DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Lisa Drucker, PharmD, MBA
Director, Regulatory Affairs - Oncology
Novartis Pharmaceuticals Corporation
180 Park Avenue, Building 104 / 3K30
Florham Park, NJ 07932

RE: NDA # 022068
Tasigna® (nilotinib) Capsules
MACMIS # 18870

Dear Dr. Drucker:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Novartis Pharmaceuticals Corporation's (Novartis) U.S. website for Tasigna® (nilotinib) 200 mg Capsules (Tasigna). This website contains a "Facebook Share" social media widget[1] that generates Novartis-created information for Tasigna[2] that can be shared with Facebook users (i.e., "shared content").[3] The shared content is misleading because it makes representations about the efficacy of Tasigna but fails to communicate **any** risk information associated with the use of this drug. In addition, the shared content inadequately communicates Tasigna's FDA-approved indication and implies superiority over other products. Thus, the shared content for Tasigna misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 202.1(e)(3)(i), (ii) & (e)(6)(i). Furthermore, these materials were neither submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550, nor submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 314.81(b)(3)(i).

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[1] Facebook Share is a way for users of Facebook to share articles, pages, video, or flash content of a site with other Facebook users. Over two billion pieces of content are shared each week through Facebook. With two clicks, visitors to a website can share any page of that website through Facebook by generating a link to the page, along with a thumbnail image and a brief description (i.e., "shared content") that will appear on the users' profiles and, depending on privacy settings, in the home page stream of all of the users' friends. Each time a link is shared by one user, potentially hundreds of new people may see and/or click through on the link.
[http://wiki.developers.facebook.com/index.php/Connect/Using_Facebook_Share. Accessed May 26, 2010.]

[2] As described below, the shared content for Tasigna generated by the Facebook Share social media widget was developed by Novartis and, although Facebook users can add additional comments that are displayed separately from the Tasigna information, the shared content cannot be modified by Facebook users who use this Facebook Share social media widget.

[3] We also note multiple Tasigna web pages contain widgets that allow users to share content via other social media applications offered via the "Share This" tool (http://sharethis.com). Some of the content available to share through these other social media applications raise similar issues to those discussed in this letter.

Background

According to its FDA-approved product labeling (PI),[4] Tasigna is "indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive [Ph+] chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib." FDA approved Tasigna for second line treatment of chronic or accelerated phase Ph+ CML on October 29, 2007, under 21 CFR 314 Subpart H regulations. The Indications and Usage section of the PI includes important limitations for Tasigna's use, including the fact that the effectiveness of Tasigna is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit such as improvement in disease-related symptoms or increased survival.

Tasigna is associated with a number of serious risks, as detailed in the Boxed Warnings, Contraindications, Warnings and Precautions, and Adverse Reactions sections of the PI. These risks include QT prolongation and sudden deaths, severe myelosuppression, elevated serum lipase, liver function abnormalities, electrolyte abnormalities, hepatic impairment, and use in pregnancy. Patients must be monitored with multiple laboratory tests during Tasigna use. Tasigna is associated with significant drug interactions and food effects that can lead to serious and potentially fatal consequences. In an attempt to minimize the occurrence of QT prolongation, a serious safety risk which may cause ventricular arrhythmias and death, FDA required a Risk Evaluation and Mitigation Strategy (REMS) for Tasigna to educate physicians and patients about the risks of the drug and about proper dosing strategies to mitigate serious adverse events.

Omission of Risk

Promotional materials, other than reminder pieces, which include the name of the drug product but do not include indications or other representations or suggestions relative to the drug product (see 21 CFR 200.200, 201.100(f), 202.1(e)(2)(i)), are required to disclose risk and other information about the drug. Such materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The healthcare professional and consumer-directed web pages of the U.S. Tasigna product website each contain a "Facebook Share" widget. Clicking on the widget takes users to a separate web page with Novartis-created content about Tasigna. Users may add additional comments, which are displayed separately from the Tasigna information, but users cannot edit the original text, URL or graphics for Tasigna created by Novartis. Clicking on the "share" option allows users to post the shared content for Tasigna on their Facebook profile walls and to share this same information with other Facebook users (i.e., the user's Friends, Friends of Friends, or Everyone) via newsfeeds or wall postings. The shared content for Tasigna may also be sent separately as a message to other specified Facebook users.

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[4] At the time this shared content was originally disseminated, the approved PI (and the version referred to within this letter) for Tasigna was the version dated August, 2009. The current PI, approved June 17, 2010, reflects approval of a new indication for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. As stated in the revised Indications and Usage section of the current PI, the effectiveness of Tasigna for the new indication "is based on major molecular response and cytogenic response rates . . . . The study is ongoing and further data will be required to determine long-term outcome."

The posted shared content available from several of the Tasigna product web pages makes representations or suggestions about the efficacy of Tasigna, but fails to communicate **any** risk information. For example, the posted shared content from the "Facebook Share" widget on the healthcare professional home page for Tasigna consists of the following claims:

- **Home – Tasigna (nilotinib) 200 mg capsules**
  http://www.us.tasigna.com

  Tasigna (nilotinib) is used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)

Similarly, the posted shared content from the "Facebook Share" widget on one of the consumer-directed web pages consists of the following claims:

- **Treating Your Ph+ CML with Tasigna | Tasigna (nilotinib) 200-mg capsules**
  www.us.tasigna.com

  In addition to taking Tasigna (nilotinib) 200-mg capsules, talking to your doctor and receiving health tips can help you treat your CML.

Other pages on both the healthcare professional and consumer sections of the U.S. Tasigna website also offer shareable content via the "Facebook Share" widget that consists of similar claims and presentations. By failing to disclose any risk information for Tasigna, the shared content misleadingly suggests that Tasigna is safer than has been demonstrated by substantial evidence or substantial clinical experience. This omission of risk information is particularly concerning given the fact that Tasigna has a Boxed Warning and a REMS program. We note that the shared content contains a hyperlink to various Tasigna product websites, which do contain risk information. However, the inclusion of such a hyperlink is insufficient to mitigate the misleading omission of risk information from these promotional materials. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any claims made about the drug.

Broadening of Indication

In several instances, the shared content posted via the "Facebook Share" widget includes a very brief statement about what Tasigna treats that misleadingly broadens the indication for this drug. Several examples include:

- **Home – Tasigna (nilotinib) 200 mg capsules**
  www.us.tasigna.com

  Tasigna (nilotinib) is used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)

- **Treating Your Ph+ CML with Tasigna | Tasigna (nilotinib) 200-mg capsules**
  www.us.tasigna.com

  In addition to taking Tasigna (nilotinib) 200-mg capsules, talking to your doctor and receiving health tips can help you treat your CML.

- **For Your Ph+ CML Patients - Tasigna (nilotinib) 200mg capsules**
  http://www.us.tasigna.com
  More information to Support your Patients

These statements of Tasigna's indication are incomplete, and misleadingly imply that the drug is approved to treat all individuals with Ph+ CML, when this is not the case. At the time this shared content was originally disseminated, Tasigna was only approved as a second-line option after failure or intolerance to prior therapy that included imatinib. Furthermore, Tasigna is only approved for use in patients with Ph+ CML in the chronic or accelerated phases. Tasigna was not approved as a first-line therapy option in any setting when this shared content was originally disseminated, and it is not approved for patients with CML in blast crisis. While we note that Tasigna was recently approved for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase, the above content was disseminated before this new indication was approved. Moreover, the statements above broaden even the newly approved indication for Tasigna (i.e., Tasigna is still not approved to treat all individuals with Ph+ CML). This shared content also fails to disclose other important limitations to Tasigna's use; i.e., that its effectiveness is based on hematologic and cytogenetic response rates and there are no controlled trials demonstrating a clinical benefit, such as improvement in symptoms or increased survival. Therefore, it misleadingly broadens the indication for Tasigna by suggesting that it is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Superiority Claims / Overstatement of Efficacy

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug when this superiority has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The shared content from the "Facebook Share" widget on one of the consumer-directed web pages makes the following claims, which compare the efficacy of Tasigna to other tyrosine kinase inhibitors for the treatment of CML (emphasis added):

- **CML (Chronic Myeloid Leukemia)Treatment – Find out if Tasigna is Right for You | Tasigna (nilotinib**
  www.us.tasigna.com

  Tasigna (nilotinib) 200-mg capsules from Novartis is a **next-generation** treatment for Ph+ Chronic Myeloid Leukemia in adult patients in chronic or accelerated phase who are resistant to Gleevec.

Referring to Tasigna as a "next generation" treatment misleadingly suggests superiority over other tyrosine kinase inhibitors approved for use in the treatment of Ph+ CML when this advantage has not been demonstrated by substantial evidence or substantial clinical

experience. DDMAC has previously provided written advisory comments to Novartis about the misleading implications of the phrase "next generation" when referring to Tasigna.[5]

Failure to Submit

FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of a drug product approved under Subpart H regulations at least 30 days prior to the intended time of initial dissemination per 21 CFR 314.550. Moreover, FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. Although the website content was submitted to FDA pursuant to 21 CFR 314.550 and 21 CFR 314.81, the shared content was not submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550, and was not submitted to FDA under cover of Form FDA-2253 at the time of initial publication, as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the shared content from the "Facebook Share" social media widget on the Tasigna U.S. websites misbrands Tasigna in violation of the Act and FDA regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 202.1(e)(3)(i), (ii) & (e)(6)(i).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Tasigna such as those described above. Please submit a written response to this letter on or before August 12, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Tasigna that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 18870 in addition to the NDA number. We remind you that only written communications are considered official.

[5] See DDMAC advisory letters dated August 14, 2008 and January 25, 2010.

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

Sincerely,

{See appended electronic signature page}

Karen R. Rulli, Ph.D.
Acting Group Leader
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22068	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	TASIGNA (NILOTINIB, AMN107)

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/s/

KAREN R RULLI
07/29/2010