DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Thierry Soursac, MD, PhD
Chief Executive Officer and Managing Director
Mayne Pharma (USA), Inc.
Mack-Cali Centre II
650 From Road, Second Floor
Paramus, NJ 07652

Re: NDA 08-809
M.V.I.-12 (Multi-Vitamin Infusion without vitamin K)
MACMIS # 13777

WARNING LETTER

Dear Dr. Soursac:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a promotional mailer (3905 MVI12) for M.V.I.-12 (multi-vitamin infusion without vitamin K) submitted by Mayne Pharma (USA), Inc. (Mayne) under cover of Form FDA 2253. The promotional mailer is false or misleading because it omits important risk information for M.V.I.-12 and thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§352(a) and 321(n). Cf. 21 C.F.R. 202.1(e)(3)(i). This is particularly concerning from a public health perspective because the lack of risk information suggests that M.V.I.-12 is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Background

The Indications and Usage section of the approved product labeling (PI) states:

> This formulation is indicated for the prevention of vitamin deficiency and thromboembolic complications in people receiving home parenteral nutrition who also receive warfarin-type anticoagulant therapy.
>
> The physician should not await the development of clinical signs of vitamin deficiency before initiating vitamin therapy.
>
> Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for two or more days as indicated by the clinical status. Clinical testing indicates that some patients do not maintain adequate levels of certain vitamins when this formulation in recommended amounts is the sole source of vitamins.

The PI reflects important contraindications, warnings, precautions, and adverse reactions. It states (in pertinent part):

Contraindications
Known hypersensitivity to any of the vitamins in this product or a pre-existing hypervitaminosis. Allergic reaction has been known to occur following intravenous administration of thiamine. This formulation is contraindicated prior to blood sampling for detection of megaloblastic anemia, as the folic acid and the cyanocobalamin in the vitamin solution can mask serum deficits.

Warnings
WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Precautions
Studies have shown that vitamin A may adhere to plastic, resulting in inadequate vitamin A administration in the doses recommended with M.V.I.-12.®

Where long-standing specific vitamin deficiencies exist, it may be necessary to add therapeutic amounts of specific vitamins to supplement the maintenance vitamins provided in M.V.I.-12 ®

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

M.V.I.-12® SHOULD BE ASEPTICALLY TRANSFERRED TO THE INFUSION FLUID.

Adverse Reactions
There have been rare reports of anaphylactoid reactions following large intravenous doses of thiamine. The risk, however, is negligible if thiamine is co-administered with other vitamins in the B group. There have been no reports of fatal anaphylactoid reactions associated with M.V.I.-12®.

There have been rare reports of the following types of reactions:
Dermatologic — rash, erythema, pruritus
CNS — headache, dizziness, agitation, anxiety
Ophthalmic — diplopia
Allergic — urticaria, periorbital and digital edema

Omission of Risk Information

The promotional mailer presents effectiveness claims for M.V.I.-12. It states that M.V.I.-12 contains "minimAL aluminum" (emphasis original) and "optimAL nutrition for individuAL needs" (emphasis original) and that M.V.I.-12 is "The **only** commercially available Multi-Vitamin Infusion **Without Vitamin K**" (emphasis original) giving practitioners "…the **option** to control vitamin K levels in TPN [total parenteral nutrition] for patients on warfarin-type anticoagulant therapy." (emphasis original) but fails to provide any information about the risks described above. The promotional mailer includes a reference to the full prescribing information; this statement, however, is not sufficient to provide appropriate qualification or pertinent information for claims made in the mailer. For the piece to be truthful and non-misleading, it must contain risk information in each part as necessary to qualify any safety or effectiveness claims made in that part. Because the piece makes effectiveness claims but contains no risk information, it is false or misleading under sections 502(a) and 201(n) of the Act, 21 U.S.C. §§352(a) and 321(n). Cf. 21 C.F.R. 202.1(e)(3)(i).

Conclusions and Requested Actions

Your promotional mailer omits important risk information about M.V.I.-12 and thus misbrands your drug in violation of the Act, 21 U.S.C. §§352(a) and 321(n). Cf. 21 C.F.R. 202.1(e)(3)(i).

DDMAC requests that Mayne immediately cease the dissemination of violative promotional materials for M.V.I.-12 such as those described above. Please submit a written response to this letter on or before February 15, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for M.V.I.-12 such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-796-9877. In all future correspondence regarding this particular matter please refer to the MACMIS ID # 13777 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for M.V.I.-12 comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas W. Abrams, RPh., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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