DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Patricia Thomas
Senior Director Oncology Development
Takeda Pharmaceuticals America, Inc.
40 Landsdowne Street
Cambridge, MA 02139

RE: NDA 203469
ICLUSIG® (ponatinib) tablets, for oral use
MA 695

Dear Patricia Thomas:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communications, "T315I Mutation", "CML OPTIC Trial Efficacy" ("OPTIC Efficacy"), and "CML PACE Trial Efficacy" ("PACE Efficacy") webpages[1,2,3] on the Healthcare Provider Branded Website (USO-ICL-0558v4.0) (website) for ICLUSIG® (ponatinib) tablets, for oral use (Iclusig) submitted by Takeda Pharmaceuticals America, Inc. (Takeda) under cover of Form FDA 2253. FDA has determined that these webpages are false or misleading. Thus, these webpages misbrand Iclusig and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The "T315I Mutation" webpage includes the following presentation regarding Iclusig's effects on progression-free survival (PFS) and overall survival (OS) in the T315I-positive chronic myeloid leukemia (CML) patient population from the PACE trial (in pertinent part, bolded emphasis original, footnotes omitted):

- "**OS 66%** estimated at 5 years (95% CI: 51%, 78%)" depicted inside of a pie chart
- "**PFS 50%** estimated at 5 years (95% CI: 32%, 65%)" depicted inside of a pie chart

Similarly, the "OPTIC Efficacy" webpage includes claims in conjunction with efficacy presentation regarding PFS and OS. These claims and presentation are found under the "Estimated OS/PFS" navigation bar (in pertinent part, bolded emphasis original, footnotes omitted):

[1] The "T315I Mutation" webpage is accessed from the "Iclusig for CML" sub-navigation menu of the website: https://www.iclusig.com/hcp/cml/t315i-mutation (last accessed September 5, 2025).
[2] The "CML OPTIC Trial Efficacy" webpage is accessed from the "Efficacy" sub-navigation menu of the website: https://www.iclusig.com/hcp/efficacy/cml-optic-trial (last accessed September 5, 2025).
[3] The "CML PACE Trial Efficacy" webpage is accessed from the "Efficacy" sub-navigation menu of the website: https://www.iclusig.com/hcp/efficacy/cml-pace-trial (last accessed September 5, 2025).

- **"ESTIMATED OS AND PFS DATA FOR OPTIC WITH A RESPONSE-BASED DOSING STRATEGY"**
    - Presentation of a Kaplan-Meier estimate graph titled, "OS," showing "Probability of OS" on the y-axis and "Time, Months" on the x-axis
    - Presentation of a Kaplan-Meier estimate graph titled, "PFS," showing "Probability of PFS" on the y-axis and "Time, Months" on the x-axis

Furthermore, the "PACE Efficacy" webpage includes claims in conjunction with efficacy presentations regarding PFS and OS for the total chronic phase (CP)-CML patient population, those resistant or intolerant to a prior kinase inhibitor, and those with T315I mutation. These claims and presentation are found under the "Estimated OS/PFS" navigation bar (in pertinent part, bolded emphasis original, footnotes omitted):

- **"CONSISTENT ESTIMATED OS/PFS THROUGH YEAR 5, EVEN IN PATIENTS WITH A T315I MUTATION"**
    - Presentation of a Kaplan-Meier estimate graph titled "OS," showing "Probability of OS (%)" on the y-axis and "Time, Months" on the x-axis
    - Presentation of a Kaplan-Meier estimate graph titled "PFS," showing "Probability of PFS (%)" on the y-axis and "Time, Months" on the x-axis

    - "**Estimated OS at 5 years**"
        - "**Total CP-CML patient population: 73% (95% CI: 66, 79)**" depicted next to a pie chart that includes shading to show the 73% OS
        - "**Resistant/intolerant: 76% (95% CI: 68, 82)**"
        - "**T315I: 66% (95% CI: 51, 78)**"

    - "**Estimated PFS at 5 years**"
        - "**Total CP-CML patient population: 53% (95% CI: 45, 60)**" depicted next to a pie chart that includes shading to show the 53% PFS
        - "**Resistant/intolerant: 52% (95% CI: 46, 62)**"
        - "**T315I: 50% (95% CI: 32, 65)**"

    - "Median OS and PFS were not reached"

As references for these representations, you cite two publications by Cortes et al[4,5], which include results from the PACE and OPTIC trials. However, these parts of the webpages misbrand Iclusig by misleadingly suggesting that PACE and OPTIC trials provided interpretable results regarding the effects of Iclusig on PFS and OS endpoints, even though the designs of the PACE and OPTIC studies were not capable of establishing improvement

[4] Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre PD, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Muller MC, Gambacorti-Passerini C, Lustgarten S, Rivera VM, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes TP, Shah NP, and Kantarjian HM, 2018, Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial, Blood, 132(4):393-404.

[5] Cortes J, Apperley J, Lomaia E, Moiraghi B, Undurraga Sutton M, Pavlovsky C, Chuah C, Sacha T, Lipton JH, Schiffer CA, McCloskey J, Hochhaus A, Rousselot P, Rosti G, de Lavallade H, Turkina A, Rojas C, Arthur CK, Maness L, Talpaz M, Mauro M, Hall T, Lu V, Srivastava S, and Deininger M, 2021, Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial, Blood, 138(21):2042-2050.

on time-to-event efficacy endpoints, such as OS or PFS. Specifically, because PACE and OPTIC were designed as single-arm trials (i.e., with no comparator arm), and PFS and OS are time-to-event efficacy endpoints, the reported PFS and OS results are uninterpretable; absent of an appropriate comparator, it is not possible to determine if the observed effect is attributable to Iclusig or to other factors, such as the natural history of the disease.

Additionally, the "T315I Mutation" webpage includes the following (in pertinent part, bolded emphasis original, underlined emphasis added, footnote omitted):

- "**NCCN CATEGORY 2A <u>PREFERRED</u> RECOMMENDATION**"
- "**Ponatinib is the <u>preferred</u> treatment option for patients with a T315I mutation in any phase.**"

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for CML V.2.2024[6] is cited to support these claims. These claims misleadingly represent that the current NCCN Guidelines® state that Iclusig is the preferred treatment option for the treatment of CML in patients with a T315I mutation in any phase when this is not the case. In fact, the recommendations made in the most current version of these NCCN Guidelines® (V.3.2025[7]), state (underlined emphasis added) "Ponatinib is <u>a treatment option</u> for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML)." We acknowledge that these claims are consistent with the reference cited; however, this is not sufficient to mitigate this misleading impression.

Conclusion and Requested Action

For the reasons described above, these webpages misbrand Iclusig and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (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 Iclusig that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Iclusig.

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.

[6] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.2.2024. National Comprehensive Cancer Network, 2024. Accessed September 5, 2025.
[7] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myeloid Leukemia V.3.2025. National Comprehensive Cancer Network, 2024. Accessed September 5, 2025.

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 695 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 5028 under NDA 203469. 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 05:10:33 PM
On behalf of George Tidmarsh, M.D., Ph.D