

**TRANSMITTED BY FACSIMILE**

Franklin Vairinhos, Ph.D.
Director, Regulatory Affairs
Cephalon, Inc.
41 Moores Road
Frazer, PA 19355 USA

RE: NDA # 021248
Trisenox® (arsenic trioxide) injection
MACMIS # 20151

Dear Dr. Vairinhos:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the healthcare professional website¹ for TRISENOX® (arsenic trioxide) (Trisenox) submitted by Cephalon, Inc. (Cephalon) under cover of Form FDA 2253. The website broadens the indication for Trisenox, minimizes and omits risks associated with the use of Trisenox, presents misleading and unsubstantiated claims, and overstates the efficacy of the drug. Thus this website misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352 (a) & (n); 321(n). See 21 CFR 202.1(e)(3)(i); (e)(5)(i); (e)(6)(i), (vii); (e)(7)(i), (iii) & (viii). These violations are concerning from a public health perspective because they suggest that Trisenox is safer, more effective, and appropriate for use in a broader patient population than has been demonstrated by substantial evidence.

Background

According to the FDA-approved Trisenox product labeling (PI):

TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha [promyelocytic leukemia/retinoic acid receptor-alpha] gene expression.

The response rate of other acute myelogenous leukemia subtypes to TRISENOX has not been examined.

Trisenox is associated with a number of serious risks, as detailed in the BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the PI. These risks include APL differentiation syndrome, ECG abnormalities including QT prolongation and complete atrioventricular block, the need for electrocardiogram (ECG) and electrolyte monitoring, hyperleukocytosis, carcinogenesis, and

¹ www.trisenox.com/hcp. Last accessed on June 1, 2011

fetal harm. As such, patients' electrolyte, hematologic and coagulation profiles as well as ECGs must be closely monitored during therapy.

The clinical efficacy of Trisenox was evaluated in 40 patients with relapsed or refractory APL, previously treated with an anthracycline and a retinoid regimen. A complete response (CR), defined as the absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow \geq 30 days later, was observed in 28 patients (70%). Molecular response, as measured by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) conversions to no detection of the APL gene rearrangement, was demonstrated in 22 of 28 (79%) of patients who met the complete response criteria. At last follow-up, 27 of 40 patients were alive with a median follow-up time of 484 days (range 280 to 755) and 23 of 40 patients remained in complete response with a median follow-up time of 483 days (range 280 to 755).

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Several pages of the Trisenox website include the following claims about the indication for Trisenox:

- “TRISENOX: Standard of Care in Relapsed and Refractory APL^[2]”
- “Successful Therapy for Relapsed and Refractory APL”
- “Initiating TRISENOX Therapy for your Relapsed or Refractory APL Patients”

These claims, presented in colorful, bold font in a prominent location at the top of the web pages, are misleading because they suggest that Trisenox is approved to treat patients with any kind of relapsed or refractory APL when this is not the case. As stated in the PI, “Trisenox is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. The response rate of other acute myelogenous leukemia subtypes to Trisenox has not been examined.” Failure to include the important limitations to the Trisenox indication misleadingly suggests that the drug is useful for a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. We note that the full indication statement is included in small type on the bottom of each web page, beneath the list of references; however, this presentation does not mitigate the misleading implication created by the bolded headers.

Minimization of Risk

Promotional materials are misleading if they fail to present information related to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information on the effectiveness of the drug, taking into account all

² National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia — v.2.2011. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve this emphasis. The web pages prominently present efficacy claims and presentations in large, bold, and colorful font and graphics, on the top portion of each page. In contrast, information about the serious and potentially fatal risks associated with Trisenox, including the Boxed Warnings, are relegated to the bottom of the pages, after the list of references, and written in small gray font and in single-spaced paragraph format. This presentation misleadingly minimizes the serious risks associated with Trisenox because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness in the piece, taking into account all techniques apt to achieve emphasis. The overall effect of this presentation greatly undermines the communication of important risk information, minimizes the risks associated with Trisenox, and misleadingly suggests that the drug is safer than has been demonstrated.

