DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

February 21, 1997

TRANSMITTED VIA FACSIMILE

Patrick J. Mahaffy
President and Chief Executive Officer
Nexstar Pharmaceuticals, Inc.
2860 Wilderness Place
Boulder, Colorado 80301

RE: NDA #50-704
DaunoXome (daunorubicin citrate liposome injection)
MACMIS # 4834

WARNING LETTER

Dear Mr. Mahaffy:

This Warning Letter concerns Nexstar Pharmaceuticals, Inc.'s, (Nexstar) promotional materials for the marketing of DaunoXome (daunorubicin citrate liposome injection). Based on materials[1] we have received as part of our monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has concluded that Nexstar is disseminating promotional materials for DaunoXome that contain statements, suggestions, or implications that are false and/or misleading, that promote unapproved uses and doses, and that do not comply with the post-marketing reporting requirements, in violation of Sections 502(a), 505(a), 502(f), and 505(k) of the Federal Food, Drug, and Cosmetic Act (Act), and applicable regulations.

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1 The materials cited in this Warning Letter are illustrative only. Many of the claims discussed in this letter were disseminated in a variety of materials and formats. Thus, the issues are not limited to the materials cited.

File Name:warnltr

Drafted: Acker	November 22, 1996
Comment: Drezin	January 2, 1997
Revised: Acker	January 7, 1997
Revised: Drezin	January 13, 1997
Comment: Abrams	January 16, 1997
Comment: BaylorHenry	January 17, 1997
Comment: Morris	January 22, 1997
Comment: Palmer	January 23, 1997
Comment: White	January 31, 1997
Comment: DeLap	January 28, 1997
Comment: Temple	February 3, 1997
Revised: Acker	February 11, 1997
Comment: Ray	February 18, 1997
Comment: Drezin	February 18, 1997
Revised: Acker	February 20, 1997
Revised: Acker	February 21, 1997

cc:
HFD-40/NDA # 50-704
HFD-40/Chron/Acker/Abrams/Drezin/BaylorHenry
HFD-1/Woodcock
HFD-2/Lumpkin
HFD-5/Axelrad
HFD-100/Temple
HFD-150/NDA # 50-704
HFD-150/RWhite/DSpillman/RDelap
HFC-1/Assoc. Comm. Reg. Affairs
HFD-205/CDER FOI
HFD-200/Rose
HFD-300/Office of Compliance
HFI-1/O'Hara
HFI-35/FOI
HF-12/Office of AIDS and Special Issues
GCF-1/Ray/Wion
HFR-SW200

MACMIS ID #4834
MACMIS Type Code:LETT
MACMIS Action Code:WARN

Due Date: March 10, 1997

2253 ID #:38992	Material ID #:8556, 8560, 8561,8564,8566,8567, 8568
2253 ID #:44447	Material ID #: NM1006, 9130
2253 ID #:40153	Material ID #: 3764
2253 ID #:46348	Material ID #: 9392
2253 ID #:42020	

2253 ID#: 47362 **Material ID #:9578**
2253 ID#: 47710
2253 ID#: 48506

Close Out: No

FOI status: RELEASABLE

COMPARATIVE SAFETY CLAIMS

Nexstar is disseminating promotional materials[2] that state or suggest that DaunoXome has a safety profile superior to conventional anthracycline-based chemotherapy or ABV (combination chemotherapy consisting of doxorubicin, bleomycin, and vincristine that is used as a regimen for the treatment of AIDS-related Kaposi's sarcoma (AIDS-KS)). For example, Nexstar is disseminating promotional materials that claim "Tolerability improved compared to conventional therapy." This claim is false and/or misleading for the reasons stated below.

The ADVERSE REACTIONS sections of DaunoXome's approved labeling describe data from Nexstar's randomized, controlled clinical trial that compared DaunoXome to ABV. Although the trial demonstrated that most adverse events occurred at a similar rate in both groups, **certain important adverse events occurred more frequently in the DaunoXome group.** The trial data indicate that: (1) severe neutropenia (<500 cells/mm^3) occurred with a higher incidence in the DaunoXome group; (2) opportunistic infections occurred more frequently in the DaunoXome group; and (3) the median time to first opportunistic infection was 198 days shorter in the DaunoXome-treated group.

Nexstar's promotional materials fail to disclose this important safety information. Instead, Nexstar claims that DaunoXome is safer than ABV by making a selected disclosure of adverse events that occurred at similar rates in, or less frequently than, the ABV group. Nexstar's misleading presentation of these data is exemplified by a slide in a "Nurses Slide Kit." The slide shows a table Nexstar entitled "Summary of Important Safety Information" that describes the incidence of alopecia, neuropathy, fatigue, diarrhea, nausea, vomiting, and fever. For the events presented, incidence rates between DaunoXome and ABV were similar, with the exception of alopecia and neuropathy, which occurred less frequently in the DaunoXome group. However, the approved product labeling contains a table entitled, "Summary of Important Safety Data." This table describes the incidence of neutropenia, opportunistic infections/illnesses, median time to first opportunistic infections, certain cardiac adverse effects, patients withdrawn from therapy due to

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[2] These materials include, but are not limited to, a press release; nurses slide kit; brochure (NM1006); product monograph (printed and diskette) and reprint by Chew and Jacobs entitled, *Pharmacology of liposomal daunorubicin and its use in Kaposi's sarcoma,* Oncology 1996; 10(6)Supp, pp 28-33.

cardiac causes, alopecia and neuropathy. As indicated in this table and above, in all of these events except alopecia and neuropathy, the incidence of occurrence was higher with DaunoXome.

Clearly, the higher incidence of opportunistic infections is important information for clinicians treating patients for AIDS-KS, and would be an important consideration in a physician's choice of treatment. The lower incidence of hair loss (alopecia) with DaunoXome, although certainly important, is not more important than the potentially life-threatening consequences of drug therapy that occurred more frequently in the DaunoXome group.

Nexstar has thus used a selective presentation of adverse event information to make false and/or misleading claims about the safety of DaunoXome.

FAILURE TO PROVIDE FAIR BALANCE

Many of Nexstar's promotional materials[3] contain no information about the risks associated with the use of DaunoXome. In those instances in which Nexstar did disclose risk information, it was not sufficiently comprehensive, and was not presented in a manner reasonably comparable in prominence to the claims of safety and effectiveness.[4] Promotional materials are misleading if they fail to present information relating to adverse consequences associated with the use of the drug, and fail to include appropriate reference to warnings, precautions, and contraindications. Such disclosures, should be presented with a prominence and readability reasonably comparable with the information relating to effectiveness of the drug.

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[3] These include, but are not limited to, journal ad; Dear Doctor letter; fact sheet and several press releases.

[4] For example, Sales aid; brochure (NM 1006); nurses slide kit; monograph (printed and diskette); and press release. Nexstar is distributing an article by Gill and Espina et al., *Phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin*, JCO 1995; 13(4), pp 996-1003, that comments on the relative lack of acute toxicity and cumulative organ damage seen with DaunoXome treatment. These statements directly contradict the approved product labeling.

Nexstar consistently failed to provide fair balance in its promotional materials by failing to disclose serious events that occurred with a higher incidence in the DaunoXome-treated patients. Nexstar also failed to disclose, or minimized the significance of, adverse events unique to DaunoXome. According to the approved product labeling, the triad of back pain, flushing, and chest tightness occurred in 13.8% of patients receiving DaunoXome.

CLAIMS OF REDUCED OR NO RISK OF CARDIAC TOXICITY

Nexstar is distributing promotional materials[5] that claim, "DaunoXome exhibits reduced risk of cardiotoxicity in Phase III trials", and that DaunoXome lacks cardiotoxicity after long-term use. These claims are unsubstantiated and inconsistent with the approved product labeling and the data Nexstar submitted to FDA, and therefore are false and/or misleading.

The boxed WARNINGS section of the approved product labeling for DaunoXome states:

> Cardiac function should be monitored regularly in patients receiving DaunoXome because of the potential risk for cardiac toxicity and congestive heart failure. Cardiac monitoring is advised especially in those patients who have received prior anthracyclines or who have pre-existing cardiac disease.

The WARNINGS section of the labeling further states:

> Cardiac function should be evaluated in each patient by means of a history and physical examination before each course of DaunoXome and determination of LVEF should be performed at total cumulative doses of DaunoXome of 320 mg/m^2, 480 mg/m^2 and every 240 mg/m^2 thereafter.

