PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR ABECMA™

Idecabtagene vicleucel

Cell suspension in one or more patient specific infusion bag(s), target dose of 450 x 10^6 CAR-positive T cells within a range of 275 to 520 x 10^6 CAR-positive T cells, for intravenous infusion

Professed Standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01X)

"Abecma (idecabtagene vicleucel), a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy, indicated for:

- the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last treatment.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Abecma please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drugproducts/notice-compliance/conditions.html"

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Date of Initial Authorization:
May 26, 2021

Date of Revision:
July 30, 2021

Submission Control Number: 244266

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Not Applicable.

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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

Abecma (idecabtagene vicleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for:

- the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last treatment.

Authorization was based on overall response rate, complete response rate and durability of response from a single-arm clinical study. An improvement in progression-free survival or overall survival has not yet been established (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): In the single-arm Phase II KarMMa clinical trial Abecma, 45 (35%) of the 128 patients treated with Abecma were 65 years of age or older. No clinically important differences in the safety or effectiveness of Abecma were observed between these patients and patients younger than 65 years of age (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

Abecma is contraindicated in patients who are hypersensitive 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving Abecma. Delay Abecma treatment if a patient has an active uncontrolled infection, an active inflammatory disorder or an unresolved serious adverse reaction from prior therapies. Monitor for CRS and provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed (see 7 WARNINGS AND PRECAUTIONS).

Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with Abecma, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic adverse reactions and provide supportive care, tocilizumab (if concurrent with CRS), or corticosteroids, as needed (see 7 WARNINGS AND PRECAUTIONS).

Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS), including fatal or life-threatening reactions has occurred in patients receiving Abecma in association with CRS and/or neurological toxicities (see 7 WARNINGS AND PRECAUTIONS).

Abecma should be administered by experienced health professionals at qualified treatment centres (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

Abecma should be administered by experienced health professionals at qualified treatment centres (see 7 WARNINGS AND PRECAUTIONS).

4.1 Dosing Considerations

- For autologous use only as single infusion product; do not infuse Abecma if the information on the patient-specific label does not match the intended patient.
- For intravenous use only; do not use a leukodepleting filter.
- Delay the infusion of Abecma up to 7 days if a patient has any of the following conditions: unresolved adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies, and active infections or inflammatory disorders.
- Abecma contains up to 752 mg sodium per dose which is equivalent to 37.6 % of the recommended maximum daily intake of sodium for an adult. To be taken into consideration when treating patients on a controlled sodium diet.
- Abecma contains up to 274 mg potassium per dose. To be taken into consideration when treating patients with impaired renal function.

4.2 Recommended Dose and Dosage Adjustment

Abecma is provided as a single dose, one-time treatment in one or more patient-specific infusion bags.

Each dose of Abecma contains a suspension of 275 to 520 x 10^6 chimeric antigen receptor (CAR)-positive T cells in one or more infusion bags. The target dose is 450 x 10^6 CAR-positive T cells.

See the accompanying Release for Infusion (RFI) Certificate for additional information pertaining to dose.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS).

Geriatrics (≥ 65 years of age): No dose adjustment is required in patients over 65 years of age (see 1 INDICATIONS).

4.4 Administration

Abecma is for autologous use only. The patient's identity must match the patient identifiers on the Abecma cassette(s) and infusion bag(s). Do not infuse Abecma if the information on the patient-specific label does not match the intended patient.

4.7 Instructions for Preparation and Use

Preparing Patient for Abecma Infusion
Confirm the availability of Abecma prior to starting the lymphodepleting chemotherapy regimen.

Pretreatment
Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m^2 intravenously (IV) and fludarabine 30 mg/m^2 IV for 3 days.

Consult the Product Monographs of cyclophosphamide and fludarabine for information on dose adjustment in renal impairment.

Abecma is to be administered 2 days after completion of lymphodepleting chemotherapy.

Delay the infusion of Abecma up to 7 days if a patient has any of the following conditions:

- unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies
- active infections or inflammatory disorders.

Premedication

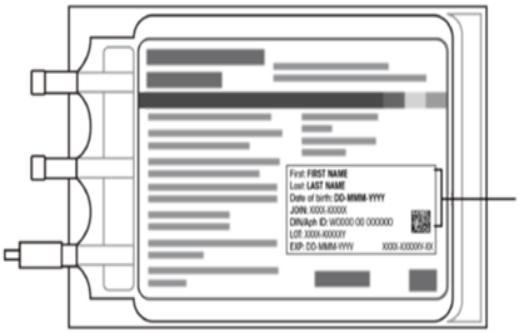
To minimize the risk of infusion reactions, administer acetaminophen (500 - 1000 mg orally) and diphenhydramine (12.5 mg intravenously or 25 to 50 mg) orally, or another H1-antihistamine approximately 30 to 60 minutes before infusion of Abecma.

Avoid prophylactic use of dexamethasone or other systemic corticosteroids, as the use may interfere with the activity of Abecma.

Preparation of Abecma for Infusion

- Confirm patient identity: Prior to preparation of Abecma, match the patient's identity with the patient identifiers on the Abecma cassette(s) and infusion bag(s).
  Note: The patient identifier number may be preceded by the letters Donor ID.
- Do not remove the Abecma infusion bag from the cassette if the information on the patient-specific label does not match the intended patient. Contact the company at 1-855-999-0170 if there are any discrepancies between the labels and the patient identifiers.
- Once patient identification is confirmed, remove the Abecma infusion bag from the cassette and check that the patient information on the cassette label matches the bag label.

Figure 1: Abecma Infusion Bag



- Inspect the infusion bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, contact the company at 1-855-999-0170.
- Place the infusion bag inside a second sterile bag per local guidelines.
- Coordinate the timing of Abecma thaw and infusion. Confirm the infusion time in advance and adjust the start time of the thaw of Abecma so that it will be available for infusion when the patient is ready.
- If more than one infusion bag has been received for treatment, thaw each infusion bag one at a time.
- Thaw Abecma at approximately 37°C using an approved thaw device or water bath until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents

of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or resuspend Abecma in new media prior to infusion.

Administration

- Do NOT use a leukodepleting filter.
- Ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period (see 7 WARNINGS AND PRECAUTIONS). Consult the Product Monograph of tocilizumab for further information on this drug.
- Central venous access may be utilized for the infusion of Abecma and is encouraged in patients with poor peripheral access.
- Confirm the patient's identity matches the patient identifiers on the Abecma infusion bag.
- Prime the tubing of the infusion set with normal saline prior to infusion.
- Infuse Abecma within 1 hour from start of thaw.
- After the entire content of the infusion bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.
- If more than one infusion bag has been received, administer all bags as directed.
- Follow the same procedure for all subsequent infusion bags for the identified patient.

Abecma contains human blood cells that are genetically modified with replication incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring

- Administer Abecma at a qualified treatment centre.
- Monitor patients at least daily for 7 days following Abecma infusion at the qualified treatment centre for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the qualified treatment centre for at least 4 weeks following infusion.

5 OVERDOSAGE

Abecma is administered only by trained medical personnel. The risks of overdose are unknown.

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	A single dose of Abecma contains a suspension of 275 x 10^6 to 520 x 10^6 chimeric antigen receptor (CAR)-positive T cells in one or more patient-specific infusion bag(s). The target dose is 450 x 10^6 CAR-positive T cells. The volume in the infusion bag ranges from 10 mL to 100 mL.	CryoStor® CS10, Magnesium chloride, Potassium chloride, Sodium acetate trihydrate, Sodium chloride, Sodium gluconate, Water for injection

The Abecma formulation contains 50% Plasma-Lyte A and 50% CryoStor® CS10, resulting in a final dimethyl sulfoxide (DMSO) concentration of 5%.

Appearance: Abecma is supplied as a cryopreserved product. Abecma is a liquid, colourless cell suspension for intravenous administration.

See the accompanying Release for Infusion (RFI) Certificate for additional information pertaining to dose and actual volume for infusion.

7 WARNINGS AND PRECAUTIONS

Please see the 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

Abecma should be administered at a qualified treatment centre with personnel trained in handling and administering Abecma and in the management of patients treated with Abecma, including monitoring and managing cytokine release syndrome and neurotoxicity. The centre should have immediate access to appropriate emergency equipment.

Abecma is intended solely for autologous use and should under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Abecma infusion bag and cassette. Do not infuse Abecma if the information on the patient-specific label does not match the intended patient (see 4 DOSAGE AND ADMINISTRATION).

Patients treated with Abecma should not donate blood, organs, tissues and cells for transplantation.

Carcinogenesis (Secondary Malignancies)

Patients treated with Abecma may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, contact the company to obtain instructions on patient samples to collect for testing (see 4 DOSAGE AND ADMINISTRATION, 4.7 Instructions for Preparation and Use).

Driving and Operating Machinery

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Abecma are at risk for altered or decreased consciousness or coordination in the 8 weeks following Abecma infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after Abecma infusion.

Immune

Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with Abecma (see 8 ADVERSE REACTIONS). The median time-to-onset of CRS, any grade, was 1 day (range: 1 to 12 days) and the median duration of CRS was 5 days (range: 1 to 63 days). The most common manifestations of CRS include pyrexia, hypotension, tachycardia, chills, increased C-reactive protein, hypoxia, headache, and fatigue. Grade 3 or higher events that may be associated with CRS include atrial fibrillation, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (see 8 ADVERSE REACTIONS).

Monitoring and Management of CRS

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. MAS is a potentially life-threatening condition, and patients should be closely monitored for evidence of MAS. Treatment of MAS should be administered per institutional standards.

Ensure that a minimum of 2 doses of tocilizumab are available prior to infusion of Abecma.

Monitor patients at least daily for 7 days following Abecma infusion at the qualified treatment centre for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion.

At the first sign of CRS, institute treatment with supportive care, tocilizumab, and/or corticosteroids as indicated. If CRS is suspected, manage according to the algorithm recommendations in Table 2. Patients who experience CRS should be closely monitored for cardiac and organ function until resolution of symptoms. For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Earlier escalation is recommended in patients with refractory CRS within 72 hours post Abecma infusion characterized by persistent fevers, end-organ toxicity (e.g. hypoxia, hypotension) and/or MAS/HLH not improving in grade within 12 hours of first line interventions.

Table 2: CRS Grading and Management Guidance

<table>
<tr><th>CRS Grade</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>Grade 1
Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td><td>If onset 72 hours or more after infusion, treat symptomatically.

If onset less than 72 hours after infusion, consider tocilizumab[a] 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>N/A</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.

Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity[b].</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Consider dexamethasone 10 mg IV every 12-24 hours.</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours).</td></tr>
</table>

<table>
<tr><td></td><td colspan="2">If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day.

If steroids are initiated, continue steroids for at least 3 doses, and taper over a maximum of 7 days.

After 2 doses of tocilizumab, consider alternative anticytokine agents.

Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.
Fever, oxygen requirement greater than or equal to 40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis.</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Administer dexamethasone (e.g., 10 mg IV every 12 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours).

If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day.

If steroids are initiated, continue steroids for at least 3 doses, and taper over a maximum of 7 days.

After 2 doses of tocilizumab, consider alternative anticytokine agents.

Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 4
Life-threatening symptoms.

Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
<tr><td colspan="2">After 2 doses of tocilizumab, consider alternative anticytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.

If no improvement within 24 hours, consider methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) or anti-T cell therapies such as cyclophosphamide 1.5 g/m^2 or others.</td></tr>
</table>

[a]*Refer to tocilizumab Product Monograph for details.*
[b]*Refer to Table 3 for management of neurologic adverse reactions.*

Hemaphagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

HLH/MAS occurred in patients receiving treatment with Abecma, including one patient who developed fatal multi-organ HLH/MAS with CRS and a second patient with fatal bronchopulmonary aspergillosis, where HLH/MAS was a considered a contributing factor.

All events of HLH/MAS reported in the Phase II KarMMa study had an onset within 10 days of the Abecma infusions (median onset of 7 days) and occurred in the setting of CRS. Two events were also reported with overlapping neurotoxicity.

Hypogammaglobulinemia

Plasma cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with Abecma and hypogammaglobulinemia was reported in patients treated with Abecma in clinical studies (see 8 ADVERSE REACTIONS).

Monitor immunoglobulin levels after treatment with Abecma and manage per local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and immunoglobulin replacement.

Use of Live vaccines

The safety of immunization with live viral vaccines during or following Abecma treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Abecma treatment, and until immune recovery following treatment with Abecma.

Hypersensitivity Reactions

Allergic reactions may occur with the infusion of Abecma. Serious hypersensitivity reactions, including anaphylaxis may be due to dimethyl sulfoxide (DMSO) in Abecma.

Prolonged Cytopenias

Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and Abecma infusion. In the Phase II KarMMa study, Grade 3 or 4 neutropenia and thrombocytopenia that had not resolved by Month 1 following Abecma infusion were very common (see 8 ADVERSE REACTIONS). In patients who recovered from Grade 3 or 4 neutropenia after Month 1, the median time to recovery from Abecma infusion was 1.9 months. For patients who recovered from Grade 3 or 4 thrombocytopenia after 1 month, the median time to recovery was 2.1 months.

Monitor blood counts prior to and after Abecma infusion. Manage cytopenias with myeloid growth factor and blood product transfusion support according to local institutional guidelines.