The website further minimizes the risks of Trisenox by understating the few risk-related statements that are disclosed more prominently on the web pages. For example, the website includes claims and presentations such as the following (emphasis added):

- “TRISENOX works with minimal chemotherapy-related side effects.”
- “TRISENOX was generally well tolerated with manageable and reversible toxicities^[3,4]”
- “TRISENOX exhibited low rates of grades 3 and 4 myelosuppression^[4,5]”
- “There was no incidence of alopecia^[4,5]”
- “QT prolongation is an expected but **manageable** event^[6]”
- “APL Differentiation Syndrome – Effectively Treated With Dexamethasone”
- “Neuropathy symptoms were mild, grade 1 in the majority^[6]”
- “No significant hepatotoxicity was observed in the multicenter trial^[6]”

These claims are presented directly below the prominent headline “Safety Profile for TRISENOX.” Although this header suggests that a recitation of the most serious and most common risks will follow, the risk discussion is instead limited to claims, including those cited above, that emphasize the absence or the low incidence of selected side effects (e.g., alopecia, neuropathy, Grade 3/4 myelosuppression, hepatotoxicity, and other unspecified “chemotherapy-related side effects”). Information from the BOXED WARNING about the potential severity of the more serious and potentially fatal adverse events such as APL differentiation syndrome and QT prolongation, and the fact that serious (Grade 3 or 4) adverse events were common, is relegated to the bottom of the page, after the list of references, as discussed earlier in this letter. The totality of the presentation seriously minimizes the significance of these risks and misrepresents the safety profile of the drug.

³ Trisenox (arsenic trioxide) injection Prescribing Information. Frazer, PA: Cephalon, Inc.

⁴ Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol.* 2005;23:2396-2410.

⁵ Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol.* 2001;19:3852-3860.

⁶ Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol.* 2003;21:3609-3615.

In addition, characterizing the serious and significant risks associated with Trisenox as “manageable” and “generally well tolerated” also minimizes these risks and contributes to the overall suggestion that Trisenox is much safer than has been demonstrated by substantial evidence or substantial clinical experience.

The “About Trisenox” portion of the website makes the following statement:

- “Salvage therapy often involves high doses of cytotoxic chemotherapy, followed by either autologous or allogeneic transplantation. With this approach, these patients are exposed to, and some patients may die from, the toxic effects of chemotherapy, an important consideration in treating young or elderly patients. TRISENOX may fill the critical need for therapeutic options in treating relapsed or refractory APL.”

This statement misleadingly suggests that Trisenox is safer than chemotherapy by implying that Trisenox does not expose patients to cytotoxic adverse effects and is not associated with potentially fatal side effects, when this is not the case. As described in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections of the Trisenox PI, patients using this medication may experience severe side effects including hyperleukocytosis, APL differentiation syndrome, and QT prolongation, some of which can be fatal. The PI also states that serious adverse reactions (Grade 3 or 4) were common in patients taking Trisenox. As such, it is misleading to suggest that Trisenox is less toxic than other chemotherapy regimens when this has not been demonstrated by substantial evidence. Moreover, the suggestion that Trisenox should be considered before chemotherapy for young patients on the basis of this implied lower toxicity profile is also unsubstantiated. In fact, the PRECAUTIONS section of the Trisenox PI explicitly states that there is “limited data about the pediatric use of Trisenox,” and that “the safety and efficacy of Trisenox has not been studied in patients younger than four years of age.”

Overstatement of Efficacy

Promotional materials are misleading if they suggest that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The website presents efficacy rates that are inconsistent with the rates described in the approved PI for Trisenox and that overstate the efficacy of the drug. For example, the website claims that, in the pivotal study, 85% (34/40) of patients achieved a complete remission (CR) and 86% of patients who achieved a CR achieved a molecular remission (MR). These rates are much higher than the CR and MR rates reported in the PI (70% and 79%, respectively). With respect to the differing response rates, the website states:

“[P]ublished remission rate data below have been adjusted based on the revised definition of remission.^[7] [Footnote omitted.] The definition was revised by the International Working Group of investigators in Madrid, Spain, 2001. The definition given in the Prescribing Information, which requires a confirmatory bone marrow, is no longer current.^[8]”

⁷ Cheson BD, Bennett JM, Kopecky KJ, et al. revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21:4642-4649.

