DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

September 29, 2005

Janet R. Dees
Managing Partner
Nephrx
10 Burke Drive
Brockton, MA 02301

Re: ANDA 76-206
Calcitriol Injection 1 mcg/mL
MACMIS # 13467

WARNING LETTER

Dear Ms. Dees:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a print advertisement for Calcitriol Injection (Calcitriol) submitted by Nephrx under cover of Form FDA 2253 and a website (URL: http://www.nephrx.com/products.htm) for Calcitriol that is maintained by Nephrx[1]. Both promotional materials omit important risk information for Calcitriol. The print ad, which also appears on your website, makes unsubstantiated superiority claims, while the website and print ad overstate the efficacy of the drug. The print ad and website, therefore, misbrand Calcitriol in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (n); 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(1); (e)(3)(i); (e)(6)(i) & (ii). Furthermore, the website was not submitted to FDA under cover of Form 2253 as required by 21 CFR 314.81(b)(3)(i).

Background
The Indications and Usage section of the PI for Calcitriol states:

> Calcitriol is indicated in the management of hypocalcemia in patients undergoing chronic renal dialysis. It has been shown to significantly reduce elevated parathyroid hormone levels. Reduction of PTH has been shown to result in the improvement in renal osteodystrophy.

[1] The print advertisement together with brief summary, identified as 27736, was submitted to FDA under cover of Form 2253 on December 21, 2004. According to your Form 2253, this advertisement was initially disseminated in January, 2005. FDA is not aware of which publication(s) ran this advertisement. The print advertisement posted on your website, which is identical to the print advertisement submitted under Form 2253, does not include this brief summary page.

The PI for Calcitriol reflects important contraindications, warnings, precautions, and adverse reactions such as:

Contraindications
Calcitriol should not be given to patients with hypercalcemia or evidence of vitamin D toxicity.

Warnings
Since calcitriol is the most potent metabolite of vitamin D available, vitamin D and its derivatives should be withheld during treatment.

A non-aluminum phosphate-binding compound should be used to control serum phosphorus levels in patients undergoing dialysis.

Overdosage of any form of vitamin D is dangerous. Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis and other soft-tissue calcification. The serum calcium times phosphate (Ca × P) product should not be allowed to exceed 70. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Precautions
Excessive dosage of Calcitriol induces hypercalcemia and in some instances hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium and phosphorus should be determined at least twice weekly. Should hypercalcemia develop, the drug should be discontinued immediately.

Calcitriol should be given cautiously to patients on digitalis because hypercalcemia in such patients may precipitate cardiac arrhythmias.

Serum calcium, phosphorus, magnesium and alkaline phosphatase and 24-hour urinary calcium and phosphorus should be determined periodically. During the initial phase of the medication, serum calcium and phosphorus should be determined more frequently (twice weekly).

Adynamic bone disease may develop if PTH levels are suppressed to abnormal levels. If biopsy is not being done for other (diagnostic) reasons, PTH levels may be used to indicate the rate of bone turnover. If PTH levels fall below recommended target range (1.5 to 3 times the upper limit of normal), in patients treated with Calcitriol, the Calcitriol dose should be reduced or therapy discontinued. Discontinuation of Calcitriol therapy may result in rebound effect, therefore, appropriate titration downward to a maintenance dose is recommended.

Adverse Reactions
Adverse effects of Calcitriol are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early: weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Late: polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated SGOT and SGPT, ectopic calcification, hypertension, cardiac arrhythmias and, rarely, overt psychosis. Occasional mild pain on injection has been observed.

Omission of Risk Information

The print advertisement and website are misleading because they fail to provide any information about the risks of Calcitriol. The print ad and website include effectiveness claims for the product (e.g., the print ad claims Calcitriol is effective in "managing renal osteodystrophy," while the website recommends administration of Calcitriol "to dialysis patients for the management of calcium deficiency (hypocalcemia) with chronic kidney failure" and claims the drug treats "elevated hormone levels and normalizes bone formation, reducing renal osteodystrophy damage"). However, the print ad does not reveal <u>any</u> risks associated with Calcitriol within the body of the ad and the website includes no risk information whatsoever.

Unsubstantiated Superiority Claim

The print ad implies that Nephrx's Calcitriol is superior in some way to other generic calcitriol products. Specifically, the ad contains claims that Calcitriol is "<u>The</u> Smart Choice For Generic Calcitriol Injection" (emphasis added) and includes a statement that "Choosing Nephrx Calcitriol is the easiest decision I've made all day" (next to a picture of what appears to be a health care provider). FDA is not aware of substantial evidence or substantial clinical experience to support a claim that Nephrx's Calcitriol is superior to other generic calcitriol products. In the absence of such evidence or additional contextual information, the representations in the ad are misleading.

Overstatement of Efficacy

The website claims that Calcitriol "normalizes bone formation." FDA is not aware of substantial evidence or substantial clinical experience (i.e. bone biopsy data) to support this claim. Thus, this claim misleadingly overstates the efficacy of the drug. In addition, the print ad alludes to Calcitriol's role in "managing renal osteodystrophy." This statement suggests that Calcitriol is effective in the overall management of the disease state (e.g. modifying the patient's diet, dialysis treatment, or medication), when in fact, it is only indicated for the management of hypocalcemia in patients undergoing chronic renal dialysis. FDA is not aware of substantial evidence or substantial clinical experience to support this claim.

Failure to Submit Under Form 2253

FDA regulations require you to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.

Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. You did not submit the website referred to in this letter to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i).

Conclusions and Requested Actions

Your print advertisement and website omit important risk information about Calcitriol; moreover, your print ad makes unsubstantiated superiority claims while your website and print ad overstate the efficacy of the drug. Therefore, these materials misbrand your drug in violation of the Act (21 U.S.C. §§ 352(a) & (n); 321(n)), and FDA implementing regulations. 21 CFR 202.1(e)(1); (e)(3)(i); (e)(6)(i) & (ii). Furthermore, the website was not submitted to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Nephrx immediately cease the dissemination of violative promotional materials for Calcitriol such as those described above. Please submit a written response to this letter on or before October 14, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Calcitriol 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 # 13467 in addition to the ANDA 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 Calcitriol 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 Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications