June 24, 2021

Hoffmann-La Roche, Ltd.
C/O Genentech, Inc.
Attention: Dhushy Thambipillai
Regulatory Project Management
1 DNA Way, Bldg 45-1
South San Francisco, CA 94080

RE: Emergency Use Authorization 099

Dear Ms. Thambipillai:

This letter is in response to Genentech, Inc.'s (Genentech) request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for the emergency use of Actemra[1] (tocilizumab) for the treatment of coronavirus disease 2019 (COVID-19) in certain hospitalized patients, as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[2] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[3]

Actemra is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors. Actemra is FDA-approved for several indications[4]; however, Actemra is not approved for the treatment of COVID-19.

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[1] For the purposes of this Letter of Authorization, the use of the tradename, Actemra, is intended to refer to the commercially available Actemra that is in United States distribution under the approved Biologics License Application 125276, only. As discussed further in Section II of this letter, Actemra that is commercially available under this licensure is authorized for emergency use consistent with the terms and conditions of this letter.
[2] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.
[3] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).
[4] The currently approved labeling for Actemra may be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125472s044lbl.pdf.

Based on review of the data from the RECOVERY clinical trial (NCT #04381936), a randomized, open-label, controlled, platform trial; the COVACTA clinical trial (NCT #04320615), a randomized, double-blind, placebo-controlled clinical trial; the EMPACTA clinical trial (NCT #04372186), a randomized, double-blind, placebo-controlled clinical trial; and the REMDACTA clinical trial (NCT #04409262), a randomized, double-blind, placebo-controlled clinical trial, it is reasonable to believe that Actemra may be effective for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), and when used under the conditions described in this authorization, the known and potential benefits of Actemra outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Actemra for the treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Actemra for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Actemra may be effective for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of Actemra outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of Actemra for the treatment of COVID-19 in hospitalized adults and pediatric patients (2

years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.[5,6]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Actemra will be used only by healthcare providers to treat COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

- Actemra may only be administered via intravenous infusion.

- The use of Actemra covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

Actemra is supplied in individual single dose vials. Actemra is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors.

Actemra injection is a preservative-free, sterile clear, colorless to pale yellow solution. The authorized product includes commercially available[7] Actemra, which is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion. Do not use beyond the expiration date on the container or package. Actemra must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials from light by storage in the original package until time of use.

[5] On October 22, 2020, Veklury (remdesivir) was approved to treat COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization. Veklury is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-COV-2. Actemra is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors. Severe COVID-19 infection has been associated with hyperinflammation. In this context, high levels of IL-6, as well as other pro-inflammatory cytokines and inflammatory markers, have been observed in some patients with severe COVID-19 infection. Thus, a product inhibiting IL-6, such as Actemra, may potentially act on the COVID-19-associated inflammatory response. This is distinct from Veklury, which acts as an antiviral agent. We also note that Veklury's FDA-approved indication is for a narrower population than the use authorized for Actemra under this EUA.
[6] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[7] Supra at Note 1.

Actemra is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients, parents, and caregivers, respectively, through Genentech's website at www.actemrahcp.com/covid-19 (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for Actemra
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Actemra for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Actemra, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Actemra may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Actemra (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Genentech and Authorized Distributors[8]

A. Genentech and authorized distributor(s) will ensure that Actemra is distributed with the FDA-approved package insert and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. Genentech and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Genentech and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving Actemra. Genentech will provide to all relevant

[8] "Authorized Distributor(s)" are identified by Genentech as an entity or entities allowed to distribute Actemra for the use authorized in this letter.

stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Genentech may request changes to this authorization, including to the authorized Fact Sheets for Actemra. Any request for changes to this EUA must be submitted to the Division of Pulmonology, Allergy and Critical Care/Office of Immunology and Inflammation/Office of New Drugs/Center for Drug Evaluation and Research (CDER). Such changes require appropriate authorization prior to implementation.[9]

E. Genentech may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of Actemra as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for Actemra are prohibited. If the Agency notifies Genentech that any instructional and educational materials are inconsistent with the authorized labeling, Genentech must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Genentech to issue corrective communication(s).

F. Genentech will report to FDA serious adverse events and all medication errors associated with the use of Actemra for its authorized use that are reported to Genentech using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

   Submitted reports under both options should state: "Actemra use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

[9] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Genentech will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this emergency use authorization for Actemra that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or

- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

Genentech will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, Genentech must submit information confirming that Genentech has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Genentech must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Genentech will manufacture Actemra to meet all quality standards and per the manufacturing process and control strategy as detailed in Genentech's EUA request. Genentech will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Through a process of inventory control, Genentech and authorized distributor(s) will maintain records regarding distribution of Actemra (i.e., lot numbers, quantity, receiving site, receipt date).

K. Genentech and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

<u>Healthcare Facilities to Whom Actemra Is Distributed and Healthcare Providers Administering Actemra</u>

L. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of Actemra.

M. Healthcare facilities and healthcare providers receiving Actemra will track serious adverse events that are considered to be potentially attributable to Actemra use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "Actemra use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 should also be provided to Genentech per the instructions in the authorized labeling.

N. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

O. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of Actemra for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

P. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Genentech and/or FDA. Such records will be made available to Genentech, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

Q. All descriptive printed matter, advertising, and promotional materials relating to the use of Actemra under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of Actemra under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.

- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Genentech that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions Q-S of this EUA, Genentech must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Genentech to issue corrective communication(s).

R. No descriptive printed matter, advertising, or promotional materials relating to the use of Actemra under this authorization may represent or suggest that Actemra is safe or effective when used for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

S. All descriptive printed matter, advertising, and promotional material, relating to the use of Actemra under this authorization clearly and conspicuously shall state that:

- Actemra has not been approved, but has been authorized for emergency use by FDA under an EUA, to treat COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; and

- The emergency use of Actemra is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,
Denise M. Hinton -S
Digitally signed by Denise M. Hinton -S
Date: 2021.06.24 17:21:00 -04'00'

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration