CADTH

CADTH DRUG IMPLEMENTATION ADVICE

Bamlanivimab for Mild-to-Moderate Symptoms of COVID-19

(Eli Lilly Inc.)

Health Canada Approved Indication: Treatment of COVID-19 in adults and adolescents (12 years and older with a body weight of at least 40 kg) with mild-to-moderate symptoms of COVID-19 and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
ED	emergency department
FCA	Focused Critical Appraisal
INESSS	Institut National d'Excellence en Santé et Services Sociaux
NAb	neutralizing antibody
NIH	National Institutes of Health
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBD	Summary Basis of Decision

Summary

- The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a global health emergency unlike anything in modern history. The worldwide collaborative response within the health and public health systems has shown an unprecedented speed and comprehensiveness in developing and approving treatments and vaccines.
- In response to the urgent need for COVID-19 diagnosis, treatment, mitigation, and prevention options, Health Canada has established Interim Orders for new pathways to facilitate the conduct of clinical trials in Canada and patient access to COVID-19 drugs and medical devices that still uphold patient safety requirements.
- As a result of such regulatory initiatives, new clinical evidence is emerging rapidly which may be different than the level and type of information normally provided for regulatory approval. When the available information is limited or preliminary, evidence- and expert-informed criteria to support the optimal use and implementation of new therapies becomes both necessary and valuable.
- Neutralizing antibodies (NAbs) may offer a therapeutic solution to fight SARS-CoV-2 infection. Bamlanivimab is the first to receive authorization for use in Canada for the treatment of patients with mild-to-moderate COVID-19, with conditions including continued ascertainment and communication of the quality, safety, and efficacy of the product by the sponsor generated by the numerous ongoing clinical trials.
- Health care organizations and panels of clinical experts have advised that, at this time, bamlanivimab should not be considered standard of care for the treatment of mild-to-moderate COVID-19 infection. They have encouraged the continued generation of evidence through clinical trials.
- Based on the existing evidence that is publicly available, the CADTH bamlanivimab implementation advice panel was unable to identify with certainty a specific patient population or setting in which the benefits of the drug exceed the potential risks to COVID-19–positive patients receiving treatment or to health care providers, other patients, and people in close contact with the patient.
- Health Canada's product monograph for bamlanivimab provides clinical criteria for the identification of patients at high risk of severe COVID-19. It recommends use in health care settings in which health care providers have immediate access to medications to treat a severe adverse event, such as a severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system if necessary.
- The bamlanivimab implementation advice panel emphasized the importance of equity of access to treatment for COVID-19. However, they noted that administration of bamlanivimab and post-infusion monitoring in certain settings may present unique challenges related to infrastructure requirements and access to advanced care practitioners, such as in long-term care facilities and rural and remote communities.
- There are important challenges with administering bamlanivimab or other future NAbs because there is not a widespread, coordinated infusion system outside of the hospital setting in the Canadian health care system. System-level challenges and challenges related to infrastructure and health care personnel, both within and outside the hospital setting, would need to be clarified and addressed to optimize the use of IV medications for COVID-19.
- A critical milestone in the fight against COVID-19 has recently been reached with Health Canada's emergency use authorization of the first 2 vaccines — many other vaccines and treatments are also being investigated or evaluated. Continued collaboration between different stakeholders within the health care system will facilitate optimal prevention and care of Canadians during this evolving public health crisis.

Introduction

Background

The pandemic associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 is a global health emergency that is changing rapidly. As of January 6, 2021, there have been more than 626,799 confirmed cases of COVID-19 and 16,369 deaths due to the disease in Canada.[1] There is an urgent need for options for COVID-19 diagnosis, treatment, mitigation, and prevention. In response to this, Health Canada has established Interim Orders that have introduced new pathways to facilitate the conduct of clinical trials in Canada and patient access to COVID-19 drugs, vaccines, and medical devices, while maintaining patient safety requirements.[2] A critical milestone in the fight against COVID-19 in Canada has recently been reached with authorization of the first 2 vaccines under Health Canada's Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19,[3] with certain conditions related to provision of new information on safety, efficacy, and product quality.[4] Health Canada is in the process of evaluating and securing access for several other leading vaccine candidates.[5]

Similarly, many potential COVID-19 treatments are being investigated and evaluated, including antiviral drugs, convalescent plasma,[6] medical gases, and monoclonal neutralizing antibodies (NAbs). There is an urgent need to find treatments for COVID-19 to mitigate the impact on overall morbidity and mortality and to preserve and protect the health care system and the health care workers caring for hospitalized patients in Canada.

