DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022405/S-009

SUPPLEMENT APPROVAL
REMS ASSESSMENT ACKNOWLEDGMENT

Genzyme Corporation
Attention: Barbara Pizza
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Pizza:

Please refer to your Supplemental New Drug Application (sNDA) dated April 3, 2015, received April 3, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CAPRELSA (vandetanib) tablets, 100 mg and 300 mg.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS). Additionally, this sNDA contains your 48 month assessment of the Caprelsa REMS. The reporting period for this assessment is February 7, 2014 to February 6, 2015.

After consultation between the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND), we found both the 48 month assessment to be complete and that the REMS was meeting its goals.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Caprelsa (vandetanib) was originally approved on April 6, 2011, and the most recent modification was approved on November 27, 2013. The REMS consists of a Medication Guide, communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of removal of the Medication Guide, removal of the communication plan, addition of the *Caprelsa REMS Patient Brochure*, additional changes to the REMS Document including updates to the goals and change in ownership, and minor clarifying edits to the following REMS materials to accurately explain the enrollment process and prioritize the presentation of risk information: Caprelsa REMS *Prescriber Training Slide Deck*, *Prescriber Training Pamphlet*, *Prescriber Training Questions*, REMS website screen shots, and *Pharmacy Enrollment Form*.

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication

Guide as an element of the approved REMS to ensure that the benefits of Caprelsa (vandetanib) outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Communication Plan: Because the assessment demonstrates that the communication plan has met its goals, we have determined that it is no longer necessary to include it as an element of the approved REMS to ensure that the benefits of the drug outweigh the risks.

Your proposed modified REMS, submitted on April 3, 2015, amended, and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on April 6, 2011.

The revised REMS assessment plan must include, but is not limited to, the following:

A. Prescriber Certification:

   i. The number of prescribers accessing the training program (during the reporting period and cumulative).

   ii. The number of prescribers who complete the training program but do not complete enrollment (during the reporting period and cumulative).

   iii. The number of prescribers enrolled in the CAPRELSA REMS (during the reporting period and cumulative) and stratified by prescriber specialty.

      - A summary of the method prescribers used to enroll (online or telephone).
      - Proportion of prescribers that correctly answer each training program question and stratified by specialty.

   iv. The number of enrolled prescribers actively prescribing CAPRELSA during the reporting period (i.e., have written at least one prescription in the in the time period).

   v. The number of CAPRELSA prescriptions from prescribers who were not enrolled.

   vi. The number of CAPRELSA prescriptions from non-enrolled prescribers that were filled and the actions to address these instances of non-compliance with the REMS program.

B. Pharmacy Certification and distributors:

   i. The number of pharmacies enrolled (during the reporting period and cumulative).

   ii. The number of pharmacies ordered/dispensed CAPRELSA who were not enrolled.

   iii. The number of distributors of CAPRELSA.

C. QT prolongation, Torsades de pointes, and sudden death:

   i. An analysis of the U.S. post-marketing cases for QT prolongation, Torsades de pointes, or sudden death reported in association with CAPRELSA to Sanofi Genzyme (during the reporting period and cumulative) with attention to possible factors that prolonged the QTc (e.g., interacting medication initiated, change in patient's health status, failure to adjust dose, lack of ECG monitoring, lack of electrolyte monitoring, etc.).

   ii. The number of patients who were dispensed CAPRELSA (during the reporting period and cumulative).

D. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

This assessment should include:

A. An evaluation of how the benefit-risk profile will or will not change with the new indication;

B. A determination of the implications of a change in the benefit-risk profile for the current REMS;

C. *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

D. *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

E. *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

F. *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system;

and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022405 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022405 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022405/S-XXX
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022405/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022405/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022405/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 022405

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Jeffery Summers, M.D.
Deputy Director for Safety
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
- Caprelsa REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFERY L SUMMERS
05/16/2017