PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBamlanivimab for injection

Solution for infusion, 700 mg/20 mL (35 mg/mL)

Anti-SARS-CoV-2 spike protein monoclonal antibody

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION

Bamlanivimab is indicated for:

The treatment of adults and pediatric patients (12 years of age or older weighing 40 kg or more) with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

The use of bamlanivimab is permitted under an interim authorization delivered in accordance with section 5 of the COVID-19 Interim order (IO)*, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. The interim authorization is associated with Terms and Conditions that need to be met by the sponsor to ascertain the continued quality, safety and efficacy of the product. For further information on authorization under this pathway, please refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

* https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8

Circulating SARS-CoV-2 viral variants may be associated with resistance to bamlanivimab. Health professionals should review pertinent information in section 7 WARNINGS AND PRECAUTIONS, General, and section 15 MICROBIOLOGY, Antiviral Resistance, for details regarding SARS-CoV-2 variants of concern.

Eli Lilly Canada Inc.	Date of Initial Authorization:
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Submission Control Number: 249525

RECENT MAJOR LABEL CHANGES

1 INDICATION	04/2021
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	04/2021
7 WARNINGS AND PRECAUTIONS, General	04/2021
15 MICROBIOLOGY, Antiviral Resistance	04/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Bamlanivimab is indicated for the treatment of adults and pediatric patients (12 years of age or older and weighing 40 kg or more) with mild to moderate coronavirus disease 2019 (COVID-19), who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- Are ≥ 65 years of age
- Have a body mass index (BMI) ≥ 35 for patients ≥ 18 years of age
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 55 years of age **AND have**
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12-17 years of age **AND have**
    - BMI ≥ 85th percentile for their age and gender, OR
    - Sickle cell disease, OR
    - Congenital or acquired heart disease, OR
    - Neurodevelopmental disorders, for example, cerebral palsy, OR
    - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
    - Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Bamlanivimab should not be used in patients hospitalized with severe COVID-19 respiratory disease as benefit of treatment has not been observed in this setting. Bamlanivimab, a monoclonal antibody, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Circulating SARS-CoV-2 viral variants may be associated with resistance to bamlanivimab. Health professionals should review pertinent information in section 7 WARNINGS AND PRECAUTIONS, General, and section 15 MICROBIOLOGY, Antiviral Resistance, for details regarding SARS-CoV-2 variants of concern.

Interim authorization is supported by a numerical reduction in hospitalization or emergency room visits in high risk patients treated with bamlanivimab compared to high risk patients treated with placebo (see **14 CLINICAL TRIALS**).

1.1 Pediatrics

Pediatrics: Based on the data submitted in this interim authorization and reviewed by Health Canada, the safety and efficacy of bamlanivimab in pediatric patients has not been established. However, because the mechanism of action of bamlanivimab, as a neutralizing IgG1 mAb against the spike (S) protein of SARS-CoV-2, is directed against the virus and not the host response to the viral infection, it is

reasonable to anticipate similar function in adolescents compared to adults. In addition, considering the acceptable safety profile observed from the adult population who weigh at least 40 kg, treating physicians may consider the use of bamlanivimab for adolescents 12 years of age or older who weigh ≥ 40 kg with high risk factors. Close monitoring in this patient population is highly recommended.

2   CONTRAINDICATIONS

Bamlanivimab is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4   DOSAGE AND ADMINISTRATION

4.1   Dosing Considerations

Bamlanivimab should only be administered in settings in which health care providers have immediate access to medications to treat a severe reaction, such as severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Bamlanivimab should be administered to patients as soon as possible after a positive test for COVID-19 using a direct SARS-CoV-2 validated testing method. The drug should be administered within 10 days following the onset of clinical signs and symptoms of infection.

4.2   Recommended Dose and Dosage Adjustment

The recommended dose of bamlanivimab is a single intravenous infusion of 700 mg bamlanivimab.

Use in Specific Populations

- o Bamlanivimab is not recommended for patients weighing less than 40 kg.

4.3   Reconstitution

No reconstitution of bamlanivimab is required.

