DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Shari G. Kamber
Sr. Regulatory Specialist
US WorldMeds, LLC
4010 DuPont Circle
Suite L-07
Louisville, Kentucky 40207

RE: ANDA 078378
Revonto® (dantrolene sodium) for injection
MA # 44

Dear Ms. Kamber:

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 US WorldMeds, LLC.'s webpage, "About Revonto," which is part of a website[1] for Revonto® (dantrolene sodium) for injection (Revonto). This webpage is false and misleading because it presents unsubstantiated superiority claims and omits and minimizes important risk information for Revonto. Therefore, this webpage misbrands Revonto in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(5); (e)(6)(ii); (e)(7)(viii).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Revonto.[2] According to its FDA-approved product labeling (PI):

> **Revonto** (dantrolene sodium for injection) is indicated, along with appropriate supportive measures, for the management of the fulminant hypermetabolism of skeletal muscle characteristic of malignant hyperthermia crises in patients of all ages. **Revonto** should be administered by continuous rapid intravenous push as soon as the malignant hyperthermia reaction is recognized (i.e., tachycardia, tachypnea, central venous desaturation, hypercarbia, metabolic acidosis, skeletal muscle rigidity, increased utilization of anesthesia circuit carbon dioxide absorber, cyanosis and mottling of the skin, and, in many cases, fever). **Revonto** is also indicated preoperatively, and sometimes postoperatively, to prevent or attenuate the

[1] The "About Revonto" webpage at www.Revonto.com (last accessed November 8, 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.

development of clinical and laboratory signs of malignant hyperthermia in individuals judged to be malignant hyperthermia susceptible.

The PI contains Warnings pertaining to the requirements for the management of malignant hyperthermia crisis and states that the use of Revonto is not a substitute for previously known supportive measures in the management of malignant hyperthermia crisis. In addition, the PI contains Warnings regarding the monitoring of vital signs due to skeletal muscle weakness, including possible respiratory depression, requirements for patients who are judged to be susceptible to malignant hyperthermia, and monitoring for early clinical and metabolic signs. Furthermore, the PI contains Precautions regarding potential tissue necrosis and considerations for the use of mannitol for late renal complications of malignant hyperthermia. The ADVERSE REACTIONS section of the PI indicates that there have been reports of fatality in malignant hyperthermia crisis, despite treatment with I.V. dantrolene. Revonto has also been associated with loss of grip strength and weakness in the legs, drowsiness, dizziness, pulmonary edema, thrombophlebitis, tissue necrosis secondary to extravasation, urticaria and erythema, anaphylaxis, and injection site reactions.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The "About Revonto" webpage includes the following claims (emphasis in original):

- "**Revonto** offers a significant advancement in patient pharmacotherapy with its improved ease of reconstitution. This feature allows operating room teams to be better equipped to manage an MH crisis."
- "**Revonto** puts time on your side. . . ."

These claims misleadingly suggest that Revonto is superior to other treatments for malignant hyperthermia (MH). Specifically, these claims imply that Revonto's "improved ease of reconstitution" represents a significant advancement in patient pharmacotherapy that will ultimately lead to operating room teams being better equipped to manage a MH crisis. While we acknowledge that the PREPARATION section of the PI for Revonto indicates support for a reconstitution time of approximately 20 seconds (which was based on nonclinical in-vitro data), no evidence has been provided which shows that this directly correlates with an improvement in overall MH crisis management compared to other MH treatments. There are no references cited to support the claims and OPDP is not aware of any substantial evidence to support these implications. Therefore, these suggestions are unsubstantiated and misleading. Generally, claims of superiority must be supported by adequate and well-controlled, head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. If you have data to support these claims, please submit them to FDA for review.

Omission/Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The "About Revonto" webpage presents various efficacy claims for Revonto, but omits important risk information from the WARNINGS and the PRECAUTIONS sections of the PI. For example, the webpage fails to disclose risks such as monitoring of vital signs due to skeletal muscle weakness, including possible respiratory depression, requirements for patients who are judged to be susceptible to malignant hyperthermia, and monitoring for early clinical and metabolic signs. We note that there are links to the Full Prescribing Information on the webpage. However, this does not mitigate the misleading impression.

Promotional materials are also misleading if they fail to present information related to the 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 implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve this emphasis. This webpage prominently presents efficacy claims in large, bold, and colorful font and graphics, on the top portion of each page. In contrast, information about the risks associated with Revonto are relegated to the bottom of the page, below the site map, and written in single-spaced paragraph format. This presentation misleadingly minimizes the serious risks associated with Revonto because it fails to convey the 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 undermines the communication of important risk information, minimizes the risks associated with Revonto, and misleadingly suggests that the drug is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, the "About Revonto" webpage misbrands Revonto in violation of the FD&C Act, 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(5); (e)(6)(ii); (e)(7)(viii).

OPDP requests that US WorldMeds, LLC. immediately cease the dissemination of violative promotional materials for Revonto such as those described above. Please submit a written response to this letter on or before November 18, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Revonto 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 Ammendale Road, 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 # 44 in addition to the ANDA number 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 Revonto comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Eunice Chung-Davies, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel M. Skariah, Pharm.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/

EUNICE H CHUNG-DAVIES
11/08/2013

SAMUEL M SKARIAH
11/08/2013