DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Rajatavo Maitra
Senior Director, US Regulatory Operations
Ipsen Biopharmaceuticals, Inc.
1 Main Street, 7th Floor
Cambridge, MA 02142

RE: NDA 211723
TAZVERIK® (tazemetostat) tablets, for oral use
MA 572

Dear Rajatavo Maitra:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, the "Clinical Trial Results" webpage[1] (webpage) on the Tazverik follicular lymphoma (FL) Healthcare Provider Website (TAZ-US-000086) for TAZVERIK® (tazemetostat) tablets, for oral use (Tazverik) submitted by Ipsen Biopharmaceuticals, Inc. (Ipsen) under cover of Form FDA 2253. FDA also received a complaint regarding other promotional communications with representations similar to those discussed in this letter. FDA has determined that the webpage is false or misleading. Thus, the webpage misbrands Tazverik and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The "Clinical Trial Results" webpage, under the "Efficacy" sub-navigation menu of the website for Tazverik, contains two additional tabs titled, "Study Endpoints" and "Additional Data." The "Additional Data" tab includes the following efficacy representations regarding "changes in tumor volume" for the wild type (WT) and mutant type (MT) cohorts (in pertinent part, emphasis original, footnotes omitted):

- Presentation of a waterfall plot titled, "***Exploratory subanalysis of the primary endpoint: Changes in tumor volume for patients in the WT Cohort***" showing "Change in tumor volume from baseline (%)" on the y-axis and "Patients (n=48)" on the x-axis with the following claim:
    - "**71% (n=34/48) of EZH2 WT patients had a reduction in tumor volume**"

- Presentation of a waterfall plot titled, "***Exploratory subanalysis of the primary endpoint: Changes in tumor volume for patients in the MT cohort***" showing "Change in tumor volume from baseline (%)" on the y-axis and "Patients (n=42)" on the x-axis with the following claim:

[1] The "Clinical Trial Results" webpage is accessed from the "Efficacy" sub-navigation menu of the website: https://www.tazverik.com/hcp/follicular-lymphoma/clinical-trial-results (last accessed September 4, 2025).

- "**98% (n=41/42) of the EZH2 MT patients had a reduction in tumor volume**"

As provided on this webpage, the percentage of patients who had a reduction in tumor volume, i.e., disease control rate (DCR), was calculated as a composite of complete response (CR), partial response (PR), and stable disease (SD). This is further illustrated by the waterfall plots which contain dark gray bars under the line for 0% change in tumor volume from baseline (i.e., the 34/48 patients in the WT cohort and 41/42 patients in the MT cohort). The patients meeting the criteria for overall response (i.e., CR + PR), are noted by the dark gray bars that meet or surpass the orange dashed line indicating a 50% decrease in tumor volume. These representations of SD and DCR make this promotional communication misleading by suggesting that Tazverik improves DCR in patients with relapsed or refractory follicular lymphoma, when the study from which the presentations were drawn could not demonstrate this result. Tazverik was approved based on an effect shown on overall response rate (ORR) and duration of response (DOR) endpoints in Study E7438-G000-101, a single arm trial. As support for these representations, you cite data on file, [2] which includes results from Study E7438-G000-101. In Study E7438-G000-101, the endpoint of ORR was comprised only of PR + CR, as defined by the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria as assessed by Independent Review Committee.[3] Because Study E7438-G000-101 was designed as a single-arm trial, the study did not establish that the SD result was attributable to the effect of the drug or if the SD result reflects the natural history of the disease. Consequently, the DCR calculations (i.e., the percent of patients who had a reduction in tumor volume), which are based on a composite that includes SD data, are not supported by the data cited. An assessment of delay in time to disease progression in patients treated with Tazverik (i.e., an assessment of SD) would need to be based on the results of a randomized controlled trial.

We acknowledge that the following text appears under the bolded header, "LIMITATIONS" in conjunction with the waterfall plots (in pertinent part, footnote omitted):

- "Tumor volume reduction is not equivalent to overall response, which requires at least 50% volume reduction and no new lesions per IWG-NHL criteria."

- "Conclusions regarding the primary endpoint of the study should not be drawn from this representation of the data."

However, these disclosures of the study's limitations in this promotional communication do not correct or mitigate the misleading representations or suggestions of the presentation. As

[2] Data on File. Ipsen Biopharmaceuticals, Inc. 2021

[3] Response was measured using the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria, which defines response criteria for lymphoid malignancies as the following: Complete Response (CR): complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. Progressive Disease (PD): Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in sum of the product of the diameters of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Partial Response (PR): at least a 50% decrease in sum of the product of the diameters of up to six of the largest dominant nodes or nodal masses. No new sites of disease should be observed. Stable Disease (SD): A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for PD. See: Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007; 25(5):579-586.

discussed above, this promotional communication makes misleading representations or suggestions about the efficacy of Tazverik by presenting DCR calculations that include SD based on Study E7438-G000-101, which, as a single-arm trial, is not capable of supporting such representations or suggestions.

Conclusion and Requested Action

For the reasons described above, the webpage misbrands Tazverik 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 Ipsen 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 Tazverik that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Tazverik.

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 572 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 5485 under NDA 211723. 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 05:08:42 PM
On behalf of George Tidmarsh, M.D., Ph.D