4.4   Administration
Preparation

Bamlanivimab for injection must be diluted with 0.9% Sodium Chloride. The solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - o Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile infusion bag.
    - Prefilled 250 mL infusion bag containing 0.9% Sodium Chloride Injection. Only 0.9% Sodium Chloride should be used for dilution.
  - o One 20 mL vial of bamlanivimab (700 mg/20 mL)
- Remove the bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake.**
- Inspect bamlanivimab visually for particulate matter and discoloration.
  - o Bamlanivimab is a clear to opalescent and colorless to slightly yellow to slightly brown solution.

- o   If particulate matter or discolorations are identified, discard the vial.
- Withdraw 20 mL bamlanivimab from 1 vial and inject into a prefilled infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Gently invert IV bag by hand approximately 10 times to mix.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, the infusion solution should be administered immediately.
    - o   If immediate administration is not possible, store the bamlanivimab infusion solution for up to 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 14 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Administration

Bamlanivimab for injection should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion:
    - o   Polyvinylchloride (PVC) or polyethylene (PE)-lined PVC infusion set
    - o   Use of an in-line or add-on 0.20/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity over at least 1 hour at a minimum infusion rate of 270 mL/h. Due to potential overfill of prefilled bags, the entire infusion solution in the bag should be administered to avoid underdosage. Do not co-infuse with electrolytes of other medications.
- Once infusion is complete, flush the tubing to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients after infusion is complete according to standard practice.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.

5   OVERDOSAGE

In the case of overdose, use supportive therapy. There is no known antidote to bamlanivimab.

For management of a suspected drug overdose, contact your regional poison control centre.

6   DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous infusion	Solution, 700 mg/20 mL (35 mg/mL)	- L-histidine - L-histidine hydrochloride monohydrate - sodium chloride - sucrose - polysorbate 80

		• water for injection

7 WARNINGS AND PRECAUTIONS

General

The limited clinical data available for bamlanivimab are derived from single intravenous doses administered in the ongoing Phase 2/3 randomized, double-blind, placebo-controlled clinical study, BLAZE-1 (Study PYAB) and blinded data from ongoing Phase 3 studies. Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab use.

Potential Risk of Treatment Failure due to Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral SARS-CoV-2 variants that are resistant to bamlanivimab. Health professionals should review the Antiviral Resistance information in section 15 MICROBIOLOGY for details regarding SARS CoV-2 variants of concern. Use of bamlanivimab alone should only be considered if other monoclonal antibodies that retain neutralization activity against prevalent variants are not available.

Clinical Worsening of COVID-19 Symptoms after Bamlanivimab Administration

Clinical worsening of COVID-19 in the 24 hours post-administration has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g. atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab.

Sensitivity

Hypersensitivity and Anaphylaxis

Serious hypersensitivity and/or anaphylactic reactions have occurred with administration of bamlanivimab. If signs and symptoms of a clinically significant hypersensitivity or anaphylactic reaction occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related Reactions

Infusion-related reactions have been observed with administration of bamlanivimab. These reactions may be severe or life threatening.

- Signs and symptoms of infusion-related reactions may include: urticaria, pruritis, rash, swelling of the face, and chest discomfort.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab provides any treatment benefit or risk to the developing fetus.

7.1.2 Breast-feeding

There are no available data on the presence of bamlanivimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and any potential adverse effects on the breastfed child from bamlanivimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

7.1.3 Pediatrics

The safety and efficacy of bamlanivimab in children have not been established, although as per above (see **1 INDICATIONS**) it is reasonable to consider a single intravenous dose of bamlanivimab in adolescents 12 years of age or older who weigh ≥ 40 kg and who are high risk of developing severe COVID-19 symptoms and/or hospitalization.

7.1.4 Geriatrics

Of the 309 patients receiving bamlanivimab in BLAZE-1, 11% were 65 years of age and older and 3% were 75 years of age and older. Based on preliminary population PK analyses, there is no difference in PK in geriatric patients compared to younger patients (see **10.3 Pharmacokinetics, Special Populations and Conditions**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical studies evaluating the safety of bamlanivimab are ongoing. The following adverse reactions have been identified as potentially associated with bamlanivimab administration based on clinical trial results and post-authorization spontaneous reports (see **7 Warnings and Precautions**):
- Anaphylaxis
- Infusion-related reaction

An acceptable safety profile of bamlanivimab was reported in patients with mild to moderate COVID-19 illness (N = 309) following single intravenous doses of bamlanivimab in the BLAZE-1 Phase II study (700 mg, 2800 mg and 7000 mg). Based on the data, after treatment, adverse events occurred in 23% bamlanivimab-treated patients and 26% of placebo-treated patients who were followed for at least 28 days. Serious adverse events occurred in 1 placebo-treated subject (1%) and in no bamlanivimab-treated subjects.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of bamlanivimab is based on exposure of approximately 1,000 ambulatory (non-hospitalized) subjects who received doses of bamlanivimab.

Two adverse drug reactions have been identified (see **7 WARNINGS AND PRECAUTIONS**):
- anaphylaxis (0.2%)
- infusion-related reactions (1.3%)

TEAEs reported in ≥ 1% of bamlanivimab-treated participants are summarized in Table 2.

Table 2 - Treatment-emergent Adverse Events in ≥ 1% of All Bamlanivimab-Treated Participants

Adverse Event	Placebo N=793 n (%[a])	Bamlanivimab N=1000 n (%[a])
Urinary tract infection	14 (1.8)	14 (1.4)
Dizziness	10 (1.3)	13 (1.3)
Hypertension	11 (1.4)	12 (1.2)

[a]   Percentage is a simple calculation of events per person in each cohort.

8.2.1   Clinical Trial Adverse Reactions – Pediatrics

The BLAZE-1 Phase 2 study did not include patients who were less than 18 years of age.

8.3   Less Common Clinical Trial Adverse Reactions

There were no significant adverse reactions reported at < 1% in patients treated with bamlanivimab.

8.4   Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

There were no clinically significant abnormal laboratory findings with bamlanivimab.

9   DRUG INTERACTIONS

9.1   Serious Drug Interactions

No serious drug interactions have been reported for bamlanivimab.

9.2   Drug Interactions Overview

No drug interaction studies have been performed. Bamlanivimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

9.3   Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4   Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5   Drug-Food Interactions

Interactions with food have not been established.

9.6   Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7   Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10   CLINICAL PHARMACOLOGY

10.1   Mechanism of Action

Bamlanivimab is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2, which can block the spike protein attachment to human ACE2 receptors, thus preventing subsequent viral entry into human cells and viral replication.

10.2   Pharmacodynamics

A Phase 2 trial evaluated bamlanivimab over a dose range of 1 to 10 times the recommended dose (700 to 7000 mg) of bamlanivimab in patients with mild to moderate COVID-19. Based on preliminary population pharmacokinetic/pharmacodynamic modelling and simulation, a flat exposure-response relationship for viral load reduction was identified for bamlanivimab within this dose range. In addition, body weight had no clinically meaningful effect on viral load reduction in adults with COVID-19 over the body weight range of 41 kg to 173 kg.

10.3   Pharmacokinetics

The pharmacokinetic profile of bamlanivimab is linear and dose-proportional between 700 mg and 7000 mg following a single IV administration. There were no differences in PK of bamlanivimab between severe/moderate participants who were hospitalized and mild/moderate ambulatory participants.

Absorption

The mean maximum concentration (Cmax) of bamlanivimab was 190 µg/mL (90% CI: 100 to 390 µg/mL) following approximately 1 hour 700 mg IV infusion.

Distribution

The mean volume of distribution (V) after a 700 mg IV dose was 2.83 L and 2.95 L for the central and peripheral compartments, respectively. The between subject variability was 22.8% CV.

Metabolism

Bamlanivimab is expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

The clearance (CL) after a 700 mg IV dose was 0.277 L/d (between subject variability 23.7% CV) and the mean apparent terminal elimination half-life was 17.4 days (between subject variability 14.2% CV).