This presentation misleadingly overstates the efficacy of Trisenox because it is based on a retrospective re-calculation of the original efficacy results using new, less stringent criteria that make the response rates appear more favorable than those reported in the PI. As stated in the CLINICAL STUDIES section of the PI, CR was defined as the “. . . absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells **with a confirmatory bone marrow ≥ 30 days later**” (emphasis added). This means that the pre-specified endpoint used in the pivotal study stipulated that patients’ bone marrow had to be clear of leukemic cells for at least 30 days after the initial response was observed in order to meet the requirements for a CR (i.e., the response had to be maintained for at least 30 days). In contrast, the values presented on the Trisenox website reflect a retrospective re-calculation of these response rates to include patients that demonstrated the initial response, patients that demonstrated the 30 day response, and also patients whose response **did not** last for at least 30 days. Thus, the response rates reported on the website overstate the efficacy of Trisenox because the definition of CR differs from what was used in the pivotal study reviewed by FDA. Due to the fact that the MR rates are based on the number of patients achieving a CR, the MR rates presented on the Trisenox website are also misleading. While we note that the IWG criteria have indeed been revised since the time of the pivotal study, the approval of Trisenox was based on criteria established in the earlier IWG publication, and it is misleading to promote inflated response rates that are inconsistent with the efficacy findings from the pivotal clinical study for this drug as reflected in the PI.

The web page entitled “EFFICACY & SAFETY - EFFICACY” includes the following misleading statements and presentations related to overall survival (OS) and relapse-free survival (RFS):

- “TRISENOX delivered both high rates of remission and survival in this type of leukemia, giving hope to APL patients who have relapsed or who did not respond to their initial therapy.”
- “In clinical studies, TRISENOX[®] (arsenic trioxide) injection has shown . . . high rates of survival for patients with relapsed or refractory acute promyelocytic leukemia (APL).^[6]”
- “Over half of the patients in the US multicenter trial were alive at the 18-month follow-up, irrespective of the number of prior therapies and/or relapses.^[8]”
- Kaplan-Meier graphs that claim an estimated 66% OS and an estimated 56% RFS at 18 months after complete remission

These claims misleadingly overstate the efficacy of Trisenox and are not supported by substantial evidence or substantial clinical experience. Although the PI reports the number of patients alive at last follow-up, OS and RFS were not endpoints in the pivotal trial, and time-to-event analyses such as these are not interpretable in a single-arm clinical trial.⁸ Furthermore, the median follow-up time reported in the PI is 484 days, which is equivalent to 16 months, not 18 months. Therefore, claims and representations that state or suggest overall survival and recurrence-free survival as efficacy measures for Trisenox are not supported by substantial evidence and overstate the efficacy of this drug.

⁸ Pazdur, R. Endpoints for Assessing Drug Activity in Clinical Trials. *The Oncologist*, 2008;13(suppl 2):19-21

The web page entitled “PRESCRIBING CONSIDERATIONS – RT-PCR Testing” makes numerous misleading claims about molecular testing and its role in Trisenox therapy. For example, the web page states (emphasis original):

- **“1. The test is predictive of relapse and survival.**
A positive PML/RAR-alpha test after consolidation therapy reliably predicts subsequent hematologic relapse, whereas repeatedly negative results are associated with long-term survival in the majority of patients.^[9]”
- **“2. Test results can guide therapy, leading to improved patient outcomes.**
Patients who convert to a positive PCR can be salvaged early with chemotherapy prior to overt disease.^[9,10] This results in a significantly improved outcome compared to delaying treatment until morphologic evidence of relapse. It is anticipated that therapy at the time of molecular relapse will be associated with a lower mortality rate than that observed with reinduction of overt disease.^[9,10]”

These statements reference clinical studies performed in patients with APL who were treated with all-*trans* retinoic acid (ATRA) or various chemotherapy agents during induction, consolidation, or salvage therapy. These studies did not examine the ability of Trisenox to affect patient outcomes before or after a molecular response. This presentation misleadingly suggests that patients treated with Trisenox will also experience similar survival outcomes based on their molecular response status. While molecular response was assessed in the pivotal trial that led to the approval of Trisenox, the correlation between levels of PML/RAR-alpha transcript and the probability of relapse or relapse-free survival was not a pre-defined endpoint in this study. We are not aware of substantial evidence to support the implication that treatment with Trisenox will improve patient outcomes in patients who exhibit a molecular relapse.

