DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Kimberly Skopitz, RAC
Director of Regulatory Affairs
Kowa Pharmaceuticals America, Inc.
530 Industrial Blvd.
Montgomery, AL 36117

RE: NDA 022363
LIVALO® (pitavastatin) tablet, for oral use
MA 609

Dear Ms. Skopitz:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer patient testimonial video montage (video) (LIV-MT-3158) posted on the website YouTube.com[1] for LIVALO® (pitavastatin) tablet, for oral use (Livalo) and submitted by Kowa Pharmaceuticals America, Inc. (Kowa) under cover of Form FDA 2253. This video makes false or misleading claims and/or representations about the risks associated with Livalo. Thus, the video misbrands Livalo within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a),(n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5); 202.1(e)(7)(viii). This video is concerning from a public health perspective because it creates a misleading impression regarding the side effects a patient may experience as a result of Livalo treatment and deemphasizes the risks associated with taking the drug. High cholesterol is a significant public health concern in the United States. Millions of Americans require medication to treat their high cholesterol. These treatments may involve serious risks and patients using these products, such as Livalo, should not be misled regarding the risks associated with their use. The video is especially concerning given that Livalo is associated with a number of serious risks, including the risk of skeletal muscle effects (e.g., myopathy and rhabdomylosis with acute renal failure secondary to myoglobinuria).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Livalo.[2] According to the FDA-approved product labeling (PI)[3]:

[1] This video is available on the internet at https://www.youtube.com/watch?v=ijlJPrJNU3g (last accessed 09/24/2019). It was also previously available on the internet at https://www.youtube.com/watch?v=h9loKRSQHJ4 (last accessed 07/10/2019).
[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.
[3] The version of the Livalo PI referred to in this letter is dated November 2016.

LIVALO® is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

Limitations of Use

Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.

The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.

LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

This product is associated with a number of serious risks. Livalo is contraindicated in patients with known hypersensitivity to any component of the product, active liver disease which may include unexplained persistent elevations of hepatic transaminase levels, co-administration with cyclosporine, and in patients who are pregnant or lactating. The PI for Livalo contains warnings and precautions regarding skeletal muscle effects, liver enzyme abnormalities, and endocrine function. The most common adverse reactions reported with Livalo were myalgia, back pain, diarrhea, constipation and pain in extremity.

False or Misleading Risk Presentations

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts 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 video includes patient testimonials such as the following (emphasis original):

Debbie D.

VOICEOVER (VO) (:04 - :06): “When I did the cholesterol panel, mine was extremely high.”
SUPER: **my** switch to **LIVALO®**
Debbie D. Switched statins 6 times due to side effects

VO (:45 - :48): “After I took LIVALO, I've had no pain and my cholesterol levels are down.”
SUPER: **my** switch to **LIVALO®**
Debbie D. Taking LIVALO for 3 years

Donnie W.

VO (:07 - :10): "My doctor recommended I start with a statin. We started with one, we had a lot of side effects."
SUPER: **my** switch to **LIVALO®**
Donnie W. Switched statins 4 times due to side effects

VO (:31 - :35): "LIVALO definitely made a positive impact in reducing my cholesterol and reduced side effects."
SUPER: **my** switch to **LIVALO®**
Donnie W. Taking LIVALO for 8 years

Robert M.

VO (:11 - :19): "The first medication I went on came with a lot of side effects, so I tried other ones after that and it was even worse."
SUPER: **my** switch to **LIVALO®**
Robert M. Switched statins 3 times due to side effects

VO (:36 - :44): "I wish I was put on LIVALO years ago, because I'm not having the side effects that I was having with the other statins."
SUPER: **my** switch to **LIVALO®**
Robert M. Taking LIVALO for 4 years

This presentation misleadingly suggests that Livalo is safer than its competitors by implying that patients switching to Livalo from other statins will experience a reduction in side effects compared to other statins, or no side effects at all. While the patient testimonials in this presentation may be an accurate reflection of these patients' own personal experiences with Livalo, the testimonials do not adequately support the suggestion in the presentation that other patients switching to Livalo from other statins will experience a similar reduction in side effects compared to other statins, or no side effects at all. We note that the video includes a SUPER during the patient testimonials stating, "Individual results may vary." However, this does not mitigate the misleading impression from the presentation. FDA is not aware of any data to support the suggestion that patients switching to Livalo from other statins will experience a reduction in side effects compared to other statins, or no side effects at all. If you have data to support this suggestion, please submit them to FDA for review.

The misleading suggestion about Livalo's side effects is especially concerning given that Livalo is associated with serious risks, several of which are the **same** as those associated with other statins. For example, **all statins**, including Livalo, are associated with the serious risk of skeletal muscle effects. Specifically, the WARNINGS AND PRECAUTIONS section of the PI for Livalo states the following regarding this risk, "**Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO**" (bolded emphasis original, underlined emphasis added).

The video is also misleading because it fails to present information relating to contraindications, warnings, precautions and adverse reactions for Livalo with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of Livalo. Specifically, benefit claims for Livalo are presented prominently as part of the patient testimonials, which encompass the majority of the screen throughout the video. However, the risk information is presented as scrolling text relegated to the bottom of the video during these patient testimonials. The patient testimonials also compete for the consumers' attention making it difficult for them to adequately process and comprehend the risk information. The overall effect of disclosing risk information in this manner as scrolling text relegated to the bottom of the video, along with the simultaneous presentation of the patient testimonials, undermines the communication of risk information and thereby misleadingly minimizes the risks associated with the use of Livalo.

Conclusion and Requested Action

For the reasons discussed above, the video misbrands Livalo within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a),(n); 321(n), 331(a). *See* 21 CFR 202.1(e)(5); 202.1(e)(7)(viii).

OPDP requests that Kowa immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before October 8, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Livalo that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

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 609 in addition to the NDA 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.

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

Sincerely,

{See appended electronic signature page}

Ankur Kalola, PharmD, RAC
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Melinda McLawhorn, PharmD, MPH BCPS, RAC
Team Leader
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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