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[5] These materials include, but are not limited to, a "homemade" piece; press release; nurses slide kit; brochure ID#NM1006; reprint by Chew and Jacobs entitled, *Pharmacology of liposomal daunorubicin and its use in Kaposi's sarcoma*; product monograph; and abstract entitled, *Lack of cardiac toxicity of liposomal encapsulated daunorubicin (DaunoXome) after long term use in AIDS-related Kaposi's sarcoma,* Gill, Wernz et al., 9th NCI-EORTC Symposium on New Drugs in Cancer Therapy; March 12-15, 1996.

The approved product labeling also states that the evaluation of cardiac toxicity in the pivotal trial was incomplete with "several instances of missing repeat cardiac evaluations." The approved product labeling presents the data on patients that experienced reductions in ejection fraction as the number of cases rather than a percentage, since the missing cardiac evaluations made the denominator for this value uncertain. The fact that, (1) some DaunoXome-treated patients experienced reductions in ejection fractions; (2) some patients were removed from DaunoXome therapy due to cardiac causes; and (3) several cardiac evaluations were missing, makes it impossible to conclude that DaunoXome has a reduced risk or no risk of cardiac toxicity.

It is our understanding that Nexstar has also disseminated a promotional piece containing a claim that DaunoXome is **"cardioprotective"**[6] even at doses exceeding a cumulative dose of 3000 mg/m^2. In addition, Nexstar has issued materials stating that **FDA has concluded** that DaunoXome reduces the cardiotoxicity normally associated with anthracyclines.[7] These claims are false.

Nexstar's various claims of reduced or no cardiac toxicity may endanger patients because physicians who rely on Nexstar's representations might fail to monitor for, or fail to heed early signs of, cardiac toxicity.

UNSUBSTANTIATED EFFECTIVENESS CLAIMS

In its promotional materials, Nexstar presents claims, inconsistent with its approved product labeling, that DaunoXome is more effective than has been demonstrated by substantial evidence. Nexstar is distributing an article by Chew and Jacobs entitled *Pharmacology of liposomal daunorubicin and its use in Kaposi's sarcoma*, Oncology 1996, 10 (6) Suppl. This article states that the pooled results of data from 95 patients in the phase II trials show that overall, 97% received important clinical benefits (complete or partial response or stable disease) from DaunoXome

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6 DDMAC has received information that a Nexstar sales representative has distributed "homemade" promotional materials that claim "Data from Ph. II-III suggests DaunoXome to be cardioprotective even at doses exceeding 3000 mg/m^2."

7 Nexstar claims in a press release that, "...review of Nexstar's Phase III data led the FDA to conclude that Daunoxome therapy reduces the cardiotoxicity normally associated with anthracycline-based therapy."

therapy. The effectiveness of DaunoXome is further exaggerated by the last statement in the conclusion of the Chew article which states that "It [DaunoXome] has arrested progression of advanced KS in more than 95% of patients and has produced actual remissions in 67% of patients."

Another reprint disseminated by Nexstar is an article by Girard, Bouchaud, et al., entitled, *Phase II study of liposomal encapsulated daunorubicin in the treatment of AIDS-associated mucocutaneous Kaposi's sarcoma,* AIDS 1996; 10:753-757. This article describes that 73% of patients achieved a partial response.

These reprints, when used as promotional labeling by Nexstar, are false and/or misleading because they report effectiveness rates that significantly overstate the effectiveness of DaunoXome. Furthermore, these rates are inconsistent with the approved product labeling. According to response data from the pivotal trials, described by Nexstar as based upon strict, nationally recognized response criteria, and as described in the approved product labeling, only 23% of DaunoXome-treated patients responded to the drug.

PROMOTION OF UNAPPROVED USES AND DOSES

Nexstar is promoting DaunoXome for unapproved uses and doses by distributing a reprint of an article by Uthayakumar et al., 1996, entitled *Randomized cross-over comparison of liposomal daunorubicin versus observation for early Kaposi's sarcoma*, AIDS 10:515-519, containing an abstract that concludes that:

> Liposomal daunorubicin is a **well tolerated and efficacious treatment for early KS**; however, the duration of response is brief. (Emphasis added)

However, according to the INDICATIONS AND USAGE section of the approved product labeling,

> DaunoXome is indicated as a first line cytotoxic therapy for **advanced** HIV-associated Kaposi's sarcoma. **DaunoXome is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma.** (Emphasis added)

Moreover, the abstract is misleading because it does not accurately summarize the article, and is inconsistent with the approved product labeling. The abstract contradicts the discussion section of the article that states:

> the brief duration of response to chemotherapy when compared to the rate of progression in the observation arm is disappointing and **suggests that there is little value in early systemic single agent chemotherapy**. This is reinforced by the absence of any complete remissions. Nevertheless liposomal daunorubicin may have a role in advanced disease or a place in combination chemotherapy.... (Emphasis added)

Notwithstanding this disclosure on the fourth page of the article (page 518), the dissemination of this article by Nexstar promotes a use of DaunoXome that is clearly not recommended in, and inconsistent with, the approved product labeling (i.e., early stage AIDS-KS).