One of Health Canada's roles during this emergency is to regulate and authorize health products to treat COVID-19 based on their efficacy and safety. The urgency to find and authorize effective treatments for COVID-19 is promoting innovation in both regulatory and scientific processes as well as close collaboration with international partners and regulators.[7] Trial results are being reported and treatments are being evaluated as soon as evidence emerges. Out of public health necessity, treatments that might or might not be approved within these timelines under normal circumstances may be considered valuable, important, and potential treatment options by patients, clinicians, and health system leaders.

CADTH works to support decision-makers within the Canadian health care system by providing health technology assessments, horizon scans of emerging therapies, reviews of existing evidence, and implementation advice reports. A *health technology assessment* is defined as a multi-disciplinary process that uses explicit methods to determine the value of a health technology at different points in its life cycle. The purpose of a health technology assessment is to inform decision-making to promote an equitable, efficient, and high-quality health system.[8] Timely evidence- and expert-informed criteria related to emerging therapies with preliminary or interim clinical data may be useful to support pandemic preparedness and decision-making for COVID-19 treatments across the Canadian health system.

Bamlanivimab

Bamlanivimab is a recombinant neutralizing human IgG1 monoclonal antibody that targets the receptor-binding domain of the spike protein of SARS-CoV-2.[9] It is one of several monoclonal antibodies being evaluated as a treatment for COVID-19 in clinical trials. It is designed to neutralize the virus by blocking viral attachment and entry into human cells.[10] On November 20, 2020, bamlanivimab became the first NAb authorized for the treatment of mild-to-moderate symptoms of COVID-19 under Health Canada's Interim Order.[3]

Health Canada has publicly released numerous documents used in their evaluation and a Summary Basis of Decision (SBD) to describe why it authorized the use of bamlanivimab as a treatment for COVID-19.[11] This CADTH report refers specifically to information presented in Health Canada's SBD. Despite uncertainty regarding the submission and the availability of limited data, the SBD noted that there was sufficient evidence to conclude that the potential benefits associated with bamlanivimab's use outweighed the potential risks, having regard to the uncertainties relating to the benefits and risks and the necessity of addressing the urgent public health need related to COVID-19.[11] As with any drug product that enters the Canadian market, Health Canada, at any time, may impose or amend the terms and conditions that need to be met by the sponsor.[3] Currently, the product monograph states that the use of bamlanivimab is permitted pending the results of ongoing clinical trials to verify its clinical benefit and that patients should be advised of the nature of the authorization. Additionally, the product monograph specifies that bamlanivimab should be administered as soon as possible after a positive test for COVID-19 using a direct SARS-CoV-2 validated testing method and within 10 days of the onset of clinical signs and symptoms of infection. It should be administered to non-hospitalized adults and pediatric patients 12 years of age or older with mild-to-moderate COVID-19, who weigh at least 40 kg, and are at high risk of progressing to severe COVID-19 illness and/or hospitalization. The dose of bamlanivimab recommended by Health Canada is 700 mg by IV infusion. The single infusion treatment duration should be at least 60 minutes, and patients should be monitored after infusion is complete for at least 1 hour, as indicated in the monograph.[12]

Based on information made available to Health Canada, the product monograph[12] defines *patients at high risk of severe COVID-19* as those who meet at least 1 of the following criteria:

- aged 65 years or older
- aged 18 years or older with a body mass index of 35 kg/m^2 or higher
- have chronic kidney disease, diabetes, or immunosuppressive disease
- are currently receiving immunosuppressive treatment
- aged 55 years or older **AND** have one of the following
  - cardiovascular disease
  - hypertension
  - chronic obstructive pulmonary disease or other chronic respiratory disease
- aged 12 years to 17 years **AND** have one of the following
  - body mass index in the 85th percentile or higher for their age and gender
  - sickle cell disease
  - congenital or acquired heart disease
  - a neurodevelopmental disorder, such as cerebral palsy
  - a medically related technological dependence, such as a tracheostomy or gastrostomy, or require positive pressure ventilation (not related to COVID-19)
  - asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control.

The product monograph indicates that treatment with bamlanivimab should be initiated as soon as possible after a positive SARS-CoV-2 test (using a direct SARS-CoV-2 validated testing method) and should be administered within 10 days following the onset of clinical signs and symptoms of infection.[12]

Objectives

The objective of this report is to provide a review of issues that require consideration for the prioritization and optimization of the use of bamlanivimab in the context of the Canadian health care system.

A synthesis of information is presented in order to summarize the different perspectives about the patient population and the implementation of bamlanivimab for the care of patients with COVID-19.