Serious Infections

Fatal and severe infections have occurred in patients treated with Abecma infusion. Patients with active infections or inflammatory disorders should not be treated with Abecma. Infections, including Grade 3 or 4 events occurred frequently in patients treated with Abecma and were due to unspecified pathogens, viral infections, bacterial infections, and/or fungal infections (see 8 ADVERSE REACTIONS). Monitor patients for signs and symptoms of infection before and after Abecma infusion and treat appropriately. Administer prophylactic, pre-emptive, and/or therapeutic antimicrobials according to local institutional guidelines.

Febrile neutropenia may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

HIV, CMV, Hepatitis B, Hepatitis C and Viral Reactivation

Cytomegalovirus (CMV) infection resulting in pneumonia and death has occurred following Abecma infusion.

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against plasma cells.

Perform screening for CMV, HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines before collection of cells for manufacturing. Patients with active viral infections should not receive Abecma. Monitor and consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice. Patients with HIV were excluded from clinical studies and there is no information on the safety and efficacy of Abecma in these individuals.

Monitoring and Laboratory Tests

- Administer Abecma at a qualified treatment centre.
- Monitor patients at least daily for 7 days following Abecma infusion at the qualified treatment centre for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the qualified treatment centre for at least 4 weeks following infusion and not to drive or operate machinery for at least 8 weeks following infusion.

Neurologic

Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with Abecma, including concurrently with CRS, after CRS resolution, or in the absence of CRS.

The median time-to-onset of the first event of neurotoxicity was 2 days (range: 1 to 10 days) andthe median duration of neurotoxicity was 3 days (range: 1 to 26 days). Some patients required at least 1 dose of corticosteroids for treatment of CAR T cell-associated neurotoxicity.

The most frequently reported neurologic or psychiatric toxicities included headache, confusional state, dizziness, anxiety, insomnia, tremor, encephalopathy, somnolence, and aphasia (see 8 ADVERSE REACTIONS).

Monitoring and Management of Neurologic Toxicities

Monitor patients at least daily for 7 days following Abecma infusion at the qualified treatment centre for signs and symptoms of neurologic toxicities (Table 3). Rule out other causes of neurologic symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. If neurologic toxicity is suspected, manage according to the algorithm recommendations in Table 3, with supportive care and/or corticosteroids as needed. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.

If concurrent CRS is suspected during the neurologic toxicity event, manage CRS according to the recommendations in Table 2, and use the more aggressive intervention for the two events specified in Table 2 and Table 3.

Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.

Table 3: Neurologic Toxicity Grading and Management Guidance

Neurologic Toxicity Grade[a]	Corticosteroids and Antiseizure Medications
Grade 1	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. Steroids are not recommended for isolated Grade 2 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.
Grade 3	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided into 4 times a day; taper within 7 days). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.
Grade 4	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g, repeated every 24 hours if needed; taper as clinically indicated). Consider cyclophosphamide 1.5 g/m^2. If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.

[a] National Cancer Institute (United States) Common Terminology Criteria for Adverse Events criteria for grading neurologic toxicities.

Reproductive Health: Female and Male Potential

Pregnancy status of females with reproductive potential should be verified via pregnancy

testing prior to starting treatment with Abecma.

Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) after Abecma administration. Sexually active males who have received Abecma should use a condom during intercourse with females of reproductive potential or pregnant women.

If either partner has received Abecma, pregnancy should be discussed with the treating physician.

See the Product Monographs for fludarabine and cyclophosphamide for information on the need for effective contraception with the use of these lymphodepleting chemotherapies.

Fertility

There are no data on the effects of Abecma on fertility. See 16 NON-CLINICAL TOXICOLOGY.

Special Populations

7.1.1 Pregnant Women

There are no available data with Abecma use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Abecma to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if Abecma has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including plasma cell aplasia or hypogammaglobulinemia. Therefore, Abecma is not recommended for women who are pregnant, and pregnancy after Abecma infusion should be discussed with the treating physician. Assess immunoglobulin levels in newborns of mothers treated with Abecma.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Abecma.

7.1.2 Breast-feeding

There is no information regarding the presence of Abecma in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ABECMA and any potential adverse effects on the breastfed infant from Abecma or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): In the Phase II KarMMa clinical trial of Abecma, 45 (35.2%) of the 128 multiple myeloma (MM) patients were 65 years of age or older and four (3.1%) patients were 75 years of age or older. No clinically important differences in safety or effectiveness of Abecma were observed between 65-74 years of age and patients younger than 65 years of age. There were too few patients aged 75 years and older to assess any important clinical differences in these elderly patients compared to younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are described under 7 WARNINGS AND PRECAUTIONS:

- Cytokine Release Syndrome
- Neurologic Adverse Reactions
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 data described in this section reflects the exposure to Abecma in the single arm Phase II KarMMa study, in which the majority (n=124) of the 128 patients with relapsed/refractory multiple myeloma received Abecma at a dose between 275 to 520 x 10^6 CAR-positive T cells (see 14 CLINICAL TRIALS), which is the recommended dose for this therapy. The median duration of follow-up was 13.3 months. The median age of the study population was 60.5 years (range: 33 to 78 years); 35% were 65 years or older and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 45%, 1 in 53%, and 2 in 2% of patients.

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included CRS, infections – pathogen unspecified, diarrhea, fatigue, nausea, viral infections, encephalopathy, pyrexia, cough, decreased appetite, headache, edema and hypogammaglobulinemia.

Serious adverse reactions occurred in 67% of patients. The most common (greater than or equal to 5%) serious adverse reactions included CRS (17%), general physical health deterioration (13%), pneumonia (9%), and febrile neutropenia (7%).

The most common (greater than or equal to 10%) Grade 3 or 4 nonlaboratory adverse reactions were febrile neutropenia (16%) and infections – pathogen unspecified (15%).

Table 4 summarizes the adverse events that occurred in at least 10% of patients treated with ABECMA.

