DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103172/S-5259

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Itrat Harrold, PhD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Harrold:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received August 29, 2017 and your amendments, submitted under section 351(a)) of the Public Health Service Act for Activase (alteplase) lyophilized powder for Injection.

This Prior Approval supplemental biologics application proposes labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text).

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added/deleted:
    - Increases the risk of bleeding. Avoid intramuscular injections. Monitor for bleeding. If serious bleeding occurs, discontinue Activase. (5.1)
    - Monitor patients during and for several hours after infusion for ~~orolingual angioedema.~~ hypersensitivity. If ~~angioedema develops~~ signs of hypersensitivity develop, discontinue Activase. (5.2)
    - ~~Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents. (5.3)~~
    - Consider the risk of reembolization from the lysis of underlying deep venous thrombi in patients with pulmonary embolism. (5.3)
    - Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents. (5.4)

2. Under **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was deleted from the second bullet:

    - Concomitant angiotensin converting enzyme inhibitors may increase the risk of ~~orolingual~~ angioedema. (7)

3. In **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS**, the following text was deleted:

~~Pregnancy: Activase is embryocidal in rabbits. (8.1)~~

4. Under **WARNINGS AND PRECAUTIONS,** the following text was added to the 5th paragraph under 5.1 Bleeding and the following bullet was deleted from the same section:

If serious bleeding occurs, terminate the Activase infusion~~. and consider appropriate symptomatic treatment.~~

- ~~likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation~~

5. Under **WARNINGS AND PRECAUTIONS,** the following sections were revised:

5.1 Bleeding

Activase can cause significant, sometimes fatal, internal or external bleeding, especially at arterial and venous puncture sites. Avoid intramuscular injections and trauma to the patient while on Activase. Perform venipunctures carefully and only as required. To minimize bleeding from noncompressible sites, avoid internal jugular and subclavian venous punctures. If an arterial puncture is necessary during Activase infusion, use an upper extremity vessel that is accessible to manual compression, apply pressure for at least 30 minutes, and monitor the puncture site closely.

Because of the higher risk of intracranial hemorrhage in patients treated for acute ischemic stroke, limit treatment to facilities that can provide timely access to appropriate evaluation and management of intracranial hemorrhage.

Fatal cases of hemorrhage associated with traumatic intubation in patients administered Activase have been reported.

Aspirin and heparin have been administered concomitantly with and following infusions of Activase in the management of acute myocardial infarction and pulmonary embolism, but the concomitant administration of heparin and aspirin with and following infusions of Activase for the treatment of acute ischemic stroke during the first 24 hours after symptom onset has not been investigated. Because heparin, aspirin, or Activase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of Activase, while patients are still receiving anticoagulant therapy.

If serious bleeding occurs, terminate the Activase infusion and treat appropriately. In the following conditions, the risks of bleeding with Activase therapy for all approved indications are increased and should be weighed against the anticipated benefits:

- Recent major surgery or procedure, (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels)
- Cerebrovascular disease
- Recent intracranial hemorrhage
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP above 175 mm Hg or diastolic BP above 110 mm Hg
- ~~High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation~~
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Significant hepatic dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site

Advanced age [see Use in Specific Populations (8.5)]

- Patients currently receiving anticoagulants (e.g., warfarin sodium)

Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

5.2 ~~Orolingual~~ Hypersensitivity

Hypersensitivity, including urticarial / anaphylactic reactions have been reported after administration of Activase (e.g., laryngeal edema, rash and shock). Rare fatal outcome for hypersensitivity was reported. Angioedema ~~Orolingual~~ Angioedema has been observed during and up to 2 hours after Activase infusion in patients treated for acute ischemic stroke and acute myocardial infarction *[see*

Adverse Reactions (6.1)]. In many cases, patients received concomitant angiotensin converting enzyme inhibitors *[see Drug Interactions (7)]*.

