DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Lisa Deluca, Ph.D.
Vice President, Regulatory Affairs
Celator Pharmaceuticals Inc.
200 Princeton South Corporate Center, Suite 180
Ewing, NJ 08628

RE: (b) (4)
CPX-351 (Cytarabine; Daunorubicin) Liposome Injection
MA 3

Dear Dr. Deluca:

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) has reviewed Celator Pharmaceuticals Inc.'s (Celator)[1] panel for its investigational product CPX-351 (Cytarabine; Daunorubicin) Liposome Injection (CPX-351) that appeared in the main exhibit hall at the American Society for Clinical Oncology (ASCO) Annual Meeting[2] (ASCO panel). This panel suggests, in a promotional context, that CPX-351, an investigational new drug, is safe and effective for the purposes for which it is being investigated or otherwise promotes the drug. As a result, CPX-351 is misbranded under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C) Act. Section 301(a) of the FD&C Act prohibits the distribution of a misbranded product into interstate commerce.

Background

CPX-351 is an investigational new drug for which there is no marketing authorization in the United States. (b) (4) CPX-351 (b) (4) CPX-351 was granted Breakthrough Therapy Designation (b) (4) for "treatment of adults with therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC)."

Misbranding of an Investigational Drug

Under section 502(f)(1) of the FD&C Act, a drug shall be deemed to be misbranded unless its labeling bears adequate directions for use. Under FDA regulations, adequate directions for use means directions under which the layman can use a drug safely and for the purposes for

[1] We note that subsequent to the ASCO annual meeting, Celator was acquired by Jazz Pharmaceuticals, Inc. on July 12, 2016. See http://investor.jazzpharma.com/phoenix.zhtml?c=210227&p=irol-sec&secCat01Enhanced.1_rs=21&secCat01Enhanced.1_rc=10 (last accessed on August 25, 2016).

[2] The ASCO Annual Meeting took place from June 3rd to 7th, 2016.

which it is intended. 21 CFR 201.5. Your panel describes the use of CPX-351 in treating cancer in general and newly diagnosed patients with high-risk AML specifically. These uses are ones for which a prescription would be needed because they require the supervision of a physician and, therefore, for which adequate directions for lay use cannot be written.

Although 21 CFR 201.115(b) provides an exemption from the adequate directions for use requirement in section 502(f)(1) of the FD&C Act if a new drug "complies with section 505(i) . . . and regulations thereunder," your investigational drug fails to do so. Among the requirements for the exemption for investigational drugs, 21 CFR 312.7 provides that "A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."

The CPX-351 ASCO panel makes claims that promote CPX-351 as safe and effective for the purposes for which it is being investigated or otherwise promote the drug, including the following:

- VYXEOS™
    - *In vitro* research has shown that a 5:1 ratio of cytarabine-daunorubicin delivers optimal anti-cancer activity.
    - A completed Phase 3 study demonstrated improved survival for VYXEOS™ compared to "7+3" in newly diagnosed patients with high-risk AML.

These claims suggest that CPX-351 (labeled on the ASCO panel only with the proprietary name "VYXEOS™") is effective for the treatment of cancer generally and newly diagnosed patients with high-risk AML specifically, when it has not been approved for these uses. The claims and presentation, including the use of a proprietary name without any accompanying identification of the investigational drug product, make conclusions that the drug has been proven to be "optimal" for the treatment of cancer and improves survival relative to "7+3" chemotherapy in newly diagnosed patients with high-risk AML, when FDA has not approved CPX-351 for any use. The cited references for this presentation include preclinical studies exploring the synergistic effects of various drug combinations at different ratios[3] and an analysis of the drug ratio-dependent synergy of cytarabine:daunorubicin[4] in various cell lines

[3] Tardi, P., Johnstone, S., Harasym, N., Xie, S., Harasym, T., Zisman, N., . . . Mayer, L. (2009). In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. Leukemia Research, 33 (1), 129-139. doi:10.1016/j.leukres.2008.06.028

[4] Mayer, L.D., Harasym, T.O., Tardi, P.G., Harasym, N., Shew, C.R., Johnstone, S.A., . . . Janoff, A.S. (2006). Ratiometric dosing of anticancer drug combinations: Controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. Molecular Cancer Therapeutics, 5 (7), 1854-1863. DOI: 10.1158/1535-7163.MCT-06-0118

and in mouse models. Neither of these studies support claims of efficacy in human patients with cancer generally or high-risk AML specifically. We note that the ASCO panel and the area surrounding the display did not include any information to indicate that CPX-351 is an investigational drug product that has not been approved for commercial distribution in the United States and that this panel appeared in the main exhibit hall at ASCO, alongside approved products.

Conclusion and Requested Action

For the reasons discussed above, CPX-351 is misbranded under section 502(f)(1) of the FD&C Act and in violation of section 301(a) of the FD&C Act. From a public health perspective, these claims and presentations are concerning because they include representations in a promotional context regarding the safety and efficacy of an investigational new drug that has not been approved by the FDA.

OPDP requests that Celator immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before September 9, 2016, stating whether you intend to comply and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.** A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 3 in addition to the (b) (4) in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds 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 CPX-351 comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Rachael Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Kathleen Davis, RN
Team Leader
Office of Prescription Drug Promotion

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/s/

RACHAEL E CONKLIN
08/25/2016

KATHLEEN T DAVIS
08/25/2016