This work is an extension of CADTH's ongoing assessment of the evidence of new treatments for COVID-19; it is not in relation to a submission by the manufacturer of bamlanivimab to the CADTH Drug Reimbursement Review process.

Methods

CADTH explored different perspectives related to the use of bamlanivimab by:

- conducting and publishing a Horizon Scan on NAbs[13]
- conducting and publishing a Focused Critical Appraisal (FCA) of a randomized controlled trial of bamlanivimab[14]
- identifying and reviewing other publicly available information about recommendations for use of bamlanivimab from Health Canada, Institut National d'Excellence en Santé et Services Sociaux (INESSS), the US National Institutes of Health (NIH), the Infectious Diseases Society of America, and the drug manufacturer
- convening and consulting a multi-disciplinary panel of clinical experts with in-depth knowledge or experience in the treatment of Canadian patients with COVID-19.

Horizon Scan of Monoclonal NAb Therapy for COVID-19

Studies of plasma from patients infected with SARS-CoV-2 revealed NAbs specific for the S protein of SARS-CoV-2, suggesting that NAbs may offer a therapeutic solution to fight SARS-CoV-2 infection. The majority of the NAbs in clinical development target the S protein. Some NAb preparations combine different NAbs to target different S protein epitopes and prevent waning efficacy of the treatment as a result of viral replication.[13] CADTH's Horizon Scan[13] identified 4 NAbs in phase III of development and many more in the pre-clinical phase; therefore, the evidence base will evolve as new information emerges.

Although bamlanivimab is the only NAb to date that has been granted an Interim Order authorization by Health Canada, there are a number of ongoing trials using bamlanivimab with or without other drugs and trials of other combinations of NAbs. Since the publication of CADTH's Horizon Scan,[13] more evidence has become available.

Bamlanivimab continues to be studied in outpatients with COVID-19 (phase II/III study, ACTIV-2).[13,15] Enrolment into a substudy of the ACTIV-3 trial, which randomized hospitalized patients with COVID-19 to receive 7,000 mg of bamlanivimab and remdesivir or placebo and remdesivir, was stopped on October 26, 2020, due to lack of clinical benefit.[16] Results of this

substudy were published in December 2020.[17] A phase III trial, Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-2), is being conducted in collaboration with the US National Institute of Allergy and Infectious Diseases to evaluate the efficacy and safety of bamlanivimab in preventing SARS-CoV-2 infection and COVID-19 in skilled nursing and assisted-living facility residents and staff.[18] A new phase IV open-label, single-arm pragmatic trial has been announced (NCT04656691) of bamlanivimab with matched controls in which outpatients with mild-to-moderate COVID-19 will be offered treatment in their own homes by a registered nurse through their medical insurer (UnitedHealth).[19]

In terms of safety issues, the CADTH Horizon Scan noted that an important caveat of treatment with NAbs is the possibility of antibody-dependent enhancement, in which binding to host cells is promoted rather than inhibited, leading to a worsened outcome.[13] Conversely, the authors concluded that NAbs offer a treatment strategy that may potentially be life-saving for individuals unable to produce a viable immune response.

The CADTH Horizon Scan highlighted that NAbs can be difficult and expensive to produce, and it would be vital to identify the specific patient population for whom the drug is likely to be most effective.[13] It was also noted that the chances that that 1 (or more) NAbs, used alone or in combination, will be identified as an effective therapeutic for treatment of COVID-19 is increased due to the diversity in antibodies being studied.

Finally, it was noted in the CADTH Horizon Scan that logistical barriers regarding the use of NAbs in the Canadian health care context are not insignificant.[13] Using IV treatment in patients who would otherwise self-isolate could increase health care worker exposure to a higher number of COVID-19–positive patients and would require early identification of eligible patients and the treatment of high-risk outpatients within days of a COVID-19 diagnosis.

Clinical Evidence Appraisals

CADTH Focused Critical Appraisal

CADTH's FCA of the potential benefits and risks of treatment with bamlanivimab for patients with mild-to-moderate symptoms of COVID-19 is a living document that will be updated as relevant evidence emerges. The current version of the FCA is on a preplanned interim analysis from the single study of efficacy that is presently available.[9] The BLAZE-1 trial (NCT04427501) is an ongoing phase II, randomized, double-blind, placebo-controlled, multi-centre study being conducted at 41 sites in the US.

The primary objective of the original BLAZE-1 trial was to characterize the effect of bamlanivimab compared with placebo on SARS-CoV-2 viral load and viral clearance. The secondary objectives were to characterize the effect of bamlanivimab compared with placebo on patient safety, SARS-CoV-2 viral load among patients within 8 days of symptom onset, symptom resolution, and clinical outcomes (i.e., death, hospitalization, and emergency department [ED] visit). Patients were assigned to 1 of 3 different doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or to a placebo group in a 1:1:1:1 ratio for comparison. The final study results will include different experimental arms using other NAb preparations in combination with bamlanivimab.