Table 4: Adverse Events Observed in at Least 10% of Patients Treated with Abecma in the Phase II KarMMa Study

Adverse Event	Any Grade [150 to 450 x 10^6] (N=128) n (%)	≥Grade 3 [150 to 450 x 10^6] (N=128) n (%)
Blood and lymphatic system disorders		
Febrile neutropenia	21 (16)	20 (16)
Coagulopathy[a]	13 (10)	3 (2)
Cardiac disorders		

Tachycardia[b]	24 (19)	0
Gastrointestinal disorders		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Constipation	20 (16)	0
Vomiting	19 (15)	0
Oral pain[c]	15 (12)	0
General disorders and administration site conditions		
Fatigue[d]	57 (46)	4 (3)
Pyrexia	32 (25)	3 (2)
Edema[e]	32 (25)	0
Pain[f]	26 (20)	0
Chills	14 (11)	0
General physical health deterioration	17 (13)	16 (13)
Immune system disorders		
Cytokine release syndrome	107 (84)	7 (5)
Hypogammaglobulinemia[g]	30 (23)	1 (1)
Infections and infestations[h]		
Infections – Pathogen unspecified	63 (49)	19 (15)
Viral Infections	35 (27)	11 (9)
Bacterial Infections	19 (15)	5 (4)
Pneumonia[i]	21 (16)	12 (9)
Upper respiratory tract infection[j]	44 (34)	3 (2)
Investigations		
Weight decreased	17 (13)	2 (2)
C-reactive protein increased	15 (12)	3 (2)
Metabolism and nutrition disorders		
Decreased appetite[k]	27 (21)	1 (1)
Musculoskeletal and connective tissue disorders		
Motor dysfunction[l]	14 (11)	0
Musculoskeletal pain[m]	59 (46)	4 (3)
Nervous system disorders		
Encephalopathy[n]	33 (26)	7 (5)
Headache[o]	28 (22)	1 (1)
Dizziness[p]	21 (16)	0
Peripheral Neuropathy[q]	21 (16)	1 (1)
Psychiatric disorders		
Insomnia[r]	16 (13)	0
Anxiety[s]	15 (12)	1 (1)
Renal and urinary disorders		
Renal Failure[t]	14 (11)	3 (2)
Respiratory, thoracic and mediastinal disorders		
Cough[u]	29 (23)	0
Dyspnea[v]	17 (13)	4 (3)
Skin and subcutaneous tissue disorder		
Rash[w]	19 (15)	1 (1)

Xerosis[x]	14 (11)	0
Vascular disorders		
Hypotension[y]	22 (17)	1 (1)
Hypertension	14 (11)	4 (3)
Hemorrhage[z]	13 (10)	4 (3)

CAR=chimeric antigen receptor.
MedDRA = Medical Dictionary for Regulatory Activities.
Adverse reactions based on MedDRA System Organ Class (SOC) and Preferred Term (PT).
Coded using MedDRA version 22.0.

Note: The target dose is 450 x 10^6 CAR-positive T cells within a range of 275 to 520 × 10^6 CAR-positive T cells.
[a] Coagulopathy includes activated partial thromboplastin time prolonged, anticoagulation drug level above therapeutic, disseminated intravascular coagulation, fibrin D dimer increased, international normalised ratio increased.
[b] Tachycardia includes sinus tachycardia, tachycardia.
[c] Oral pain includes oropharyngeal pain, oral pain, toothache.
[d] Fatigue includes asthenia, fatigue, malaise.
[e] Edema includes edema, face edema, fluid overload, fluid retention, generalized edema, peripheral edema, peripheral swelling, scrotal edema, scrotal swelling, swelling.
[f] Pain includes bladder discomfort, breast pain, cancer pain, ear pain, flank pain, groin pain, infusion site pain, non-cardiac chest pain, pain, pain in extremity, pain in jaw, pain of skin, pelvic pain.
[g] Hypogammaglobulinemia includes blood immunoglobulin G decreased, hypogammaglobulinemia, hypoglobulinemia.
[h] Infections and infestations System Organ Class (SOC) adverse events are grouped by pathogen type.
[i] Pneumonia includes bronchopulmonary aspergillosis, lung infection, pneumonia, pneumonia aspiration, pneumonia cytolomegaloviral, pneumonia pneumococcal, pneumonia pseudomonal. Pneumonias may also be included under pathogen categories.
[j] Upper respiratory tract infection includes laryngitis, pharyngeal erythema, pharyngitis, respiratory tract congestion, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection bacterial. Upper respiratory tract infections may also be included under pathogen categories.
[k] Decreased appetite includes decreased appetite, hyophagia.
[l] Motor dysfunction includes dysphonia, eyelid ptosis, hypotonia, motor dysfunction, muscle spasms, muscular weakness, restless leg syndrome.
[m] Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, spinal pain.
[n] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, disturbance in attention, dyscalculia, dysgraphia, encephalopathy, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, toxic encephalopathy.
[o] Headache includes headache, head discomfort, sinus headache.
[p] Dizziness includes dizziness, presyncope, syncope, vertigo.
[q] Peripheral neuropathy peripheral includes carpal tunnel syndrome, hypoesthesia, hypoesthesia oral, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, sciatica
[r] Insomnia includes insomnia, sleep deficit, sleep disorder.
[s] Anxiety includes anxiety, feeling jittery, nervousness.
[t] Renal Failure includes includes acute kidney injury, renal failure, chronic kidney disease, renal impairment and blood creatinine increased.
[u] Cough includes cough, productive cough, upper-airway cough syndrome.
[v] Dyspnea includes dyspnea, dyspnea exertional.
[w] Rash includes acne, dermatitis, dermatitis bullous, erythema, rash, rash macular, rash papular, urticarial.
[x] Xerosis includes dry eye, dry mouth, dry skin, dry lip, xerosis.
[y] Hypotension includes hypotension, orthostatic hypotension.
[z] Hemorrhage includes cerebral hemorrhage, conjunctival hemorrhage, epistaxis, post procedural hemorrhage, hematuria, hyphaema.

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions that occurred in less than 10% of patients treated with Abecma include the following:

- *Cardiac disorders:* atrial fibrillation (4.7%), cardiomyopathy[a] (1.6%), ventricular tachycardia (0.8%).

- *Gastrointestinal disorders:* gastrointestinal hemorrhage[b] (3.9%).
- *Immune system disorders:* hemophagocytic lymphohistiocytosis (3.1%).
- *Infections and infestations:* fungal infections (7.8%).
- *Nervous system disorders:* tremor (7.8%), aphasia[c] (7.0%), ataxia[d] (2.3%), paresis[e] (2.3%), seizure (1.6%).
- *Psychiatric disorders:* delirium[f] (5.5%).
- *Respiratory, thoracic, and mediastinal disorders:* hypoxia (3.1%), pulmonary edema (2.3%).

[a] Cardiomyopathy includes stress cardiomyopathy, ventricular hypertrophy.
[b] Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, hemorrhoidal hemorrhage, melena, mouth hemorrhage.
[c] Aphasia includes aphasia, dysarthria.
[d] Ataxia includes ataxia, gait disturbance.
[e] Paresis includes hemiparesis, cranial nerve disorder.
[f] Delirium includes delirium, disorientation, hallucination.

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

Clinical Trial Findings

Table 5 describes the most common Grade 3 or 4 laboratory abnormalities, based on laboratory data occurring in at least 10% of patients.