Nexstar is also distributing a reprint and abstract[8] that promotes the use of DaunoXome at doses up to 60 mg/m^2 every two weeks. However, the approved product labeling states that DaunoXome should be administered at a dose of 40 mg/m^2 every two weeks. Thus, promotion of DaunoXome at a dose of 60 mg/m^2 promotes an unapproved dosage. Promotion of this dosage could present a serious risk to patients. As you know, DaunoXome has significant risks even at recommended doses. This risk is compounded by Nexstar's promotional materials that fail to disclose, or minimize, important safety information.

FAILURE TO SUBMIT UNDER FDA FORM 2253

Some of the materials that are the subject of this Warning Letter were not submitted to FDA by Nexstar pursuant to the post-marketing reporting requirements for promotional labeling and advertising, 21 CFR 314.81(b)(3).

CONCLUSIONS AND REMEDIAL ACTIONS

The materials and promotional messages disseminated by Nexstar contain false and/or misleading information about the safety and effectiveness of DaunoXome. Such information could directly endanger patients whose physicians are either not aware of DaunoXome's risks, or received information that minimizes such risks.

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[8] Gill, Espina, Muggia et al., *Phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin*, JCO 1995; 13(4), pp 996-1003; Gill, Wernz, Myers, et al.,Treatment of AIDS-related bronchopulmonary Kaposi's sarcoma with liposomal encapsulated daunorubicin (DaunoXome). Presented at NCI-EORTC, March 12-15, 1996.

Accordingly, Nexstar should propose a corrective action plan, including the mailing and publication of a "Dear Healthcare Professional" letter to correct the false and/or misleading messages discussed in this letter to all health care providers, institutions, and organizations who received the violative messages.

This corrective action plan should also include:

A. Immediately ceasing the dissemination of all materials that state, suggest, or imply (1) that DaunoXome is less toxic than other therapies; (2) that DaunoXome has reduced risk, or has no risk, of cardiac toxicity; (3) that DaunoXome is more effective than has been demonstrated by substantial evidence; (4) that DaunoXome is safe and effective for unapproved uses or doses; or (5) that otherwise contain violative claims of the type discussed in this letter.

B. A written statement of Nexstar's intent to comply with "A" above.

C. A complete listing of all advertising and promotional materials that will remain in use and those that will be discontinued. Also provide two copies of all promotional materials for DaunoXome that Nexstar intends to continue to distribute.

D. Within 15 days of the date of this letter, disseminating a message to all Nexstar sales representatives and marketing personnel involved in the marketing and sales of DaunoXome, instructing them to immediately cease dissemination of all promotional materials and messages discussed in this letter and providing each person with a copy of this letter.

The Dear Healthcare Professional letter and Nexstar's corrective action plan should be submitted to DDMAC for approval. After such approval, the letter should be disseminated by both direct mail and through a paid advertisement in all journals that contained advertisements for DaunoXome during the 12 months prior to the date of this letter.

The violations discussed in this letter do not necessarily constitute an exhaustive listing. We are continuing to evaluate other aspects of Nexstar's campaign for DaunoXome and we may determine that additional remedial measures will be necessary to fully correct the false and/or misleading messages resulting from Nexstar's violative conduct.

Nexstar should respond to this letter no later than March 10, 1997. Please send your response to Dr. Tracy Acker at the Division of Drug Marketing, Advertising, and Communications, 5600 Fishers Lane, HFD-40, Rockville, Maryland 20857. If you have any questions in regard to this Warning Letter, please contact either Mr. Norman Drezin or Dr. Tracy Acker at (301) 827-2831. DDMAC reminds Nexstar that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #4834.

Failure to respond to this letter may result in regulatory action, including seizure and/or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, RPh, JD
Director
Division of Drug Marketing,
Advertising, and Communications