Special Populations and Conditions

The PK of bamlanivimab was not affected by age (18 to 86), sex, race, or disease severity based on a preliminary population PK analysis.

Hepatic Insufficiency:
No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of bamlanivimab.

Renal Insufficiency:
No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of bamlanivimab. Bamlanivimab is not expected to be eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab.

Pediatrics:
The pharmacokinetics of bamlanivimab in pediatric patients have not been evaluated. Using modeling and simulation, the recommended dosing regimen is expected to result in comparable plasma exposures of bamlanivimab in pediatric patients ages 12 years of age or older who weigh at least 40 kg as observed in adult patients.

11   STORAGE, STABILITY AND DISPOSAL

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or expose to direct heat.

This product is preservative free and therefore, the prepared solution should be administered immediately. If immediate administration is not possible, store solution for infusion for up to 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and 14 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion duration.

12   SPECIAL HANDLING INSTRUCTIONS

Protect from direct heat and light. Do not shake.

PART II: SCIENTIFIC INFORMATION
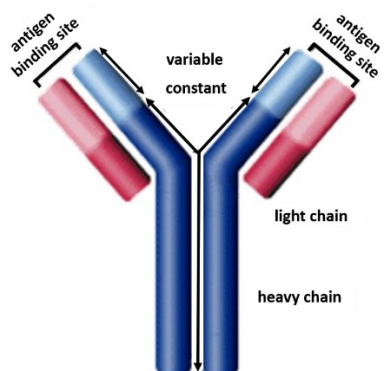
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: bamlanivimab for injection

Chemical name: bamlanivimab

Molecular mass: 146439 Da

Structural formula:

Figure 1: Structure of bamlanivimab

Product Characteristics:

Bamlanivimab is a fully human immunoglobulin G (IgG1 variant) mAb consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced by a CHO cell line.

Bamlanivimab for injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of bamlanivimab, and L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bamlanivimab solution has a pH range of 5.5-6.5.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Mild to Moderate COVID-19 (BLAZE-1)

The data supporting this interim authorization are based on an interim analysis from Part A of BLAZE-1 that occurred after all enrolled subjects completed at least Day 29 of the trial. BLAZE-1 Part A is a Phase 2 randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment

of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment with bamlanivimab was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156).

At baseline, median age was 45 years (with 12% of subjects aged 65 or older); 55% of subjects were female, 88% were White, 44% were Hispanic or Latino, and 6% were Black; 44% of subjects were considered high risk (as defined in Section 1, see **INDICATIONS**). Subjects had mild (76%) to moderate COVID-19 (24%); the mean duration of symptoms was 5 days; mean viral load by cycle threshold (CT) was 24 at baseline. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups.

14.2   Study Results

The pre-specified primary endpoint in the BLAZE-1 Phase 2 trial was change in viral load from baseline to Day 11 for bamlanivimab versus placebo. However, most subjects, including those receiving placebo, effectively cleared virus by Day 11 (not shown); therefore, no statistically significant reduction in viral load, as detected by viral RNA, was observed in subjects treated with bamlanivimab compared to subjects treated with placebo.

Evidence of the efficacy of bamlanivimab in subjects with mild to moderate COVID-19 related illness is limited to the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. Numerically, a lower proportion of bamlanivimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects (Table 3). Results for this endpoint were suggestive of a relatively flat dose-response relationship.

Table 3 - Proportion of Subjects with Events of Hospitalization or Emergency Room Visits within 28 Days After Treatment

Treatment	N[a]	Events	Proportion of Subjects %
Placebo	156	9	5.8%
bamlanivimab 700 mg	101	1	1.0%
bamlanivimab 2800 mg	107	2	1.9%
bamlanivimab 7000 mg	101	2	2.0%
All bamlanivimab doses	309	5	1.6%

[a]   Abbreviations: N = number of treated patients in analysis.