Table 5: Grade 3 or 4 Laboratory Abnormalities Occurring in at Least 10% of Patients Treated with Abecma in the Phase II KarMMa Study (N=128)

Laboratory Abnormality	Target Dose of Abecma (CAR-Positive T Cells) Grade 3 or 4 N (%)
	[150 to 450 x 10^6] (N=128) n (%)
Lymphopenia	128 (100)
Leukopenia	125 (98)
Neutropenia	125 (98)
Anemia	98 (77)
Thrombocytopenia	85 (66)
Hypophosphatemia	59 (46)
Hyponatremia	19 (15)
aPTT Increased	13 (10)

aPTT=activated partial thromboplastin time; CAR=chimeric antigen receptor; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute (United States).
Laboratory tests were graded according to NCI CTCAE Version 4.03. Laboratory abnormalities are sorted by decreasing frequency in the 150 to 450 $\times$ 10^6 column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with Abecma include the following: alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hyperglycemia, hypoalbuminemia, hypocalcemia, hypofibrinogenemia, hypokalemia, and hypomagnesemia.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal interaction studies have been performed with Abecma.

9.4 Drug-Drug Interactions

Pharmacokinetic Interactions

No pharmacokinetic drug interaction studies have been performed with Abecma.

T cells are known to be susceptible to immune-suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, should be considered as these can be lymphotoxic.

Pharmacodynamic Interactions

The immunization with vaccines during or following Abecma treatment has not been studied. The effectiveness of vaccines may be affected by prolonged plasma cell aplasia and hypogammaglobulinemia (see 7 WARNINGS AND PRECAUTIONS, Hypogammaglobulinemia).

The safety of immunization with live viral vaccines has not been investigated in patients treated with Abecma. Vaccination with live viral vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Abecma treatment, and until immune recovery following treatment with Abecma.

9.7 Drug-Laboratory Test Interactions

HIV and the lentivirus used to make Abecma have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received Abecma.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Abecma is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of ABECMA results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

10.3 Pharmacokinetics

Following Abecma infusion, the CAR-positive cells proliferate and undergo rapid multi-log expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood (T_{max}) occurred 11 days after infusion. Abecma can persist in peripheral blood for up to 1 year post-infusion. A summary of T_{max}, $AUC_{0\text{-}28days}$, and C_{max} by target dose level and across doses is provided in Table 6.

Table 6: Pharmacokinetic Parameters of Abecma in Patients with Relapsed/Refractory Multiple Myeloma in the Phase II KarMMa Study

Pharmacokinetic Parameter	Summary Statistic	Total [150 to 450 × 10^6] CAR-Positive T Cells
T_{max} (days)	Median (Range)	11 (7-30) N = 127
C_{max} (copies/µg)	Geometric mean (geometric CV%)	231,278 (178) N = 127
$AUC_{0\text{-}28days}$ (days*copies/µg)	Geometric mean (geometric CV%)	2,860,340 (197) N = 125

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days post-infusion; C_{max} = the maximum transgene level; T_{max} = time of maximum observed transgene level.

Abecma transgene levels were positively associated with objective tumor response (partial response or better). The median C_{max} levels in responders (N = 93) were approximately 4.5-fold higher compared to the corresponding levels in non-responders (N = 34). Median $AUC_{0\text{-}28days}$ in responding patients (N = 93) was approximately 5.5-fold higher than non-responders (N = 32).

Tocilizumab and Corticosteroid Use

Some patients required tocilizumab and/or corticosteroid for the management of CRS. Abecma can continue to expand and persist following tocilizumab or steroid administration (see 7 WARNINGS AND PRECAUTIONS, Immune, CRS).

Patients with CRS treated with tocilizumab had higher Abecma cellular expansion levels, as measured by 1.4-fold and 1.6-fold higher median C_{max} (N = 66) and $AUC_{0\text{-}28days}$ (N = 65), respectively, compared to patients who did not receive tocilizumab (N = 61 for C_{max} and N = 60 for $AUC_{0\text{-}28days}$).

Patients with CRS treated with corticosteroids had higher Abecma cellular expansion levels, as measured by 1.7 fold and 2.2-fold higher median C_{max} (N = 18) and $AUC_{0\text{-}28days}$ (N = 18), respectively, compared to patients who did not receive corticosteroids (N = 109 for C_{max} and N = 107 for $AUC_{0\text{-}28days}$).

Special Populations and Conditions

- Pediatrics: The pharmacokinetics of Abecma in patients less than 18 years of age have not been evaluated (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).
- Geriatrics: There is limited pharmacokinetic data of Abecma in patients 75 years and older (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics). Age (range: 33 to 78 years) had no significant impact on expansion parameters.
- Hepatic Insufficiency: Hepatic impairment studies of Abecma were not conducted.
- Renal Insufficiency: Renal impairment studies of Abecma were not conducted.
- Other Intrinsic Factors: Based on population PK modelling, gender, race, and ethnicity had no significant impact on Abecma expansion parameters. Subjects with lower body weight, however, had higher cellular expansion levels. Due to high variability in pharmacokinetic cellular expansion, the overall effect of weight on the pharmacokinetics of ABECMA is considered not to be clinically relevant.

11 STORAGE, STABILITY AND DISPOSAL

Incompatibilities

- This medicinal product must not be mixed with other medicinal products.

Storage

- Abecma must be stored frozen in ethylene vinyl acetate (EVA) freezing bags in a container for cryogenic storage in the vapor phase of liquid nitrogen (≤ -130°C).
- Thawed product should not be refrozen.

Stability

- Abecma is stable for 1 year when stored frozen in the vapor phase of liquid nitrogen (≤ -130°C).
- The volume intended for infusion within each bag must be completely infused within 1 hour from start of thaw.

Disposal

- Unused medicine must be disposed of in compliance with local guidelines for the disposal of medicinal products containing blood borne pathogens and genetically modified cells.

12 SPECIAL HANDLING INSTRUCTIONS

Abecma contains human blood cells that are genetically modified with replication incompetent lentiviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: idecabtagene vicleucel

Physicochemical properties: idecabtagene vicleucel is a liquid, colourless cell suspension for intravenous administration.

