



Health
Canada

Health Products
and Food Branch

Santé
Canada

Direction générale des produits
de santé et des aliments

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November 20, 2020

Dossier ID: HC6-024-E244947
Control #: 244947
Document #: 1612721

INTERIM ORDER AUTHORIZATION – TERMS AND CONDITIONS

In accordance with section 10 of the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19*, the following Terms and Conditions are imposed on the authorization issued in respect of Bamlanivimab (LY3819253, LY-COV555):

CLINICAL:

1. Provide results, if and when they become available, from **BLAZE-2** - A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 in Preventing SARS-CoV-2 Infection and COVID-19 in Skilled Nursing and Assisted Living Facility Residents and Staff; a National Institute of Allergy and Infectious Diseases (NIAID) and Lilly Collaborative Study. The estimated primary completion date will be updated in clinicaltrials.gov as protocol amendments are approved.
2. Provide results, if and when they become available, from **ACTIV-2** - A Study for Outpatients with COVID-19. This study is being conducted by the NIAID in collaboration with Eli Lilly and Company and the AIDS Clinical Trials Group. The study is designed to transition from phase II to phase III in the same trial (adaptive design), with or without a pause in enrollment, depending on the speed of enrollment and interim results. Up to two dose levels of bamlanivimab (700 mg and 7000 mg) are planned. Bamlanivimab may enter directly into phase III evaluation if sufficient safety and efficacy data are available from outside the trial. At present, the estimated primary completion date is November 2020 with an estimated study completion date of February 2021; however, these dates are subject to change as determined by the NIAID.
3. Provide results, if and when they become available, from the treatment arms containing adolescents (i.e., Treatment Arms 7 to 10) of **BLAZE-1** – A Phase II Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Participants with Mild to Moderate COVID-19 Illness. The timeline for investigation of the monotherapy in treatment arms containing adolescents is still being developed as part of Eli Lilly's global pediatric study plans; Eli Lilly intends to seek feedback from the United States Food and

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Drug Administration (US FDA) and the European Medicines Agency (EMA) on these plans in Q1 of 2021.

4. Provide updated and comprehensive population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation reports at the time of filing of the new drug submission.
5. Provide fulsome responses to the outstanding clinical and clinical pharmacology clarification requests (clarifax) raised during the review of submission control number 244947 no later than mid-December 2020.
6. Provide, if and when they become available, responses to information requests from the US FDA regarding the combination of etesevimab and bamlanivimab treatment under Emergency Use Authorization (EUA) 000094. Updates on global regulatory strategies, including anticipated timelines, for conditional and full marketing authorization applications will be provided twice a year.

CHEMISTRY AND MANUFACTURING:

7. As proposed in the response to the Eli Lilly Terms and Conditions received Thursday, November 19, 2020:
 - Going forward, product to be sold in Canada will be tested according to the updated specifications and the drug substance will be tested at the sites noted in Eli Lilly's response.
8. As the processes are not formally validated, provide information as it becomes available regarding:
 - Any failed, or aborted drug substance or drug product lots and a detailed description of the issue(s) with a discussion on any potential impact on quality, safety and efficacy.
9. The day after submitting similar information to the US FDA, file an amendment(s) to the IO authorization to provide all information related to manufacturing facilities.
10. Within 1 week of filing your Biologic License Application (BLA) to the US FDA, file an amendment(s) to the interim order (IO) authorization to provide:
 - Process validations related to manufacturing sites
 - Any available stability data from lots included in the IO authorization; indicate the new data points and any extensions to drug substance or drug product expiry date.
 - Any supporting studies; as filed to the US FDA
11. Bamlanivimab has been placed in Lot Release Evaluation Group 3 of this Directorate's Lot Release Program. Products in Lot Release Evaluation Group 3 require review by the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) and issuance of a formal lot release decision letter prior to their release for sale on the Canadian market.

A lot release request may be made by providing:

- A cover letter which includes:
 - Details for the lot for which release is requested;
 - The person to whom the lot release decision letter should be addressed as well as their job title;

- Contact information in the case that clarification of your request is needed;
 - An e-mail address to which the lot release decision letter should be sent. It is advisable to provide a group e-mail, rather than a single e-mail address, and
 - The list of documents to support your request.
- In the case of Bamlanivimab, the following documents to support your request:
 - All Certificates of Analysis for the drug substance lot(s) used in the manufacture of the drug product lot;
 - The semi-finished drug product Certificate of Analysis;
 - A lot tree to link the drug substance lot(s) to the semi-finished drug product that has been and may be packaged into lots for sale in Canada;
 - Confirmation that third party oversight of drug substance manufacturing and testing activities for the lot(s) was satisfactorily conducted; and
 - Certificate of Manufacture.

