did 23 unaffected infants (25.8 ± 2.2 U/kg/day). He also states that no cases of E-Ferol syndrome occurred in infants who received an E-Ferol dose <20 U/kg/day (which would contain <72 mg polysorbate-80/kg/day). However, since both affected and not affected infants received E-Ferol for similar periods of time (mean: 14.5 days in affected and 10.7 days in unaffected infants), the effect of administering a lower doses of E-Ferol for longer periods of time or administering a higher dose for shorter periods could not be evaluated in this series.

When E-Ferol was withdrawn from the market in April 1984, no further cases of this syndrome were reported.

Controversy still exists as to whether the adverse effects observed were related to the large doses of vitamin E administered or to the polysorbates contained in the preparation. The January 26, 2000 FRN states: "...the issue of whether the solubilizers used in pediatric preparations contribute to toxicity remains unsolved." Post-mortem analysis of tissue, serum and body fluids of infants who received pharmacological doses of vitamin E intravenously revealed excessive accumulation of vitamin E especially in the liver. Animal toxicology studies conducted at the FDA in newborn rats demonstrated toxicity after E-Ferol administration that was similar to toxicity after administration of polysorbates alone (Arrowsmith et al in Pediatrics 83:244-249, 1989). Also, Nityanand and Kapoor (Indian J Med Res 69:664-70, 1979) reported congestion and degenerative changes in the liver, heart and kidney of rats receiving polysorbate-80 at 1%, 2% and 4% concentrations orally for 90 days.

Several authors (e.g. Bove, Balistreri and Martone) emphasize the need to obtain more information on the metabolism and safety of vitamin E and polysorbates administered intravenously to infants, especially low-birth-weight infants. Bove states that the routine daily administration of the then marketed intravenous multivitamin preparations in itself presents a burden of polysorbate, which may be toxic to low-birth-weight-infants: 24-72 mg/day for infants weighing 1-3 kg and 10-24 mg/day for infants

weighing <1 kg. However, he also states: "no evidence to date suggests that this exposure is harmful" (Bove et al in JAMA 254:2422-2430, 1985).

In summary, the reported data demonstrate the overlap in vitamin E and polysorbate doses among affected/probably affected and unaffected low birth weight infants who received E-Ferol. However, in Martone's series, the lowest dose at which the E-Ferol syndrome occurred in low birth weight infants was 20 U vitamin E/kg/day containing 72 mg/kg/day polysorbate-80. If one assumes a birth weight of 500g to be the minimum weight compatible with survival, then, following the dosing guidelines in the package insert, the maximal daily dose of vitamin E and polysorbate-80 that an infant would receive from either MVI-Pediatric or from Multi-12/K$_1$ Pediatric would be ~ 4.5 U vitamin E/kg/day and 32.5 mg polysorbate-80/kg/day. This is approximately one-fifth of the lowest daily dose of vitamin E and ~one-half the lowest daily dose of polysorbate-80 which was associated with the development of the E-Ferol syndrome. Furthermore, no cases of the E-Ferol syndrome have been reported in low-birth-weight infants receiving these recommended daily doses of MVI Pediatric and this product has been on the U.S. market since 1983. Therefore, the available data suggest that both NVI Pediatric and Multi-12/K$_1$ Pediatric are safe to administer to low-birth-weight infants at the recommended daily doses. However, if low-birth-weight infants receive multiples of the recommended daily dosage of either of these products, they would then receive polysorbates in the dose range at which the E-Ferol syndrome occurred. Therefore, it is critical that a single daily dose of either MVI Pediatric or Multi-12/K$_1$ Pediatric not be exceeded in these infants. This should be so stated in the label as well the potential for toxicity if the recommended daily dose is exceeded in low-birth-weight infants.

V. NDA Amendment dated 11/27/00 regarding aluminum:

This amendment was submitted in accordance with the January 26, 2000 Federal Register Notice on "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition". This FRN requires a statement in the Warnings section of these products that states that parenteral levels of aluminum > 4-5 ug/day has been associated with central nervous system and bone toxicity in patients with impaired kidney function, including premature infants. The sponsor has submitted labeling to comply with this Notice. Please refer to VI. Labeling Review, WARNINGS, for modification of the first sentence.

VI. Labeling Review:

The package insert (PI) for MVI-12/K$_1$ Pediatric should be revised as follows to conform to that for MVI Pediatric given the similar composition of the two products:

DESCRIPTION:

a. The specific amounts of the inactive ingredients in vials 1 and 2 should be specified.

b. After the contents of vial 2, add:

Vitamin A 2,300 IU equals 0.7 mg
Vitamin D 400 IU equals 10 mcg
Vitamin E 7 IU equals 7 mg

c. Delete the word "Aqueous" which precedes "**multiple vitamin preparation for intravenous infusion**" and capitalize the "m" in "multiple".

INDICATIONS AND USAGE:

Add the following sentence to the end of the fifth paragraph: "Blood vitamin concentrations should be periodically monitored to ensure maintenance of adequate levels, particularly in patients receiving parenteral multivitamins as their sole source of vitamins for long periods of time."

PRECAUTIONS:

Under "General", delete the first sentence which begins with: "Unlike the adult formulation..."

Revise the second sentence of the first paragraph to read: "In such patients, vitamin K may antagonize the hypoprothrombinemic response to anticoagulant drugs. Add "/INR response" after "prothrombin time" in the third sentence.

Unbold paragraphs 2 and 3 which respectively begin with: "Adequate blood levels..." and "Studies have shown..."

Add the word "may" before "require" in the fourth paragraph.

Add the following after the fourth paragraph:

"In patients receiving parenteral multivitamins, blood vitamin concentrations should be periodically monitored to determine if vitamin deficiencies or excesses are developing.

Polysorbates have been associated with the E-Ferol syndrome (thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) in low birth weight infants.

Multi-12/K_1 Pediatric should be aseptically transferred to the infusion fluid."

Replace the *Drug interactions* section with:

Drug-Drug Interactions

Physical Incompatibilities

Multi-12/K_1 Pediatric is not physically compatible with alkaline solutions or moderately alkaline drugs such as Acetazolamide, Chlorothiazide sodium, Aminophylline or sodium bicarbonate. Multi-12/K_1 Pediatric is not physically compatible with ampicillin and it may not be physically compatible with tetracycline HCl. It has also been reported that folic acid is unstable in the presence of calcium salts such as calcium gluconate. Direct addition of Multi-12/K_1 Pediatric to intravenous fat emulsions is not recommended. Consult appropriate references for listings of physical compatibility of solutions and drugs with the vitamin infusion. In such circumstances, admixture or Y-site administration with vitamin solutions should be avoided.

Some of the vitamins in Multi-12/K_1 Pediatric may react with vitamin K bisulfite or sodium bisulfite; if bisulfite solutions are necessary, patients should be monitored for vitamin A, thiamine and acsorbic acid deficiencies."

Clinical Interactions

A number of interactions between vitamins and drugs have been reported which may affect the metabolism of either agent. The following are examples of these types of interactions.

Folic acid may lower the serum concentration of phenytoin resulting in increased seizure frequency. Conversely, phenytoin may decrease serum folic acid concentrations and, therefore, should be avoided in pregnancy. Folic acid may decrease the patient's response to methotrexate therapy.

Pyridoxine may decrease the efficacy of levodopa by increasing its metabolism. Concomitant administration of hydralazine or isoniazid may increase pyridoxine requirements.

In patients with pernicious anemia, the hematological response to vitamin B_{12} therapy may be inhibited by concomitant administration of chloramphenicol.

Several vitamins have been reported to decrease the activity of certain antibiotics. Thiamine, riboflavin, pyridoxine, niacinamide, and ascorbic acid have been reported to decrease the antibiotic activity of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid and riboflavin.

Vitamin K may antagonize the hypoprothrombinemic effect of oral anticoagulants

Consult appropriate references for additional specific vitamin-drug interactions.

Add the following section after **Drug-Drug Interactions**:

Drug-Laboratory Test Interactions

Ascorbic acid in the urine may cause false negative urine glucose determinations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Add: "and mutagenicity" after the word: "Carcinogenicity".

WARNINGS:

Revise the first sentence to read: "Multi-12/K_1 Pediatric is administered in intravenous solutions which may contain aluminum that may be toxic."

ADVERSE REACTIONS:

Revise the first sentence to read: "There have been rare reports of anaphylactic reactions following parenteral multivitamin administration."

Follow this first sentence with: "Rare reports of anaphylactoid reactions have also been reported after large intravenous doses of thiamine."

The adverse reactions after "Allergic" should read: urticaria, shortness of breath, wheezing and angioedema.

OVERDOSAGE:

Replace the second and third sentences with: "Clinical manifestations of hypervitaminosis A have been reported in patients with renal failure receiving 1.5 mg/day retinol. Therefore, vitamin A supplementation of renal failure patients should be undertaken with caution."

DOSAGE AND ADMINISTRATION:

In the first paragraph, add: "and children" after "infants".

Revise the beginning of the third paragraph to read: "A daily dose of Multi-12/K_1 Pediatric should be added directly to not less than 100 ml..."

Revise the sequence of dosing based on body weight from smallest to largest (i.e. **For administration to infants weighing < 1 kg** should be placed first).

Revise **For administration to infants weighing < 1 kg** as follows:

The daily dose is 30% of the contents of Vial 1 (1.2 ml) and Vial 2 (0.3 ml). Do not exceed this daily dose. A supplemental vitamin A may be required for low-birth-weight infants.

Revise **For administration to infants weighing ≥ 1 kg and < 3 kg** as follows:

The daily dose is 65% of the contents of Vial 1 (2.6 ml) and Vial 2 (0.65 ml). Do not exceed this daily dose. A supplemental vitamin A may be required for low-birth-weight infants.

Revise **For administration to infants and children weighing ≥ 3 kg up to 11 years of age** as follows:

The daily dose is the entire contents of Vial 1 (4 ml) and of Vial 2 (1 ml) unless there is clinical or laboratory evidence for increasing or decreasing the dosage.

VI. Conclusions and Recommendations:

Multi-12/K_1 Pediatric is generically equivalent to MVI Pediatric, which has been on the U.S. market since 1983. However, since MVI Pediatric did not receive full approval until September 21, 2000 (see I. Introduction and Background for details), Sabex submitted this NDA as a 505(b)(2) application. Both of these products meet the vitamin requirements of full term infants and children up to age 11 years receiving parenteral nutrition. However, these products are not ideally formulated to meet the special needs of low-birth-weight infants and more research is need in this special patient population. As stated in the January 26, 2000 FRN: "Future approval of a more appropriate formulation for low birth weight infants may restrict the labeling of the current formulation to use in infants weighing more than 3 kilograms (kg)."

Regulatory action for Multi-12/K_1 Pediatric: Approval of Multi-12/K_1 Pediatric from the clinical standpoint provided the appropriate changes are made to the PI as delineated above.

/S/

Jean Temeck, M.D.

cc. NDA Arch NDA Division file HFD-510: Mr. S. McCort

Concur

/S/

1-10-01

No safety review need. No clinical studies needed.