Patients were eligible for the original BLAZE-1 trial if they were 18 years of age or older, were not hospitalized, had a positive SARS-CoV-2 test within 3 days before the start of study drug infusion, and reported at least 1 mild-to-moderate symptom of COVID-19.[20,21] Mild symptoms could include "fever, cough, sore throat, malaise, headache, muscle pain, (and/or) gastrointestinal symptoms, without shortness of breath or dyspnea" and moderate symptoms were defined as "any symptom of mild illness or shortness of breath with exertion" or clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate of 20 breaths or more per minute, oxygen saturation greater than 93% on room air at sea level, and a heart rate of 90 beats or more per minute.[21] Of 467 randomized patients, 452 were included in the primary analysis: 143 received placebo and 309 patients received bamlanivimab (101 received 700 mg, 107 received 2,800 mg, and 101 received 7,000 mg).[9]

The CADTH FCA presented a detailed report on the trial's objectives, methods, and interim results and discussed the strengths and limitations of the evidence (Bamlanivimab (LY-CoV555) in the Treatment of Outpatients With COVID-19: A Critical Appraisal of an Interim Analysis of the BLAZE-1 Trial). Given the limitations associated with the interim report of the BLAZE-1 trial, the FCA report concluded that a phase III trial comparing bamlanivimab to placebo with a clinically important primary end point is necessary to determine the true benefits and risks to outpatients with mild-to-moderate COVID-19.[14]

Appraisals by Other Health Care Organizations

Similar conclusions have been reported by other health technology assessment agencies and organizations in Quebec, France, and Australia. In their rapid review of NAbs for the treatment of COVID-19, INESSS concluded that there was insufficient evidence to recommend the routine use of bamlanivimab in outpatients with mild-to-moderate disease and that participation in clinical trials should be encouraged to generate more evidence.[22] In a rapid review of treatments for COVID-19, the Haute Autorité de Santé concluded that bamlanivimab should not be used outside of a clinical trial setting.[23] A clinical trial paradigm was also the recommendation of the National COVID-19 Clinical Evidence Taskforce in Australia,[24] the British Columbia COVID-19 Therapeutics Committee[25], and the Ontario COVID-19 Clinical Practice Guidelines[26].

Infectious Diseases Society of America Guidelines on the Treatment and Management of COVID-19

Based on a review of evidence from the BLAZE-1 interim analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach , the Infectious Diseases Society of America rated the level of certainty of benefit of bamlanivimab compared to no bamlanivimab for non-hospitalized patients with COVID-19 as low for increased viral clearance and very low for risk of hospitalization. The level of certainty for safety in terms of serious adverse events (AEs) and infusion-related AEs were also rated as low.[27]

Based on this review, the Infectious Diseases Society of America suggested against the routine use of bamlanivimab for ambulatory patients with COVID-19 but stated that bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain AEs. It was also noted that NAbs could soon prove effective in increasing protection in populations where immune responses to vaccines may be less robust, such as older patients, young infants, or those with immunocompromising conditions.

Logistical challenges related to the administration of IV therapy in the ambulatory care setting were highlighted as were concerns about the spread of contagion in IV clinics. Finally, concerns were raised about equity since NAbs will likely be in short supply for the near future.

Guidance From the NIH

On November 18, 2020, the NIH's COVID-19 Treatment Guidelines Panel published a statement on the emergency use authorization of bamlanivimab.[28] Based on available evidence, the NIH panel determined that bamlanivimab should not be considered the standard of care and that there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild-to-moderate disease.

The NIH COVID-19 Treatment Guidelines Panel determined that more data are needed to assess the impact of bamlanivimab on the disease course and to identify people who are most likely to benefit. However, through the Emergency Use Authorization, they recommended that patients at highest risk for COVID-19 progression should be prioritized due to challenges related to drug administration and the possibility of a limited supply of the drug.[28] They encouraged health care providers to discuss participation in a clinical trial with their patients, and that patients hospitalized for COVID-19 should not receive bamlanivimab outside of a clinical trial.

The NIH panel determined that bamlanivimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19, and the clinician believes that the potential benefit of the drug outweighs the potential risk.

The NIH panel advised that these recommendations will be updated as more information becomes available.