Product Characteristics:

A genetically modified autologous T cell immunotherapy consisting of T cells transduced with lentiviral vector (LVV) encoding a chimeric antigen receptor (CAR) that recognizes B-cell maturation antigen (BCMA). The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for recognizing B cell maturation antigen (BCMA) followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signaling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Binding of Abecma to BCMA-expressing target cells leads to signaling initiated by CD3ζ and 4-1BB domains, and subsequent CAR-positive T cell activation. Antigen-specific activation of Abecma results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Abecma is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells which are then transduced with the replication incompetent lentiviral vector containing the anti-BCMA CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension (dispersion) in a patient-specific infusion bag. The product is thawed prior to infusion (see 4 DOSAGE AND ADMINISTRATION, 4.4 Administration and 12 SPECIAL HANDLING INSTRUCTIONS).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7: Summary of patient demographics for the Clinical Trial in Relapsed/Refractory Multiple Myeloma

Study # Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
BB2121-MM-001 US, Canada, EU (KarMMa) Phase 2, multicenter, open-label, single-arm study to evaluate the efficacy and safety of idecabtagene vicleucel in patients with relapsed and refractory multiple myeloma	Single intravenous infusion of Abecma within the recommended dose range of 275 to 520 x 10^6 CAR+ T cells (target dose of 450 x 10^6 CAR+ T cells)	140 patients underwent leukapheresis; 128 patients received Abecma (124 patients received Abecma at a dose between 275 to 520 x 10^6 CAR+ T cells)	Leukapheresed and Treated group: 60.5 years (range: 33 to 78)	Leukapheresed: 82 (59%) males 58 (41%) females Treated: 76 (59%) males 52 (41%) females

KarMMa was an open-label, single-arm, multicenter Phase II study that evaluated the efficacy and safety of Abecma in adult patients with relapsed/refractory multiple myeloma who had received at least three prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

The study included patients with ECOG performance status of 0 or 1. The study excluded patients with known central nervous system (CNS) involvement with myeloma or any history or presence of CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or other CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis. Patients were excluded if they had a prior allogeneic stem cell transplant, evidence of HIV infection, active HBV or HCV infection, a creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal and left ventricular ejection fraction <45%. Patients were also excluded if absolute neutrophil count <1000 cells/mm^3 and platelet count <50,000/mm^3. Patients had measurable disease by IMWG 2016 criteria at enrollment. Bridging therapy with corticosteroids, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies to which patients were previously exposed was permitted for disease control between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

Lymphodepleting chemotherapy consisted of cyclophosphamide (300 mg/m^2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of Abecma. Patients were hospitalized for 14 days after Abecma.

The median number of prior therapies was 6 (Range: 3 to 16), and 88% of the patients received 4 or more prior lines of therapy. Ninety-four percent of the subjects were refractory to an anti-CD38 antibody. Eighty-four percent were triple class refractory, and 26% were penta-refractory. Ninety-four percent had received prior autologous stem cell transplantation.

The study consisted of pretreatment (screening, leukapheresis, and bridging therapy [if needed]); treatment (lymphodepleting chemotherapy [LDC] and Abecma infusion); and post-treatment (ongoing) for a minimum of 24 months following Abecma infusion or until documented disease progression, whichever was longer. The LDC period was one 3-day cycle of cyclophosphamide (300 mg/m^2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of Abecma. Patients were hospitalized for 14 days after Abecma infusion to monitor and manage potential CRS and neurotoxicity.

Of 140 patients who underwent leukapheresis, 128 patients received Abecma. One of the 140 patients did not receive the product due to manufacturing failure. Eleven other patients were not treated with Abecma, due to physician decision (n=3), patient withdrawal (n=4), adverse events (n=1), progressive disease (n=1), or death (n=2), prior to receiving Abecma. With exception of 4 individuals, the patients enrolled on study received the Abecma dose between 275 to 520 x10^6 CAR-positive T cells, with a target dose of 450 x 10^6 CAR-positive T cells.

Table 8: Baseline and Demographic/Disease Characteristics for Study Population

Characteristic	**Treated Population (N=128)**	**Enrolled Population (N=140)**
Age (years)		
Median (Min, max)	60.5 (33, 78)	60.5 (33, 78)
Age category, n (%)		

<65 years	83 (64.8)	92 (65.7)
≥65 years	45 (35.2)	48 (34.3)
<75 years	124 (96.9)	135 (96.4)
≥75 years	4 (3.1)	5(3.6)
Sex, n (%)		
Male	76 (59.4)	82 (58.6)
Female	52 (40.6)	58 (41.4)
Race, n (%)		
Asian	3 (2.3)	3 (2.1)
Black or African American	6 (4.7)	8 (5.7)
White	103 (80.5)	113 (80.7)
Unknown/Other	16 (12.5)	16 (11.4)
Ethnicity, n (%)		
Hispanic or Latino	11 (8.6)	13 (9.3)
Not Hispanic or Latino	103 (80.5)	112 (80.0)
Not reported/Unknown	14 (10.9)	15 (10.7)
ECOG Performance Status, n (%)		
0	57 (44.5)	60 (42.9)
1	68 (53.1)	77 (55.0)
2[a]	3 (2.3)	3 (2.1)
Patients with Extramedullary Plasmacytoma, n (%)	50 (39.1)	52 (37.1)
Baseline Cytogenetic High Risk[b,c]	45 (35.2)	46 (32.9)
Revised ISS Stage at Baseline (derived)[d], n (%)		
Stage I	14 (10.9)	14 (10.0)
Stage II	90 (70.3)	97 (69.3)
Stage III	21 (16.4)	26 (18.6)
Unknown	3 (2.3)	3 (2.1)
Time since Initial Diagnosis (years), Median (min, max)	6 (1.0, 17.9)	6 (1.0, 17.9)
Patients with Prior Stem Cell Transplant, n (%)	120 (93.8)	131 (93.6)
Number of Prior Antimyeloma Regimens[e], Median (min, max)	6 (3, 16)	6 (3, 17)
Creatinine Clearance (mL/min), n (%)		
<30	1 (0.8)	3(2.1)
30 to <45	8 (6.3)	9 (6.4)
45 to <60	10 (7.8)	13 (9.3)
60 to <80	36 (28.1)	38 (27.1)
≥80	73 (57.0)	77 (55.0)

CAR=chimeric antigen receptor; ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System; min=minimum; max=maximum.

[a] These patients had ECOG scores of <2 at screening for eligibility but subsequently deteriorated to ECOG scores of ≥2 at baseline prior to start of lymphodepleting chemotherapy.

[b] Baseline cytogenetic abnormality was based on baseline cytogenetics from central laboratory if available. If central laboratory was not available or was unknown, cytogenetics prior to screening was used.

[c] High-risk defined as deletion in chromosome 17p (del[17p]), translocation involving chromosomes 4 and 14 (t[4;14]), or translocation involving chromosomes 14 and 16 (t[14;16]).

[d] Revised ISS was derived using baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase.

[e] Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen.

Most patients (88%) treated with Abecma received bridging therapy for control of their multiple

myeloma during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range: 24 to 55 days) and the median time from leukapheresis to infusion was 40 days (range: 33 to 79 days).

Efficacy was established on the basis of overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as assessed by the Independent Response committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. ORR was defined as percentage of patients who achieved a partial response or better as assessed by the IRC among the Abecma-treated population. The ORR was tested against the null hypothesis of ≤ 50%.

