Health Canada | Santé Canada

Health Products and Food Branch | Direction générale des produits de santé et des aliments

TERMS AND CONDITIONS

Company: AstraZeneca Canada Inc.

Product: Evusheld (tixagevimab/cilgavimab)

Dossier ID: HC6-024-E256406

Background:

The Food and Drug Regulations allows the Minister to impose or amend terms and conditions, and request additional information, in relation to a COVID-19 drug submission, Drug Identification Number (DIN), or establishment licence, at any time while it is in effect. In light of the severity of the COVID-19 pandemic, this allows the Minister to act quickly to gather important safety information or mitigate risk in a timely manner.

Depending on the requirement, terms and conditions can be ongoing (e.g., require a monthly report), have a defined time (e.g., a report is due to Health Canada on a specific day) or are to be completed once the data is available (e.g., a clinical trial is completed).

The status of the Terms and Conditions will be updated on a regular basis.

Status as of April 4, 2023:

Total Number: 14

Ongoing/pending: 10

Closed: 4

Table: Terms and Conditions

	Terms and Conditions	Issued	Status
1	Provide the final study reports for PROVENT, STORM CHASER and TACKLE.	April 14, 2022	Ongoing
2	Provide the final study report for the PROVENT repeat dose substudy: *A phase III Multi-center, Open-label Sub-study in Adults to Assess the Safety, PK, and Immunogenicity of Repeat Doses of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD7442 and AZD1061) (The PROVENT Repeat Dose Sub-study) (D8850C002A01).*	April 14, 2022	Ongoing
3	Provide the interim analysis results through Day 28 for the first 50 subjects to receive a second dose from the PROVENT repeat-dose sub-study.	April 14, 2022	Closed

	Terms and Conditions	Issued	Status
4	Provide data from baseline and all subsequent study visits, of the following biomarkers from the PROVENT repeat-dose sub-study: d-dimer, P-selectin, thrombin, and Factor VIII.	April 14, 2022	Ongoing
5	Provide topline data, to include safety, pharmacokinetic, ADA, and biomarker results for thrombotic events from the first 9 months of the PROVENT repeat-dose sub-study.	April 14, 2022	Ongoing
6	Provide the results, and any interim analysis, of the randomized, dose-ranging clinical trial investigating safety, immunogenicity, pharmacokinetic, pharmacodynamics and efficacy in individuals with moderate to severe immunocompromises who may not mount an adequate immune response to COVID-19 vaccination evaluating the following dosing regimens for COVID-19 pre-exposure prophylaxis: a. Evusheld (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections followed 3 months later by Evusheld (150 mg tixagevimab and 150 mg cilgavimab) administered as two consecutive IM injections with subsequent redosing every 3 months. b. Evusheld (600 mg tixagevimab and 600 mg cilgavimab) administered as an intravenous infusion followed 6 months later by Evusheld (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections with subsequent re-dosing every 6 months.	April 14, 2022	Ongoing
7	Provide the final report of the study evaluating the potential for tixagevimab and cilgavimab to mediate antibody-dependent enhancement of infection using sub-saturating concentrations of each monoclonal antibody.	April 14, 2022	Closed
8	Provide regular updates to Health Canada regarding the activity and/or clinical efficacy/effectiveness of tixagevimab and cilgavimab against the current and future variants of concern and variants of interest identified by the World Health Organization (WHO). Data will be submitted upon availability when additional variants of interest/variants of concern are identified by WHO. The WHO lists variants of concern and variants of interest in its weekly epidemiological update on COVID-19, which can be accessed on its website: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports	April 14, 2022	Ongoing
9	The Sponsor shall provide an updated Canadian-specific Risk Management Plan (RMP) Addendum following authorization, no later than DATE [30 days post approval]. The updated Canadian-Specific Addendum shall include follow-up questionnaires to collect additional data from the reporter on spontaneous reports for the following concerns:	April 14, 2022	Closed