Health Canada Summary Basis of Decision

Health Canada's SBD,[11] published on January 8, 2021, indicated that the interim authorization was based on more information than was publicly available in the report of the BLAZE-1 interim analysis.[9] The document highlighted that the secondary outcomes of the interim analysis of the BLAZE-1 trial supported the potential efficacy of bamlanivimab based on a reduction in the proportion of patients requiring hospitalization or a visit to an ED. For the 700 mg, 2,800 mg, 7,000 mg, and combined bamlanivimab groups, the proportion of patients requiring hospitalization or an ED visit were 1.0%, 1.9%, 2.0%, and 1.6%, respectively, compared with 5.8% for the placebo group. Within the subgroup of patients who met the high-risk criteria, as per the recommended indication, the proportion of patients requiring hospitalization or a visit to an ED in the 700 mg, 2,800 mg, 7,000 mg, and combined bamlanivimab groups were 2.2%, 2.2%, 4.5%, and 2.9%, respectively, compared with 10.1% in the placebo group. Health Canada noted that these results suggested that there may be no additional benefit associated with higher doses. Based on this, 700 mg was recommended as the treatment dose. It was considered important that the findings for COVID-19–related hospitalizations or visits to an ED appear to be driven mainly by patients who were within the target population identified in the product monograph, which encompasses patients with risk factors associated with progression to severe COVID-19 or hospitalization. However, it was also recognized that these results are associated with uncertainties or limitations, such as the small sample size, the lack of control for type I error, and that the trial enrolled a population of patients with different risks for progression to severe COVID-19 or hospitalization.

The SBD also highlighted that there was a statistically non-significant reduction in the median time to symptom improvement for patients who received the recommended 700 mg bamlanivimab dose (median = 6 days) compared to those patients who received a placebo (median = 8 days), and that this reduction was consistently observed across all 3 monotherapy doses of bamlanivimab compared with placebo.[11]

In regards to safety, the SBD highlighted that the interim results of the BLAZE-1 trial suggest that the safety profile of bamlanivimab 700 mg is relatively unremarkable, and that doses up to 7,000 mg have been administered without any notable increase in the rates of treatment-emergent or serious AEs.[11] The SBD noted that the most important AEs associated with bamlanivimab were infusion reactions and that hypersensitivity and anaphylactic events may also occur during the treatment. Although such reactions were rarely observed in the clinical study, the SBD notes that the product monograph provides warnings regarding all these potential AEs, and advises prescribers that the product should only be administered in a setting where health care professionals have the necessary means to treat such severe reactions.

Although not studied in the clinical trial, the SBD indicated that inclusion of patients younger than 18 years of age in the indication was supported by the acceptable safety profile observed in adults and an extrapolation approach for efficacy based on exposure matching.[11] Additionally, preliminary population pharmacokinetic modelling and simulation predicted similar pharmacokinetic exposures following a 700 mg dose of bamlanivimab in adolescent patients weighing more than 40 kg to those observed in adult patients.

The SBD also noted that preliminary population pharmacokinetic analyses showed that there was no difference in the pharmacokinetics of bamlanivimab in patients 65 years of age or older compared with patients younger than 65 years of age.[11]

Health Canada emphasized that the unmet medical need and the emergency context of the COVID-19 pandemic were considered in assessing whether the potential benefits outweigh the potential risks associated with bamlanivimab. As part of a Risk Management Plan imposed on the interim authorization, the sponsor is required to collect and assess safety information on an ongoing basis and submit safety reports to Health Canada. An updated Canadian Addendum Risk Management Plan must also be provided within 2 months that should include monitoring. The sponsor must also provide results, when they become available, from:

- BLAZE-2, a phase III randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of LY3819253 (LY-CoV555) in preventing SARS-CoV-2 infection and COVID-19 in skilled nursing and assisted-living facility residents and staff[18]
- ACTIV-2, a study for outpatients with COVID-19[15]
- the treatment arms including adolescents (i.e., treatment arms 7 to 10) in the BLAZE-1 trial, 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.[20]

Manufacturer Information

The Eli Lilly Canadian *Lilly Bamlanivimab Antibody Playbook* provides information to support planning and administration of bamlanivimab at existing hospital- or community-based infusion sites and other clinical spaces approved to administer infusion therapies.[29] The playbook addresses preparation, storage, and handling of bamlanivimab, and has a chapter

dedicated exclusively to education about monoclonal antibody drugs. It also provides information and estimates about the total time required for each bamlanivimab infusion of 165 to 225 minutes. information about the time required to administer and monitor patients following infusion, including patient consent, securing IV access, IV infusion, and post-infusion patient observation. Separate documents provide information specifically to health professionals and to patients.[29]

In terms of safety, the playbook is consistent with the product monograph stating that infusion-related reactions have been observed and that there is potential for a serious hypersensitivity reaction. Therefore, for safe administration of bamlanivimab, the playbook states that administration should only occur in settings in which health care providers have immediate access to medications to treat a severe infusion reaction and the ability to activate the emergency medical system if necessary.[12] For general COVID-19 risk reduction, the playbook also recommends that patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear a mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high-touch" surfaces, and wash hands frequently) according to public health guidelines.