Monitor patients treated with Activase during and for several hours after infusion for ~~orolingual angioedema.~~ hypersensitivity. If signs of hypersensitivity occur, e.g. anaphylactoid reaction or angioedema develops, discontinue the Activase infusion and promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, epinephrine).

5.3 Thromboembolism

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with high likelihood of left heart thrombus, such as patients with mitral stenosis or atrial fibrillation. Activase has not been shown to adequately treat underlying deep vein thrombosis in patients with PE. Consider the possible risk of reembolization due to the lysis of underlying deep venous thrombi in this setting.

~~5.4 Reembolization of Deep Venous Thrombi during Treatment for Acute Massive Pulmonary Embolism~~

~~Activase has not been shown to treat adequately underlying deep vein thrombosis in patients with PE. Consider the possible risk of reembolization due to the lysis of underlying deep venous thrombi in this setting.~~

6. Under **ADVERSE REACTIONS**, the following text was added/deleted from the bulleted list:

The following adverse reactions are discussed in greater detail in the other sections of the label:

- Bleeding *[see Contraindications (4), Warnings and Precautions (5.1)]*
- ~~Orolingual Angioedema~~ Hypersensitivity *[see Warnings and Precautions (5.2)]*
- Thromboembolism *[see Warnings and Precautions (5.3)]*
- Cholesterol Embolization *[see Warnings and Precautions (5.4)]*
- ~~Reembolization of Deep Venous Thrombi during Treatment for Acute Massive Pulmonary Embolism [*see Warnings and Precautions (5.4)].*~~ *]*

7. Under **ADVERSE REACTIONS/Clinical Trials Experience**, the last paragraph in the section was deleted:

> ~~*Allergic Reactions*~~
> ~~Allergic-type reactions, e.g., anaphylactoid reaction, laryngeal edema, orolingual angioedema, rash, and urticaria have been reported. When such reactions occur, they usually respond to conventional therapy.~~

8. Under **ADVERSE REACTIONS/Post Marketing Experience,** the word "embolism" was added to the second paragraph.

9. Under **DRUG INTERACTIONS,** the word "orolingual was deleted from the second paragraph.

10. Under **USE IN SPECIFIC POPULATIONS,** the following text was added/deleted:

> **8.1 Pregnancy**
>
> ~~Pregnancy Category C~~
>
> ~~Activase~~Risk Summary
>
> Published studies and case reports on alteplase use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Alteplase is embryocidal in rabbits when intravenously administered during organogenesis at the clinical exposure for AMI, but no maternal or fetal toxicity was evident at lower exposure in pregnant rats or rabbits (see Data).
>
> All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
>
> Clinical Considerations
>
> Maternal Adverse Reactions
>
> The most common complication of thrombolytic therapy is bleeding. Pregnancy may increase this risk [see Warnings and Precautions (5.1)].

Data

Animal Data

Alteplase is embryocidal in rabbits when administered intravenously during organogenesis in doses ~~of~~(3 mg/kg) ~~approximately two times (3 mg/kg)~~ equal to the human exposure (based on AUC) at the dose for AMI. No maternal or fetal toxicity was evident at ~~0.65~~ doses (1 mg/kg) approximately 0.3 times the human exposure. In pregnant rats, no maternal or fetal toxicity was evident at doses (1 mg/kg) approximately 0.6 times ~~(1 mg/kg)~~ the human dose ~~in pregnant rats and rabbits~~ for AMI (based on body weight) dosed during the period of organogenesis.

8.2 Lactation

Risk Summary

There are no adequate and well controlled studies in pregnant women. data on the presence of alteplase in human milk, the effects on the breastfed infant, or the effects on milk production.

~~**8.3 Nursing Mothers**~~

~~It is not known whether Activase is excreted in human milk. Many drugs are excreted in human milk.~~

11. The Table of Contents was updated.

12. The revision date was updated.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or 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).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call:

Lori Anne Wachter RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
02/28/2018