DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Patricia Thomas, Senior Director
Global Regulatory Affairs, Advertising & Promotion
Takeda Pharmaceuticals USA, Inc.
40 Landsdowne Street
Cambridge, MA 02139

RE: NDA 217564
FRUZAQLA™ (fruquintinib) capsules, for oral use
MA 174

Dear Patricia Thomas:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, the "Quality of Life" webpage[1] (US-FRZ-0459v2.0)[2] (webpage) on the FRUZAQLA Consumer Website, for FRUZAQLA™ (fruquintinib) capsules, for oral use (Fruzaqla) submitted by Takeda Pharmaceuticals USA, Inc. (Takeda) under cover of Form FDA 2253. FDA has determined that the webpage is false or misleading. Thus, the webpage misbrands Fruzaqla and make the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The "Quality of Life" webpage, under the "FRUZAQLA Results" sub-navigation menu of the consumer website for Fruzaqla, includes the following representations (in pertinent part, emphasis original):

- "**IN THE FRESCO-2 STUDY FRUZAQLA HELPED PRESERVE CERTAIN QUALITY OF LIFE MEASURES**"
- **"A quality of life survey taken as part of the study showed more than 70% of people living with metastatic colorectal cancer (mCRC) taking FRUZAQLA + BSC reported their symptoms staying the same or taking longer to get worse compared with people taking placebo + BSC."**
- "People taking FRUZAQLA completed several questionnaires that used different scales to measure well-being.
    - These scales measure **the time it takes for symptoms of cancer to get worse**
    - The questions cover how well people lived their lives with the disease (in terms of physical, emotional, and social functioning) and how bad their symptoms were"

[1] The "Quality of Life" webpage is accessed from the "FRUZAQLA Results" sub-navigation menu of the website: https://www.fruzaqla.com/life-with-fruzaqla. (last accessed September 8, 2025).
[2] The material ID referenced on the "Quality of Life" webpage does not include "v2.0."

- "**Symptoms that took longer to get worse with FRUZAQLA + BSC vs placebo + BSC:**
  - **Emotional health**
  - **Social well-being**
  - **Tiredness (fatigue)**
  - **Nausea/vomiting**
  - **Trouble sleeping (insomnia)"**
- **"Symptoms that stayed the same with FRUZAQLA + BSC vs placebo + BSC:**
  - **Physical health**
  - **Brain functions (like memory or attention)**
  - **Pain"**

These representations create a misleading impression that Fruzaqla has demonstrated a benefit on the patient reported outcome (PRO) measure of global quality of life (QoL),[3,4] when this is not the case. The webpage defines QoL as the measure of "a person's physical and emotional well-being…[and] their ability to do activities or functions of daily living." However, there are significant limitations to the PRO analysis described in the FRESCO-2 clinical trial,[5] which preclude the drawing of such conclusions regarding Fruzaqla's benefits related to QoL.[6]

First, while PROs for global QoL were included in the FRESCO-2 study as secondary endpoints**,** there was no alpha-allocation. Since there was no alpha-allocation, and therefore, no specified false positive error rate, it is not known whether the QoL outcome data represent a false positive finding that occurred by chance alone. The PRO data are, therefore, considered exploratory (i.e., hypothesis generating), and they do not demonstrate that "Fruzaqla helped preserve certain quality of life measures." Additionally, the number of patients who received the treatment and were eligible to complete the PRO questionnaire at each subsequent cycle decreased due to attrition. Due to this attrition of patients over the course of the study, notably in the placebo arm, and the lack of multiplicity adjustments for any PRO endpoints, no comparisons between the treatment arm and the placebo arm, such as those in the webpage described above, can be made.

Second, the PRO assessments were not frequent enough to collect data to support the overall treatment QoL claims. Specifically, the PRO data from the QLQ-C30 and EQ-5D-5L questionnaires were collected at baseline and on the first day of each 28-day cycle, through the end of treatment. However, the QLQ-C30 questionnaire only included a seven-day recall

[3] European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). Global QoL is a summary score which measures a patient's perception of their overall health and/or overall quality of life in a given timeframe.
[4] Visual Analog Scale (VAS) is a component of the European Quality of Life Group 5-Dimension 5-Level questionnaires (EQ-5D-5L). The EQ VAS provides an alternative way to elicit an individual's rating of their own overall current health.
[5] FRESCO-2 Clinical Trial. See: https://clinicaltrials.gov/study/NCT04322539 (accessed September 9, 2025)
[6] We note that FDA encourages thoughtful inclusion of patient-reported outcomes in the design and conduct of clinical trials, where appropriate. See, for example, FDA's Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making; and the Draft Guidance for Industry: Core Patient-Reported Outcomes in Cancer Clinical Trials.

period (i.e., patients were only asked about their QoL in the past seven days), meaning that patients' perceptions of their QoL outside of that seven-day period likely were not captured. Furthermore, the seven-day recall period aligned with Day 22 to Day 28 (the days patients were off of treatment), and it did not capture the timeframe during which patients were on active treatment (Day 1 through Day 21 of each cycle). The EQ-5D-5L questionnaire only measured the patient's perception of his/her current health status at the moment that the questionnaire was provided and is not appropriate to assess QoL continually over each cycle. Therefore, due to the infrequency, the PRO assessments did not adequately account for concerns that QoL could fluctuate significantly throughout an entire 28-day treatment cycle.

Third, the PRO endpoint of global QoL can be confounded by non-treatment and non-disease related factors, such as non-cancer related health conditions (e.g., gout, migraines), personal difficulties (e.g., loss of a loved one), or acute events unrelated to cancer or treatment (e.g., a car accident). Because the study was not designed to account for these potential confounding factors, the outcome may reflect elements of a patient's QoL that are not directly related to the condition or the treatment being studied.

Fourth, PRO outcome endpoints that use time to deterioration in the analysis (i.e., amount of time for symptoms of disease to get worse or stay the same) are difficult to interpret. For example, patients who discontinued treatment (e.g., due to clinical worsening or unacceptable toxicity) have not been accounted for in the analysis of QoL. Once treatment was discontinued, such patients would not complete subsequent QoL assessments. Thus, the QoL worsening potentially caused by the clinical worsening would not be captured as meeting the definition of deterioration used in the study, which would result in skewed QoL results. We acknowledge the disclaimer on the webpage that states, "The surveys did not consider other factors that can impact how quickly or slowly symptoms of disease progress;" however, this does not correct or mitigate the overall misleading suggestion created by the presentation of the PRO representations.

Conclusion and Requested Action

For the reasons described above, the webpage misbrands Fruzaqla and makes the distribution of the drug in violation of the FD&C Act.

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Takeda take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above). Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Fruzaqla that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Fruzaqla.

If you believe that your product is not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to 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. Please refer to MA 174 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. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 5123 under NDA 217564. Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

George Tidmarsh, M.D., Ph.D.
Director
Center for Drug Evaluation and Research

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/

CARTER M BEACH
09/09/2025 05:19:14 PM
On behalf of George Tidmarsh, M.D., Ph.D