Importantly, the patient medication information document states that "It is possible that bamlanivimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bamlanivimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks."[29]

Based on clinical trial experience, the playbook also identifies the recommended non-consumable materials and consumable personal protection equipment and infusion and general supplies that are needed at an infusion site of care. It also provides information about the time needed to treat patients, including the time for patient consent, IV preparation, IV infusion, and patient observation; a total time of 165 to 225 minutes is estimated for each patient.

Consultation With an Interdisciplinary CADTH Implementation Advice Panel

CADTH convened a panel of 7 clinicians to provide guidance on the implementation of bamlanivimab. Each clinician involved in the panel had expertise in at least 1 of the following areas: infectious disease, emergency medicine, community and family medicine, internal medicine, geriatric medicine, pediatrics, pharmacy, clinical pharmacology, pharmacokinetics, and epidemiology. Panel members who participated represented a number of jurisdictions in Canada; all confirmed an absence of conflicts of interest in a formal declaration. The panel did not include a patient or public representative.

Two virtual meetings were held. The first was on December 4, 2020, after which a preliminary report including a summary of the panel's input was provided to the members and representatives of Eli Lilly. Discussion of all feedback received was occurred during the second meeting on December 11, 2020. The panel was provided CADTH's Horizon Scan and FCA for the BLAZE-1 trial, the US *Lilly Bamlanivimab Antibody Playbook* [10](because the Canadian version had not yet been finalized or released when the panel convened), and the NIH and Infectious Disease Society of America guidance documents.

To explore different perspectives regarding the use of bamlanivimab in Canada, the panel of clinical experts reviewed the above documents and discussed the following 3 questions:

1. What criteria should be used to prioritize access to the treatment, based on:
   - risk factors for severe disease or hospitalization
   - inability to mount an antibody-mediated immune response?
2. What should be the parameters for monitoring patients following the IV infusion regarding:
   - staffing requirements
   - access to ambulatory care?
3. What parameters would need to be considered for IV administration in long-term care facilities?

The CADTH implementation advice panel was unable to propose specific clinical or population-level criteria for the use of bamlanivimab based on the evidence available. The panel expressed uncertainty about the clinical relevance of reduction in SARS-CoV-2 viral load. Although panel members were unanimous about the importance of reducing hospitalizations as an outcome from both a patient and health system perspective, they were concerned about the benefit of bamlanivimab being measured as a composite end point of ED visits and hospitalizations. They argued that although almost all US trial participants who visited the ED were admitted to the hospital, this would not necessarily be true in Canada. Indeed, according to publicly available data from the Canadian Institute of Health Information, of 48,605 people who presented at an ED with confirmed or suspected COVID-19 from January to August, 2020, only 21.3% were admitted to hospital.[30] Moreover, the panel felt that the effective treatment of severe disease and reduction in mortality was a more important goal at this point in the epidemic in Canada than reducing hospitalizations.

Issues related to the use and implementation of bamlanivimab were discussed in the context of the current challenges being faced by the Canadian health care system and the ongoing public health emergency of the COVID-19 pandemic. Responding to these questions, the interdisciplinary expert panel were asked to consider the use of bamlanivimab in the indicated population based on the available clinical evidence and their own real-world experiences in the management of COVID-19. The expert panel was unanimous in their opinion that administration of bamlanivimab to the currently high number of people with mild-to-moderate symptoms of COVID-19 may not be feasible in the Canadian health care setting due to the lack of a widespread, coordinated infusion system in the Canadian health care system and the already heavy burden on hospitals and EDs because of COVID-19. The panel noted that the time from symptom onset to testing, confirmation, and patient notification of diagnosis may be longer in the real-world health care setting than that reported in the BLAZE-1 clinical trial.

The panel also emphasized that, regardless of the treatment setting, delivery of bamlanivimab would likely require intensive use of health care resources and that decisions about when and where this treatment could be delivered requires careful consideration. Specifically, panel members spoke of the current health care personnel capacity challenges being experienced across many health care settings. The panel stressed that the provision of treatment with bamlanivimab should not have a deleterious impact on the provision of other treatments recognized as the standard of care to other patients in the Canadian health care system. From a public health perspective, the panel considered it problematic to require patients with COVID-19 in the outpatient setting to leave their home to receive IV administration of bamlanivimab in a hospital or IV clinic.

Furthermore, the panel members emphasized the importance of equity in access to COVID-19 treatments. They noted that IV administration of bamlanivimab and post-infusion monitoring may present unique challenges in long-term care facilities and rural and remote areas due to infrastructure requirements and access to nurses or advanced care practitioners.

In light of these concerns and the high level of uncertainty of clinical benefit based on currently available evidence, the panel was unable to provide advice on the optimal use of bamlanivimab or propose specific clinical criteria for bamlanivimab. The panel supported the generation of additional evidence for further review (which is a stated condition of the Health Canada interim authorization).

Patient Perspective

Although CADTH recognizes and values the patient and public perspective in all its work, given the condensed timeline to complete the review, neither perspective was sought and therefore are not incorporated in this report. However, the outcome measures reported in the BLAZE-1 trial in relation to treatment of COVID-19 (viral load clearance and risk of hospitalization) have been shown in the published literature to be important to patients, their families, and other stakeholders within the health care system.[31,32] Future CADTH reports concerning the optimal use of bamlanivimab or NAbs will endeavour to consider the patient and/or public perspective to weigh the benefits and risks of these novel therapies.

Understanding the Place of Bamlanivimab in Therapy for Non-Hospitalized Patients With COVID-19

Bamlanivimab is the first NAb — and the first COVID-19 therapy — to be authorized under the Interim Order for use to prevent progression of COVID-19 to a level of severity requiring hospitalization. Health Canada's review concluded that the potential benefits associated with bamlanivimab outweighed the potential risks when taking into account the uncertainties relating to the benefits and risks and the necessity of addressing the urgent public health need related to COVID-19.

Evidence Collection for Bamlanivimab

The Health Canada interim authorization is conditional on additional clinical data being gathered to support the efficacy and safety of the drug.[3] This collection of additional clinical data is also supported by several health technology agencies, the CADTH implementation advice panel, and health care organizations. More robust, peer-reviewed evidence, including analysis of the final results of the BLAZE-1 trial, from trials with clinically important outcomes is needed to provide clear recommendations about the place of bamlanivimab in the treatment of COVID-19 and whether bamlanivimab should be standard of care for patients with mild-to-moderate COVID-19 symptoms.[14,22-24,27,28]

Administration of Bamlanivimab

Logistical challenges surrounding the administration of IV bamlanivimab were identified.

The BLAZE-1 clinical trial involved the IV administration of bamlanivimab in people with mild-to-moderate symptoms of COVID-19 who had a positive SARS-CoV-2 test in the previous 3 days and had characteristics associated with a high risk of severe disease.[9] However, within the Canadian health care system there are important challenges associated

with the IV administration of bamlanivimab and other future NAbs because there is not a widespread, coordinated infusion system outside of the hospital setting. Moreover, from a public health perspective, it is problematic to require patients with COVID-19 in the outpatient setting to leave their home to receive IV administration of bamlanivimab in a hospital or IV clinic.

By providing IV therapy to outpatients with COVID-19, there is risk of exposure to SARS-CoV2 from patients who might otherwise quarantine at home. The Infectious Diseases Society of America, the expert panels convened by INESSS and CADTH, and the Canadian manufacturer's playbook all highlighted that protection of health care providers and other outpatients receiving care for other health conditions from infection with SARS-CoV2 should be considered.[22,27] Exposing health care workers in IV clinics to increased numbers of COVID-19 patients could also increase their risk of contracting the disease. Accordingly, the manufacturer's playbook stresses the need for appropriate use of personal protective equipment and that patients treated with bamlanivimab should continue to self-isolate and use infection control measures.[10]

Safety Issues Around the Administration of Bamlanivimab

A number of organizations and documents (Health Canada Product Monograph, CADTH Horizon Scan, NIH, Infectious Diseases Society of America) have discussed safety precautions when prescribing bamlanivimab that ensure health care providers have immediate access to medications to treat a severe reaction, such as a severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system if necessary.[12,13,27,28]

