DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Colin Vechery, PharmD
Senior Global Program Manager, Regulatory Affairs
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One Health Plaza
East Hanover, NJ 07936-1080

RE: NDA 209092
KISQALI® (ribociclib) tablets, for oral use
MA 1344

Dear Dr. Vechery:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer broadcast advertisement (TV ad), "KISQALI_MBC_Long Live-Post Meno_US_11.22" for KISQALI® (ribociclib) tablets, for oral use (Kisqali) submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA 2253. The TV ad makes false or misleading representations about the efficacy of Kisqali. Thus, the TV ad misbrands Kisqali within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352 (n); 321(n); 331(a). 21 CFR 202.1(e)(5). This violation is particularly concerning because the overstated representations about Kisqali's efficacy could lead patients with advanced or metastatic breast cancer, an incurable condition whose treatment involves serious risks, to believe that Kisqali has been shown to be more effective in treating their condition and symptoms (e.g., with respect to overall survival and quality of life) than was actually demonstrated. Breast cancer is a serious public health concern in the United States with 297,790 new cases and 43,170 deaths estimated in 2023 in female patients.[1]

Background

Below are the indications and summary of the most serious and common risks associated with the use of Kisqali.[2] According to the INDICATIONS AND USAGE section of the FDA-approved Prescribing Information (PI):

> KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

[1] National Cancer Institute: Surveillance, Epidemiology, and End Results Program. See: https://seer.cancer.gov/statfacts/html/breast.html.

[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.

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

Kisqali is associated with a number of risks, and the PI includes warnings and precautions regarding interstitial lung disease/pneumonitis, severe cutaneous adverse reactions, QT interval prolongation, increased QT prolongation with concomitant use of tamoxifen, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity. The most commonly reported adverse reactions, including laboratory abnormalities, are leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, aspartate aminotransferase increased, gamma glutamyl transferase increased, alanine aminotransferase increased, infections, nausea, creatine increased, fatigue, platelets decreased, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, back pain, and glucose serum decreased.

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to benefits. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails 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 promotional communication.

The TV ad includes the following claims:

- Voice over (VO) frames eight and nine: “And KISQALI helps preserve quality of life so you’re not just living, you’re living well.”
- GRAPHIC frames eight and nine: “PRESERVES QUALITY OF LIFE”
- Superimposed text (SUPER) frame nine: “Quality of life was a secondary outcome measure of the trial. At a 26-month check-in, median time to worsening of at least 10% in quality of life score was 27.7 months with KISQALI + letrozole vs 27.6 months with placebo + letrozole. This analysis was not pre-planned to detect a false positive.”

The claims that Kisqali “preserves quality of life” and that patients taking the drug are “living well” create a misleading impression that Kisqali has demonstrated a benefit on the patient reported outcome (PRO)[3] measure of global quality of life[4] (QoL). In fact, we note significant

[3] A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.

[4] Global QoL (i.e., global health status) is a component of the European Organization for Research and Treatment of Cancer Quality of Life 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.

limitations to the PRO analysis described in the cited reference[5] (the MONALEESA-2 clinical trial) which preclude the drawing of such conclusions regarding benefits related to QoL.[6] Specifically, while PROs for health-related QoL were included in the trial 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 represents a false positive finding that occurred by chance alone. The PRO data in the cited references are, therefore, considered exploratory (i.e., hypothesis generating), and they do not, as you have claimed, demonstrate that Kisqali "helps preserve quality of life" or that it supports patients "living well."

The SUPER on frame nine presents 26-month check-in data from MONALEESA-2. The presentation of these data creates a misleading impression regarding the benefits of Kisqali because of the significant limitations to the PRO analysis performed in the MONALEESA-2 trial. First, you have not demonstrated that the PRO assessments were frequent enough to collect data to support the claims regarding QoL at the 26-month check-in. Specifically, in MONALEESA-2, global QoL was assessed only every eight weeks for the first 18 months and then every 12 weeks thereafter. You have not accounted for concerns that QoL could fluctuate significantly between these assessment points and that in the context of patients with advanced or metastatic breast cancer, variations in QoL across the assessment period may be greater than in the general population. There was no assessment to demonstrate the appropriateness of the intervals used to assess global QoL in this study and, additionally, the fact that the measurement tool included only a seven-day recall period (i.e., patients were only asked about their QoL in the past seven days) means that patients' perceptions of their QoL *outside* of that seven-day period likely were not captured. Second, these claims are based on the PRO endpoint of global QoL, which 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 loved one), and/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 disease and treatment being studied. Third, the study measured global QoL based on a 10% deterioration threshold with no confirmation of or justification for a 10% decrease in global health score being a meaningful deterioration specifically for patients with metastatic breast cancer who are undergoing treatment. Lastly, you have not demonstrated that the time to deterioration endpoint, as assessed in this trial, is appropriate for evaluating PROs. For example, you have not accounted for the potential that patients who experience a persistent decrease in QoL may stop taking the drug, and patients