The subgroup of subjects who met the risk criteria (see **1 INDICATIONS**) also experienced a numerical reduction in the proportion of subjects who required COVID-19 related hospitalisations or emergency room visits (Table 4).

Table 4 - Proportion of Subjects with Events of Hospitalization or Emergency Room Visits for Subjects at Higher Risk of Progression to Severe COVID-19 Illness[a]

Treatment	N[b]	Events	Proportion of Subjects %
Placebo	69	7	10.1%
bamlanivimab 700 mg	46	1	2.2%
bamlanivimab 2800 mg	46	1	2.2%
bamlanivimab 7000 mg	44	2	4.5%
All bamlanivimab doses	136	4	2.9%

[a] Higher risk for progression to severe COVID-19 illness as defined in section 1 **INDICATIONS**.
[b] Abbreviations: N = number of treated patients in analysis.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

14.3   Immunogenicity

Immunogenicity has not yet been investigated. Samples for immunogenicity assessments have been collected and stored. Analysis will occur once validated anti-drug antibody assays are available.

15   MICROBIOLOGY

Antiviral Activity

The cell culture neutralization activity of bamlanivimab against SARS-CoV-2 was measured in a dose-response model using cultured Vero E6 cells. Bamlanivimab neutralized SARS-CoV-2 with an estimated EC50 value = 0.03 μg/mL and an estimated EC90 value = 0.09 μg/mL.

Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity on reporter Jurkat cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bamlanivimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

In Vivo Efficacy Pharmacology

Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 $\log_{10}$ decreases in viral load (genomic RNA) and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation. The applicability of these findings to a prophylaxis or treatment setting is not known.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab.

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the spike protein identified six amino acid substitutions at four positions (E484D/K/Q, F490S, Q493R and S494P) in the spike protein receptor binding domain, which had reduced susceptibility to bamlanivimab as determined in neutralization assays using SARS-CoV-2 (F490S and S494P: > 485-fold and > 71-fold reduction, respectively), vesicular stomatitis virus-based pseudovirus (all variants > 100-fold reduction), or binding assessment if pseudovirus construction was unsuccessful (E484D).

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab is ongoing. Pseudovirus harboring the concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), the Brazil origin P.1 variant lineage (K417T + E484K + N501Y), California origin B.1.427/B.1.429 variant lineage, and New York origin B.1.526 variant lineage exhibited reduced susceptibility to bamlanivimab. Bamlanivimab retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage (Table 5).

Table 5 – Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab Alone

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	E484K	> 2,360[c]
P.1 (Brazil origin)	E484K	> 2,360[c]
B.1.427/B.1.429 (California origin)	L452R	> 1,020[c]
B.1.526 (New York origin)[d]	E484K	> 2,360[c]

[a] For variants with more than one substitution of concern, only the one with the greatest impact on activity is listed.
[b] No change: < 5-fold reduction in susceptibility.
[c] No activity was observed at the highest concentration tested. Bamlanivimab alone is unlikely to be active against variants from this lineage.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

It is not known how pseudovirus data correlate with clinical outcomes; however, reduction in susceptibility of > 1,000-fold indicates that there will likely be no activity of bamlanivimab alone against these variants.

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab resistance-associated spike variations in clinical trials. Known bamlanivimab-resistant variants at baseline were observed at a frequency of 0.3% (1/375) in the clinical trial BLAZE-1. In the same trial, treatment-emergent variants were detected at spike protein amino acid positions E484, F490 and S494, and included E484A/D/G/K/Q/V, F490L/S/V and S494L/P; only E484K/Q, F490S and S494P have been assessed phenotypically to date. Considering all variants detected at positions E484, F490 and S494, 9.2% (9/98) and 6.1% (6/98) of participants in the 700 mg bamlanivimab arm harbored such a variant post-baseline at ≥ 15% and ≥ 50% allele fractions, respectively, compared with 8.2% (8/97) and 4.1% (4/97), respectively, of participants in the placebo arm. Most of these variants were first detected on Day 7 following treatment initiation and many were detected only at a single time point (700 mg arm: 5/9 and 2/6 at ≥ 15% and ≥ 50% allele fractions, respectively; placebo arm: 8/8 and 4/4, respectively).