Unsubstantiated Claims

Promotional materials are false or misleading if they contain favorable data or conclusions from nonclinical studies in a way that suggest clinical significance when in fact no such clinical significance has been demonstrated. The website presents an animated video titled “How Trisenox Works” that contains several claims related to the mechanisms of action of Trisenox. These include:

- “APL cells are uniquely sensitive to TRISENOX (arsenic trioxide).”
- “TRISENOX selectively targets and degrades the PML/RAR α protein. This releases the maturation block to enable partial differentiation.”

According to the PI, “The mechanism of action of TRISENOX is not completely understood. Arsenic trioxide causes morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells in vitro. Arsenic trioxide also causes

⁹ Lowenberg B, Griffin JD, Tallman MS. Acute myeloid leukemia and acute promyelocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2003;82-101.

¹⁰ Lo Coco F, Diverio D, Avvisati G, et al. Therapy of molecular relapse in acute promyelocytic leukemia. *Blood*. 1999;94: 2225-2229.

damage or degradation of the fusion protein PML/RAR-alpha." The PI does not indicate that Trisenox selectively targets and degrades the PML/RAR α protein in vivo, or that these functions confer a clinical benefit to patients with APL. The references cited describe in vitro studies performed in cell culture with differing concentrations of arsenic trioxide. These findings do not necessarily correlate to in vivo activity or support any claim of clinical benefit. We note that the animated video includes the statement "[t]he mechanisms of action of TRISENOX are not completely understood and are actively studied;" however, this statement is insufficient to mitigate the misleading implications made by the claims in the video.

Misleading Claims

The website makes multiple claims regarding the dosing and administration of Trisenox, including the following, or variants of the following:

- "Manageable dosing, sensitive to patient needs"
- "TRISENOX[®] (arsenic trioxide) injection offers manageable administration schedules for patients and healthcare providers[.]"

As outlined in the PI, during the induction phase, patients receive Trisenox by intravenous infusion every day for up to 60 days (2 months), with each infusion lasting anywhere from one to four hours. Frequent laboratory and ECG monitoring is also required. Thus, it is misleading to claim that dosing or administration of Trisenox is "manageable" given the fact that patients may be spending four hours a day, every day, for two months (60 days) being infused with this medication.

In addition, the "PRESCRIBING CONSIDERATIONS – Patient Management" web page claims that Trisenox has a "Manageable Monitoring Profile." This statement is followed by a list of monitoring recommendations for adverse reactions such as APL differentiation syndrome, cardiac abnormalities, and hyperleukocytosis. Instructions include the careful and frequent monitoring of patients for fever, sudden weight gain, musculoskeletal pain, fluid retention and/or dyspnea. Cardiac assessment via ECG is recommended at least weekly, with an increased frequency in the event of QT abnormalities. In addition, instructions are included regarding the administration of steroids and/or potassium sparing diuretics if needed, and information is provided regarding the target ranges for which serum potassium and magnesium levels should be maintained. Given the extent to which patients must be monitored, and the potential for serious adverse effects if they are not carefully monitored, it is misleading to characterize this complex regimen as "manageable" for patients or their providers.

Omission of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The website fails to include important risk concepts from the WARNINGS and PRECAUTIONS sections of the PI, including the warnings that Trisenox is a human carcinogen and may cause fetal harm when administered to a pregnant woman, and the precaution against using Trisenox while nursing.

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Trisenox in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352 (a) & (n); 321(n). See 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (vii); (e)(7)(i), (iii) & (viii).

DDMAC requests that Cephalon immediately cease the dissemination of violative promotional materials for Trisenox such as those described above. Please submit a written response to this letter on or before July 5, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Trisenox as of the date of this letter that contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 20151 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 Trisenox comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Karen Rulli, Ph.D.
Group Leader
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/

KAREN R RULLI
06/21/2011