14.2 Study Results

Efficacy results are shown in Table 9. Six patients are excluded from the efficacy analysis due to absence of measurable disease at the time of Abecma infusion.

Table 9: Summary of Efficacy based on Independent Response Committee Review According to IMWG Criteria

	Enrolled Population[a] (N=140)	Treated Population with Measurable Disease at the time of Abecma Infusion [150 to 450 x 10^6] (N=122)
Primary Endpoint		
Overall Response Rate (PR or Better), n (%)	**90 (64)**	**90 (74)**
95% CI[b]	56, 72	65, 81
Key Secondary Endpoint		
CR or sCR, n (%)	**39 (28)**	**39 (32)**
95% CI[b]	21, 36	24, 41
Other Secondary Endpoints		
VGPR, n (%)	**24 (17)**	**24 (20)**
95% CI[b]	11, 24	13, 28
Duration of Response[c] (PR or Better)		
Median[d] (months)	11	11
95% CI[d]	9, 11	9, 11
Duration of Response (CR or Better)		
Median[d] (months)	19	19
95% CI[d]	11, NE	11, NE

CAR=chimeric antigen receptor; CI=confidence interval; CR=complete response; IMWG=International Myeloma Working Group; max=maximum; Min=minimum; NE=not estimable; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

[a] All patients who underwent leukapheresis. Response data for patients with non-measurable disease at baseline are not included (n=6).

[b] For 150 to 450 x 10^6 and "Enrolled population": Clopper Pearson exact CI.

[c] Response is defined as achieving sCR, CR, VGPR, or PR according to IMWG criteria.

[d] Median and 95% CI is based on Kaplan-Meier estimation.

For patients who had a response to therapy (PR or better), the median time to response (TTR)

was 1 month (min, max: 0.5, 2.9) from the time of Abecma infusion.

14.4 Immunogenicity

Abecma has the potential to induce anti-product antibodies. In clinical studies, humoral immunogenicity of ABECMA was measured by determination of anti-CAR antibody in serum pre- and post-administration.

In the KarMMa study, 3.9% of patients (5/128) tested positive for pre-infusion anti-CAR antibodies and treatment-induced anti-CAR antibodies were detected in 48% (61/128) of the patients. There is no evidence that the presence of pre-existing or post-infusion anti-CAR antibodies impact the cellular expansion, safety, or effectiveness of Abecma.

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL TOXICOLOGY

Due to the nature of this product, traditional toxicity, fertility, and pharmacokinetic studies with Abecma were not conducted.

Carcinogenicity and Genotoxicity: Genotoxicity assays and carcinogenicity studies in rodents are not appropriate to assess the risk of insertional mutagenesis for genetically modified cell therapy products. No alternative adequate animal models are available.

In vitro expansion studies with CAR-positive T cells (Abecma) from healthy donors and patients showed no evidence for transformation and/or immortalisation of T cells. A genomic insertion site analysis of the lentiviral vector was performed on Abecma samples including patient lots and there was no evidence for preferential integration near genes of concern or preferential outgrowth of cells harboring integration sites of concern.

17 SUPPORTING PRODUCT MONOGRAPHS

1) PrACTEMRA (tocilizumab, 20 mg/mL [Concentrate Solution for Infusion]; 162 mg/0.9 mL [Solution for Injection]), Control No. 235547, Product Monograph, Hoffmann-La Roche Limited. [Jan 04, 2021].

2) PrFludarabine Phosphate, Sterile Solution for Injection 25 mg/mL (2 mL per vial), Control No. 190383, Product Monograph, Teva Canada Limited. [March 1, 2016].

3) PrPROCYTOX [(cyclophosphamide tablets USP: 25 mg, 50 mg; cyclophosphamide for injection: 200 mg, 500 mg, 1000 mg, 2000 mg (powder for injection) per vial], Control No. 155509, Product Monograph, Baxter Corporation. [September 7, 2012].

4) PrSOLU-MEDROL (methylprednisolone sodium succinate for injection USP, Sterile Powder, 500 mg, 1 g Vials), Control No. 213593, Product Monograph, Pfizer Canada Inc. [May 9, 2018].

5) PrDEXAMETHASONE OMEGA UNIDOSE (dexamethasone sodium phosphate injection USP, 10 mg/mL), Control No. 154533, Prescribing Information, Omega Laboratories Limited. [June 12, 2012].

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ABECMA™

(idecabtagene vicleucel)

Read this carefully before you start taking Abecma and each time you get a refill. 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 Abecma.

Serious Warnings and Precautions

Abecma can cause serious side effects. Sometimes, these serious side effects are life-threatening and can lead to death. The following serious side effects have been seen in people taking Abecma:

- Fever and chills which may be symptoms of a serious side effect called cytokine release syndrome (CRS), which can be severe or fatal. Other symptoms of CRS are difficulty breathing, dizziness or light-headedness, nausea, headache, fast heartbeat, low blood pressure or fatigue, vomiting, diarrhea, muscle pain and joint pain.
- Neurological problems like confusion, difficulty with memory, difficulty speaking or slowed speech, difficulty understanding speech, loss of balance or coordination, disorientation, being less alert (decreased consciousness) or excessive sleepiness, loss of consciousness, delirious, fits (seizures), shaking or weakness with loss of movement on one side of the body.
- Fever, low blood pressure, shortness of breath, low blood counts, bleeding, kidney, liver, spleen and other organ damage which may be symptoms of a serious side effect called Hemophagocytic Lymphohistiocytosis/ Macrophage activation syndrome (HLH/MAS) and can be life-threatening or fatal if not recognized early and treated.

Abecma will only be given by an experienced healthcare professional at qualified treatment centres.

What is ABECMA used for?

- Abecma is used to treat adults with a type of cancer called multiple myeloma which is a cancer of the bone marrow.
- It is given when your cancer has not responded to at least three different treatments or has come back after these treatments.

For the following indication Abecma has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional."

- the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last therapy.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.
Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Abecma work?

Abecma is made from your own white blood cells. These cells are taken from your blood and are modified to recognize the myeloma cells in your body. It takes about 4 weeks from the time your cells are received at the manufacturing site and are available to be shipped back to your healthcare professional. You may be given other therapies to treat your cancer while Abecma is being made. When these cells are introduced back into your blood, they can recognise and attack the myeloma cells.

What are the ingredients in Abecma?

Medicinal ingredients: idecabtagene vicleucel

Non-medicinal ingredients: CryoStor® CS10, Magnesium chloride, Potassium chloride, Sodium acetate trihydrate, Sodium chloride, Sodium gluconate, Water for injection.