	Terms and Conditions	Issued	Status
	a. Lack of Efficacy - in particular related to effectiveness against circulating Variants of Concern b. Cardiac disorders c. Embolic and thrombotic events d. Exposure during Pregnancy		
10	The Sponsor shall submit Periodic Benefit-Risk Evaluation Reports (PBRERs) for Evusheld every 6 months following ICH E2C (R2) guidelines, unless otherwise specified by Health Canada. The PBRERs will be aligned with the international birth date (IBD: November 14, 2021). <u>All PBRER analyses should include, but not be restricted to, the following</u>: a. Analyses of spontaneous cases, including case-level discussion and reporting trends over time. b. Number of Adverse Drug Reactions (ADR) in Canada and internationally. c. Accurate interval and cumulative patient exposure data, stratified by country, age groups where possible. d. Ongoing and closed signals in the interval from the Marketing Authorization Holder (MAH) and other regulators. e. Discussion and cumulative analyses of the data relevant to the following safety concerns/missing information: i. Use in pregnancy ii. Serious Cardiovascular Events iii. Off-Label Use in children <12 years iv. Off-label dosing – doses greater than 300 mg v. Long-term safety data, including data from ongoing clinical studies vi. Effects of tixagevimab/cilgavimab use on immune response to SARS-CoV-2 vaccination/immunization (vaccine interaction) vii. Use in immunocompromised patients, including issues with impaired viral clearance, off-label dose adjustments and treatment-emergent variants in this population viii. Treatment failure due to SARS-CoV-2 Variants, including variants of concern and treatment-emergent variants f. Analysis of scientific literature. g. Studies conducted by the sponsor and/or public health authorities. h. Risk/benefit considerations.	April 14, 2022	Ongoing

11	AstraZeneca Canada Inc. to submit final snapshots of all components of the electronic platform (linked to any foreign or Canadian specific labels), containing the approved Canadian-specific information for Evusheld in French and English for Health Canada's review and records, prior to launch of the electronic platform, and for each subsequent update.	April 14, 2022	Ongoing

	Terms and Conditions	**Issued**	**Status**
12	AstraZeneca Canada Inc. is requested to develop and distribute a Health Product Risk Communication (HPRC), in French and English, should a decision be made to import, for Canadian sites, non-Canadian labelled supplies. In this case, the HPRC would need to be developed with Health Canada approval and endorsement, to inform healthcare professionals that AstraZeneca Canada Inc. will delay implementation of Canadian-specific inner/outer labels following NDS-CV approval for Evusheld, and that interim non Canadian inner/outer labels will be used for the short term. Please note the following: a. AstraZeneca Canada Inc. should include images and texts of these labels in the HPRC and clearly outline all deviations from Canadian requirements; b. The HPRC should direct healthcare professionals to the electronic platform where they can find information about the approved Canadian-specific labelling in both official languages; c.The HPRC should include an alternative method for the health care professionals to obtain a paper copy of the HPRC and/or Product Monograph by mail or fax from AstraZeneca Canada Inc., if they cannot access the internet.	April 14, 2022	Closed
13	AstraZeneca Canada Inc. to commit to implementing Canadian specific bilingual labelling for Evusheld once supplies are transitioned to Canadian dedicated supplies. Health Canada should be kept informed of estimated timelines and proposed strategies concerning the implementation of Canadian-specific bilingual labels.	April 14, 2022	Ongoing
14	AstraZeneca Canada Inc. is requested to develop and distribute a company-led customer communication, in English and French, should a decision be made to import non-Canadian labelled supplies for Canadian sites. The customer communication should aim to inform healthcare professionals that AstraZeneca Canada Inc. will delay the implementation of Canadian-specific inner/outer labels following NDS-CV approval for Evusheld (tixagevimab/cilgavimab), and that interim inner/outer labels will be used for the short term. Please note the following: a. AstraZeneca Canada Inc. should consider including images and texts of these labels in the customer communication and clearly outline all	April 4, 2023	Ongoing

	deviations from Canadian requirements; b. The customer communication should direct healthcare professionals to the electronic platform where they can find information about the approved Canadian-specific labelling in both official languages c. The customer communication should not resemble a Health Canada-endorsed Health Product Risk Communication and should not reflect a red banner at the top of the document. A company-led risk communication may take the form of a letter carrying the company letterhead, for example. The company-led customer communication does not require review by Health Canada; however, AstraZeneca Canada Inc. is welcome to seek courtesy feedback from BRDD. AstraZeneca Canada Inc. is expected to exercise due discretion to ensure prompt finalization and dissemination of the customer communication. Please provide a copy of the final, signed customer communication in English and French via eCTD once available.		