RISK MANAGEMENT PLAN:

12. Eli Lilly is required, as per the IO, to collect and assess safety information on an ongoing basis and determine whether there has been a significant change in what is known about the risks and benefits of Bamlanivimab and notify Health Canada without delay of such changes.
13. Eli Lilly is required to submit reports of any domestic serious expected and unexpected adverse drug reaction and any foreign serious unexpected adverse reactions within 15 days of receiving the information to Health Canada (as per C.01.017 of the Food and Drug Regulations [FDR]). As per the IO, Eli Lilly will:
 - a. Treat adverse reactions associated with Bamlanivimab as priority and submit the corresponding reports to Health Canada without delay.
 - b. Identify in the report that the Bamlanivimab is a COVID-19 product authorized under the IO.
14. After authorization and commencing 30 January 2021, Eli Lilly is required to submit monthly safety reports for the period of the IO authorization, unless otherwise determined by Health Canada. The monthly safety reports should include the following:
 - a. Canadian and Global data on:
 - i. Number of doses distributed
 - ii. All serious adverse events
 - iii. Serious adverse events reported in special populations including pregnant women, breast-feeding, pediatrics, geriatrics, hepatic insufficiency and renal insufficiency
 - iv. Causality assessment of fatal cases
 - v. Details regarding medication errors
 - b. Line listing of clinical trial and post-marketing SAEs regardless of causality
 - c. Summary outcome of registries, questionnaire and all ongoing studies
 - d. Identified and ongoing signals from other regulators.
15. Eli Lilly is required, at any time, to prepare an issue-related summary report (as per C.01.019 of the FDR) should an emerging issue be identified. An issue-related summary report is a concise, critical analysis of a specific safety or effectiveness issue. Authorization holders should refer to the guidance document Preparing and Submitting Summary Reports for Marketed Drugs and Natural

Health Products - Guidance Document for Industry for information on how to prepare and submit an issue-related summary report.

16. Eli Lilly is required to:
 - a. Provide an updated Canadian Addendum Risk Management Plan (RMP) with the information discussed on November 15, 2020, no later than after two (2) months on the market. This updated Canadian addendum RMP should include the following:
 - i. Close monitoring activities on pediatric patients in Canada
 - ii. Updated pregnancy questionnaire
 - iii. Information regarding studies (ongoing or planned) and timelines for long-term safety
 - b. Provide an updated Canadian Addendum RMP in a timely manner if a signal of safety issue is observed in post-authorization surveillance. The RMP format should follow the guidance (Guidance Document Submission of Risk Management Plans and Follow-Up Commitments) and should include the following in the context of the COVID-19 drugs submitted for authorization under the IO:
 - i. A safety specification that details the identified risks, potential risks, and missing information for the product, with a focus on risks in COVID-19 patients.
 - ii. A pharmacovigilance plan that details specific measures to be taken to identify and report safety issues in COVID-19 patients, including adverse reaction reporting, periodic reporting, and ongoing/planned studies.
 - iii. A risk minimization plan, if applicable, to manage risks that may require additional measures beyond those considered standard (for instance, labelling).

LABELLING:

17. Prior to launch of the website where Canadian-specific labelling and information will be found, Eli Lilly is required to provide Health Canada with the final snapshots of the web pages for Health Canada's review and files.
18. Eli Lilly is required to develop and distribute a Dear Healthcare Professional Letter in French and English with Health Canada approval to inform healthcare professionals about the authorization of bamlanivimab under the IO with English-only vial and carton labels, to expedite the global supply of the drug in the context of the pandemic. The letter should point healthcare professionals to the website where they can find information about Canadian-specific labelling in both official languages and should be issued before the product is distributed.
19. Eli Lilly is required to commit to keeping Health Canada informed on the plans to develop and implement Canadian-specific labelling and work towards developing such labelling at a point when the global supply and pandemic situation will allow.