For the 700 mg bamlanivimab arm, these variants were detected more frequently in high-risk participants (14.0% [6/43] and 9.3% [4/43] at ≥ 15% and ≥ 50% allele fractions, respectively, vs 2.4% [1/41] and 0% [0/41], respectively, in the placebo arm). The clinical relevance of these findings is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16   NON-CLINICAL TOXICOLOGY

Carcinogenicity, Genotoxicity and Reproductive and Developmental Toxicology:

Not conducted.

General Toxicology:

Toxicology studies in the rat uncovered no adverse effects when bamlanivimab was administered intravenously. Non-adverse increases in neutrophils were observed.

Special Toxicology:

Antibody Dependent Enhancement (ADE) of Infection

The risk that bamlanivimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of bamlanivimab down to 100-fold below the EC50 value.

Tissue Cross-Reactivity

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected.

PATIENT MEDICATION INFORMATION

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBamlanivimab

Bamlanivimab for injection

Read this carefully before you start taking **bamlanivimab**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **bamlanivimab**.

What is bamlanivimab used for?

Bamlanivimab is a medicine being studied for the treatment of COVID-19. Bamlanivimab may help limit the amount of the COVID-19 causing virus in your body; this may help you get better faster. Bamlanivimab may be given if you or your child are 12 years of age or older and weigh at least 40 kg (kilograms) and are not already in the hospital. Bamlanivimab is only given to patients at high-risk of having the disease get worse. Your healthcare professional will decide if you or your child should take bamlanivimab.

How does bamlanivimab work?

COVID-19 is caused by a virus called a coronavirus. Bamlanivimab may help limit the amount of virus in your body, which may help you get better faster.

What are the ingredients in bamlanivimab?

Medicinal ingredients: bamlanivimab

Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sodium chloride, sucrose, water for injection

Bamlanivimab comes in the following dosage forms:

Bamlanivimab solution, 700 mg/20 mL (35 mg/mL)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take bamlanivimab. Talk about any health conditions or problems you may have, including if you:

- Have any allergies
- Are pregnant or plan to become pregnant

- Are breast-feeding a child
- Have any serious illnesses
- Are taking any medications (prescription, over-the-counter, vitamins, or herbal products)
- Have reactions during or after the infusion. Symptoms of a possible allergic reaction include:
  - Changes to blood pressure or heart rate, low oxygen level in the blood, high temperature, shortness of breath, wheezing, swelling of the face, lips, tongue, or throat, rash/hives/itching, feeling sick or nauseous, sweating, shivering, muscle soreness, dizziness, headache

  Tell your doctor if you get any of these signs or symptoms.
- Have sudden, severe worsening in COVID-19 symptoms

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take bamlanivimab:

- Bamlanivimab will be given to you by a healthcare professional through a vein (intravenous or IV) for at least 1 hour.

Usual dose:

Bamlanivimab is given once. The recommended dose is 700 mg.

Overdose:

If you think you, or a person you are caring for, have taken too much bamlanivimab, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using bamlanivimab?

Possible side effects of bamlanivimab are:
- Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low blood pressure, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, and dizziness.
- Worsening symptoms after treatment: You may experience new or worsening symptoms after infusion, including fever, difficulty breathing, rapid or slow heart rate, tiredness, weakness or confusion. If these occur, contact your healthcare provider or seek immediate medical attention as some of these events have required hospitalization. It is unknown if these events are related to treatment or are due to the progression of COVID-19.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of bamlanivimab. Not a lot of people have been given bamlanivimab. Serious and unexpected side effects may happen. Bamlanivimab is still being studied so

it is possible that all of the risks are not known at this time.

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. Talk to your healthcare provider if you have any questions.

If you experience any side effects not listed here, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about bamlanivimab:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

This leaflet was prepared by Eli Lilly Canada, Inc.

Last Revised April 14, 2021

A4.0 NL-BAM-0001-EUA-CA-PM-YYYYMMDD