



James Burrus, Director
HCC Regulatory Advertising & Promotion, J&J Intl.
On behalf of Janssen Biotech Products, L.P.
800 Ridgeview Drive, H2-3364
Horsham, Pennsylvania 19044-3607

RE: NDA # 050718
DOXIL[®] (doxorubicin HCl liposome injection) for Intravenous Infusion
MA # 422

Dear Mr. Burrus:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Doxil[®] healthcare professional website¹ section entitled "*For Recurrent Ovarian Cancer – Evaluating CA-125 Levels*" (08D10005C) (website). This website is misleading because it makes unsubstantiated claims associated with Doxil. Therefore, this website misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) & (n). See 21 CFR 202.1(e)(7)(i), (iii).

Background

Below are the indications and summary of the most serious and most common risks associated with the use of Doxil.² According to the FDA-approved product labeling (PI), Doxil is indicated, among other things, for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

Doxil is associated with a number of serious risks, as detailed in the PI. Specifically, Doxil has a Boxed Warning regarding cardiotoxicity, infusion reactions, myelosuppression, liver impairment, and accidental substitution of Doxil for doxorubicin HCl. Doxil is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil. The PI for Doxil also contains Warnings and Precautions regarding hand-foot syndrome, radiation recall reaction, fetal mortality, toxicity potentiation, and monitoring of complete blood counts, including platelets. The most common adverse reactions observed with Doxil include asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand and foot syndrome, rash, neutropenia, thrombocytopenia, and anemia.

¹ <http://www.doxil.com/hcp/for-recurrent-ovarian-cancer/evaluating-ca-125-levels>. Last accessed May 22, 2013.

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Unsubstantiated Claims

The section of the website entitled “*For Recurrent Ovarian Cancer – Evaluating CA-125 Levels*” contains five sub-sections titled: Clinical benefits and limitations, Correlation with disease progression, Correlation with response, Length of therapy, and Time to decline variations. The totality of the claims and presentations within these sections is misleading because it makes unsubstantiated claims associating levels of the CA-125 biomarker with clinical responses to Doxil therapy that have not been demonstrated by substantial evidence or substantial clinical experience. The references cited to support the claims on the website concerning CA-125 consist of retrospective evaluations of primary data performed in a post-hoc manner³, retrospective single institution chart reviews^{3,4}, a retrospective sub-group analysis⁵, and exploratory studies that cite the sponsor’s data on file⁶. Retrospective studies and institutional chart reviews do not constitute substantial evidence or substantial clinical experience to support the claims and presentations related to CA-125 contained on this website. When looking for differences between treatment groups, a study must be prospectively designed to look for these differences, and must be sufficiently powered. We acknowledge that the approved product label for Doxil includes CA-125 in a table of baseline demographic characteristics; however, the pivotal trials did not evaluate changes in CA-125 levels as a measure of response to therapy.

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Doxil in violation of the FD&C Act. 21 U.S.C. 352(a) & (n). See 21 CFR 202.1(e)(7)(i), (iii).

OPDP requests that Janssen immediately cease the dissemination of violative promotional materials for Doxil such as those described above. Please submit a written response to this letter on or before June 6, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Doxil that contain violations such as those described above, 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 Amundson Avenue, Beltsville, Maryland 20705-1266** or by facsimile at (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 #422 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

³ Coleman RL, Gordon A, Barter J, et al. Early changes in CA125 after treatment with pegylated liposomal doxorubicin or topotecan do not always reflect best response in recurrent ovarian cancer patients. *The Oncologist* 2007;12:72-78.

⁴ Sabbatini P, Mooney D, Iasonos A, et al. Early CA-125 fluctuations in patients with recurrent ovarian cancer receiving chemotherapy. *Int J Gynecol Cancer*. 2007;17(3):589-594.

⁵ Rustin GJS, Timmers P, Nelstrop A, et al. Comparison CA-125 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel versus cisplatin and cyclophosphamide. *J Clin Oncol*. 2006; 24(1):45-51.

⁶ Data on file, J&J Pharmaceutical Research & Development, 1999.

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

Sincerely,

{See appended electronic signature page}

Gina McKnight-Smith, PharmD, MBA, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Karen Rulli, Ph.D.
Team Leader
Office of Prescription Drug Promotion

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

/s/

GINA P MCKNIGHT-SMITH
05/22/2013

KAREN R RULLI
05/22/2013