Summary

- The emergence of the novel SARS-CoV-2 has created a global health emergency unlike anything in modern history. The worldwide collaborative response within the health and public health systems has shown an unprecedented speed and comprehensiveness in developing and approving treatments and vaccines.
- In response to the urgent need for COVID-19 diagnosis, treatment, mitigation, and prevention options, Health Canada has established Interim Orders for new pathways to facilitate the conduct of clinical trials in Canada and patient access to COVID-19 drugs and medical devices that still uphold patient safety requirements.
- As a result of such regulatory initiatives, new clinical evidence is emerging rapidly which may be different than the level and type of information normally provided for regulatory approval. When the available information is limited or preliminary, evidence- and expert-informed criteria to support the optimal use and implementation of new therapies becomes both necessary and valuable.
- NAbs may offer a therapeutic solution to fight SARS-CoV-2 infection. Bamlanivimab is the first to receive authorization for use in Canada for the treatment of patients with mild-to-moderate COVID-19, with conditions including continued ascertainment and communication of the quality, safety, and efficacy of the product by the sponsor generated by the numerous ongoing clinical trials.
- Health care organizations and panels of clinical experts have advised that, at this time, bamlanivimab should not be considered standard of care for the treatment of mild-to-moderate COVID-19 infection. They have encouraged the continued generation of evidence through clinical trials.

- Based on the existing evidence that is publicly available, the CADTH bamlanivimab implementation advice panel was unable to identify with certainty a specific patient population or setting in which the benefits of the drug exceed the potential risks to COVID-19–positive patients receiving treatment or to health care providers, other patients, and people in close contact with the patient.
- Health Canada's product monograph for bamlanivimab provides clinical criteria for the identification of patients at high risk of severe COVID-19. It recommends use in health care settings in which health care providers have immediate access to medications to treat a severe adverse event, such as a severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system if necessary.
- The bamlanivimab implementation advice panel emphasized the importance of equity of access to treatment for COVID-19. However, they noted that administration of bamlanivimab and post-infusion monitoring in certain settings may present unique challenges related to infrastructure requirements and access to advanced care practitioners, such as in long-term care facilities and rural and remote communities.
- There are important challenges with administering bamlanivimab or other future NAbs because there is not a widespread, coordinated infusion system outside of the hospital setting in the Canadian health care system. System-level challenges and challenges related to infrastructure and health care personnel, both within and outside the hospital setting, would need to be clarified and addressed to optimize the use of IV medications for COVID-19.
- A critical milestone in the fight against COVID-19 has recently been reached with Health Canada's emergency use authorization of the first 2 vaccines — many other vaccines and treatments are also being investigated or evaluated. Continued collaboration between different stakeholders within the health care system will facilitate optimal prevention and care of Canadians during this evolving public health crisis.

Conclusions

Unprecedented times require unprecedented system responses. The global pandemic has created an urgent necessity for effective, safe COVID-19 treatments and vaccines. Given the extraordinary impact of COVID-19 on health care systems, economies, and health care providers and patients, the process for reviewing potentially effective new therapies through Health Canada's Interim Order enables both faster review and faster access than would ordinarily be the case. This accelerated process could help mitigate some of the overall impact of COVID-19. In addition, in some specific circumstances and for reasons that may be unique and situational, clinicians and patients may decide that although the evidence of clinical benefit is not overwhelmingly strong, a product's use presents value in an area of unmet clinical need. The substantial regulatory requirements on pharmaceutical manufacturers and others to ensure appropriate and ongoing monitoring for safety and efficacy will help to refine the appropriate use of this COVID-19 treatment.

Several groups and clinical advisory panels, including the one CADTH convened, commented that the available evidence from the interim analysis of a single phase II study is insufficient to conclude that IV administration of bamlanivimab should be standard of care, will lead to faster recovery, or will reduce the risk of hospitalization or time in hospital. There is currently no evidence that bamlanivimab improves mortality from COVID-19. Although IV administration of bamlanivimab was not associated with any serious AEs in the trial setting with 28 days of follow up, longer term safety is currently unknown.

The ideal current use of bamlanivimab should be in a context in which additional evidence can be generated concerning its efficacy, effectiveness, and safety and including a more diverse patient population to determine which sub-groups would be most likely to benefit. A well-designed randomized trial in the outpatient setting would help to determine the optimal role of this relatively new technology in the care of outpatients with mild-to-moderate symptoms of COVID-19 who are at risk of developing severe disease that requires hospital care. Measured outcomes should distinguish between ED and hospitalization outcomes, rather than a composite outcome, and should measure the impact on mortality with consideration of levels of patient comorbidities.

In the Canadian health care setting, IV administration of bamlanivimab in non-hospitalized patients with COVID-19 would require increased use of currently overburdened and, in some cases, scant health care resources. Advisory panels have expressed concern about the risk of increased transmission of the SARS-CoV-2 virus among health care providers and other members of the community sharing the same health care setting. Moreover, if established infusion clinic infrastructures were to be used for the administration of bamlanivimab, concerns have been raised about the potential impact on delivery of infusions of other medications recognized as the standard of care.

This report will be updated as evidence for the use of bamlanivimab and the treatment of COVID-19 with NAbs evolves.

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