[5] MONALEESA-2 Clinical Trial. See: https://clinicaltrials.gov/study/NCT01958021 (accessed January 17, 2024)

[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.

who have cancer progression may go on to another treatment. Such patients would not complete subsequent QoL assessments. This information regarding discontinuation or switching therapies would not be captured as meeting the definition of deterioration used in your study, which could have resulted in missing data that skewed the QoL results.

Finally, we note that the claim that Kisqali "helps preserve quality of life so . . . [patients] are living well" presupposes that patients are "living well" at trial baseline (i.e., before they begin treatment with Kisqali), which is not necessarily the case for patients living with metastatic breast cancer and who have received prior lines of therapy. The exploratory PRO analyses in MONALEESA-2 were not designed to capture the concept of "living well." Therefore, claims that patients who are taking Kisqali are "living well" are unsupported.

We note the statement in the SUPER on frame nine that "[t]his analysis was not pre-planned to detect a false positive"; however, this is not sufficient to mitigate the overall misleading impression created by the presentation of the PRO claims and data.

Frame seven of the TV ad includes prominent claims and presentations in the voice over and graphic that patients taking Kisqali will "live longer." Similar claims and presentations on frames 3, 4, 5, 6, 20, and 21 also focus on benefits of "living longer," "[l]ong live family time," "[l]ong live dreams," "long live you," "[l]ong live hugs and kisses," and "long live life" when patients are treated with Kisqali. The bottom of frames seven and eight include a SUPER that qualifies these claims, which states:

> Overall survival (OS) was a secondary end point of the trial. Overall survival (OS) is the length of time patients are alive from the start of treatment. At an 80-month check-in, median OS was 63.9 months for KISQALI + an NSAI [non-steroidal aromatase inhibitor] vs 51.4 months for an NSAI alone.

However, the presentation of the SUPER is undermined by multiple, competing presentational aspects that distract the viewer from material information about the benefits of Kisqali and, therefore, creates a misleading impression about the drug's efficacy. Specifically, the presentational aspects of the TV ad undermine the communication of material information regarding the overall survival data in the SUPER, which is needed to qualify the amount of time that patients can expect to "live longer" when treated with Kisqali plus an NSAI compared to an NSAI alone.

The SUPER that includes the material information for the "long live" and "live longer" claims in the ad presents 48 words in approximately 5 seconds, which translates to a reading speed of 576 words per minute (wpm). A recent review and meta-analysis found that the average silent reading rate for adults in English is 238 wpm for uninterrupted non-fiction reading, with most adults falling in a range of 175 to 300 wpm.[7] The number of words in the SUPER is

[7] Brysbaert, Marc. (2019). How many words do we read per minute? A review and meta-analysis of reading rate. 10.31234/osf.io/xynwg.

more than twice the number of words, on average, than an adult can read within 5 seconds. Moreover, during the 5-second period that the SUPER appears, there are multiple competing audio and visual presentations. The audio states, “KISQALI is a pill proven to help women live longer when taken with an aromatase inhibitor. And KISQALI helps preserve quality of life…”; music plays in the background; the visuals include a scene change starting with three women by a lake and then changing to two adults and two children on a staircase; and GRAPHICs with the claims “HELPS WOMEN LIVE LONGER” appear on frame seven and “PRESERVES QUALITY OF LIFE” appear on frame eight in a much larger type size and more central location on the screen than the SUPER with the material information.

Overall, by presenting compelling and attention-grabbing visuals as well as information in other competing modalities during the presentation of the SUPER, which itself is presented in a manner that would not allow most viewers to read, process, and comprehend the material information it presents, the TV ad misleadingly undermines the communication of material information about the drug’s efficacy.

Conclusion and Requested Action

For the reasons discussed above, the TV ad misbrands Kisqali within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352 (n); 321(n); 331(a). 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Novartis cease any violations of the FD&C Act. 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 Kisqali that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Kisqali.

If you believe that your products are 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 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. Please refer to MA 1344 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 6861 under NDA 209092. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Koung Lee, RPh, MSHS
Regulatory Review Officer
Division of Advertising & Promotion Review 1
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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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