Abecma comes in the following dosage forms:

Abecma is a liquid, colourless cell suspension for infusion in one or more infusion bags. Abecma is given to you by drip into a vein as a single, one-time treatment.

Do not use Abecma if:

- you are allergic to Abecma or any of the other ingredients of this medicine (listed in "What are the ingredients in Abecma"?). If you think you may be allergic, ask your doctor for advice.

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

- have any lung or heart problems.
- have low blood pressure.
- have an infection. The infection will be treated before Abecma infusion.
- notice the symptoms of your cancer getting worse. In myeloma this might include fever, feeling weak, bone pain, unexplained weight loss.
- have had a cytomegalovirus, hepatitis B virus, hepatitis C virus or human immunodeficiency virus infection.
- have had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

- have had any symptoms of severe allergic reactions, such as shortness of breath or trouble breathing, skin rash, swelling of the lips, tongue, or face, chest pain, feeling dizzy or faint.
- are pregnant, or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Abecma in pregnant or breast-feeding women are not known and it may harm your unborn baby or breastfed child.
- are pregnant or think you may be pregnant after treatment with Abecma, talk to your doctor immediately. You will be given a pregnancy test before treatment starts. Abecma should only be given if the results show you are not pregnant.
- are a man and you plan to father a child after Abecma treatment.
- are breast-feeding or plan to do so.

Other warnings you should know about:

- Do not drive, operate heavy machinery, or do other activities that could be dangerous for at least 8 weeks after you get Abecma. This is because the treatment can cause temporary memory and coordination problems, sleepiness, confusion, dizziness, and seizures.
- Do not donate blood, organs, tissues and cells for transplantation after Abecma treatment.
- Abecma contains up to752 mg sodium per dose which is equivalent to 37.6 % of the recommended maximum daily intake of sodium for an adult.
- Abecma contains up to 274 mg potassium per dose. This should be taken into consideration if you have reduced kidney function

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

The following may interact with Abecma:

- Corticosteroids, chemotherapy, and other medications that can weaken your immune system. This is because these medicines may interfere with the effect of Abecma and may make Abecma less effective.
- Live vaccines: You must not be given certain vaccines called live vaccines:
  - in the 6 weeks before you are given a short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for Abecma.
  - during Abecma treatment.
  - after treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

How you will receive Abecma:

Giving blood to make Abecma from your white blood cells

- Your doctor will take some of your blood using a tube (catheter) in your vein. Some of your white blood cells will be separated from your blood and the rest of your blood is returned to your body. This is called 'leukapheresis' and can take 3 to 6 hours. This process may need to be repeated.
- Your white blood cells will then be frozen and sent away to make Abecma.

Other medicines you will be given before Abecma

- A few days before you receive Abecma, you will be given a short course of chemotherapy. This is to clear away your existing white blood cells.
- Shortly before you receive Abecma, you will be given acetaminophen and an

antihistamine medicine. This is to reduce the risk of infusion reactions and fever.

How Abecma is given to you

- Your doctor will check that the Abecma was prepared from your own blood by checking the patient identity information on the medicine labels matches your details.
- Abecma is given as an infusion drip through a tube into your vein.

After Abecma is given to you

- Stay close to the treatment centre where you received Abecma - for at least 4 weeks.
- You may be monitored daily in the treatment centre for at least 7 days.
- This is so your doctor can check if your treatment is working - and help you if you have any side effects.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to the hospital.
- Your healthcare professional will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare professional as soon as possible to reschedule.

Usual dose:

Abecma comes as a cell suspension in one or more infusion bag(s). The target dose is 450×10^6 CAR-positive T cells within a range of 275 to 520×10^6 CAR-positive T cells. Abecma should be given to you as a single-dose, one-time treatment.

What are possible side effects from using Abecma?

These are not all the possible side effects you may have when taking Abecma. If you experience any side effects not listed here, tell your healthcare professional.

Very common:

- headache
- feeling dizzy, tired or lack of energy
- fast heartbeat
- low blood pressure, dizziness upon standing or high blood pressure
- cough
- decreased appetite
- constipation
- nausea, vomiting
- diarrhea
- swollen ankles, arms, legs and face
- joint pain
- low number of white blood cells (neutrophils, leucocytes and lymphocytes), with or without fever, which can increase your risk of infection
- laboratory test results showing low levels of antibodies, called immunoglobulins (hypogammaglobulinemia) that are important in fighting infections
- laboratory test results showing increased levels of liver enzymes (abnormal liver function test) or a higher level of a protein (C-reactive protein) in blood that may indicate inflammation.

Common:

- difficulty sleeping
- muscle pain

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Fever, chills, difficulty breathing, dizziness or light-headedness, nausea, headache, fast heartbeat, low blood pressure or fatigue may be symptoms of a side effect called cytokine release syndrome or CRS, which can be severe or fatal.		√	√
Confusion, difficulty with memory, difficulty speaking or slowed speech, difficulty understanding speech, loss of balance or coordination, disorientation, being less alert (decreased consciousness) or excessive sleepiness, loss of consciousness, delirious, fits (seizures), shaking or weakness with loss of movement on one side of the body		√	√
Any signs of an infection, which may include fever, chills or shivering, rapid pulse or depending on the location of infection, you may also experience sore throat, cough, shortness of breath or rapid breathing, chest pain, or painful urine or blood in urine		√	√
Feeling very tired or weak or shortness of breath –which may be signs of low levels of red blood cells (anaemia)		√	√
Bleeding or bruising more easily without cause, including nosebleeds or bleeding from the mouth or bowels, which may be a sign of low levels of platelet cells in your blood		√	√
Shortness of breath with or without exercise		√	

Fatigue, muscle weakness or cramps or an irregular heartbeat which may be a sign of low levels in the blood of calcium, potassium, sodium, magnesium, phosphate or albumin		√	
COMMON			
Severe inflammation due to activation of your immune system which could lead to fever, decrease in blood cell levels, difficulty breathing, low blood pressure, dizziness, an increased risk of bleeding, serious damage to the kidneys, liver, spleen or other organs in the body and could be life-threatening or fatal		√	√
Spontaneous or prolonged and excessive bleeding (coagulopathy)		√	√
Extreme shortness of breath or difficulty breathing, feeling suffocated, anxious, restless, cough, frothy sputum with or without blood, blue colored lips, or fast heartbeat, caused by fluid in the lungs (possible symptoms of pulmonary edema)		√	√
Abnormal body movements or lack of coordination		√	
Uneven or irregular heartbeat		√	
Shortness of breath, confusion or drowsiness which may be a sign of low oxygen level in the blood (hypoxia)		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, 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 Abecma:

- 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.celgene.ca/en, or by calling 1-866-463-6267.

This leaflet was prepared by Celgene Inc., a Bristol Myers Squibb company.

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