ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Abecma 260 - 500 x 10^6 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Abecma (idecabtagene vicleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex-vivo* using a replication incompetent lentiviral vector (LVV) encoding a chimeric antigen receptor (CAR) that recognises B-cell maturation antigen (BCMA), comprising a murine-derived, anti-human BCMA single chain variable fragment (scFv) linked to a 4-1BB costimulatory domain and a CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Abecma contains idecabtagene vicleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-BCMA chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one or more infusion bags overall containing a cell dispersion of 260 to 500 x 10^6 CAR-positive viable T cells suspended in a cryopreservative solution.

Each infusion bag contains 10-30 mL, 30-70 mL or 55-100 mL of dispersion for infusion.

The cellular composition and the final cell number varies between individual patient batches. In addition to T cells, natural killer (NK) cells may be present. The quantitative information of medicinal product, including the number of infusion bag(s) to be administered, is presented in the release for infusion certificate (RfIC) located inside the lid of the cryoshipper used for transport.

Excipients with known effect

This medicinal product contains 5% dimethyl sulfoxide (DMSO), up to 752 mg sodium and up to 274 mg potassium per dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A colourless dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

Abecma must be administered in a qualified treatment centre.

Abecma therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for the administration and management of patients treated with Abecma.

A minimum of one dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion of Abecma. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

Abecma is intended for autologous use only (see section 4.4).

Treatment consists of a single dose for infusion containing a dispersion of CAR-positive viable T cells in one or more infusion bags. The target dose is 420 x 10^6 CAR-positive viable T cells within a range of 260 to 500 x 10^6 CAR-positive viable T cells. See the accompanying release for infusion certificate (RfIC) for additional information pertaining to dose.

Pre-treatment (lymphodepleting chemotherapy)
Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV should be administered for 3 days. See the prescribing information for cyclophosphamide and fludarabine for information on dose adjustment in renal impairment.

Abecma is to be administered 2 days after completion of lymphodepleting chemotherapy, up to a maximum of 9 days. The availability of Abecma must be confirmed prior to starting the lymphodepleting chemotherapy. If there is a delay in Abecma infusion of more than 9 days, then the patient should be re-treated with lymphodepleting chemotherapy after a minimum of 4 weeks from last lymphodepleting chemotherapy prior to receiving Abecma.

Pre-medication
It is recommended that premedication with paracetamol (500 to 1,000 mg orally) and diphenhydramine (12.5 mg IV or 25 to 50 mg orally) or another H_1-antihistamine, be administered approximately 30 to 60 minutes before the infusion of Abecma to reduce the possibility of an infusion reaction.

Prophylactic use of systemic corticosteroids should be avoided as the use may interfere with the activity of Abecma. Therapeutic doses of corticosteroids should be avoided 72 hours prior to the start of lymphodepleting chemotherapy and following Abecma infusion except for the management of CRS, neurologic toxicities and other life-threatening emergencies (see section 4.4).

Clinical assessment prior to infusion
Abecma treatment should be delayed in some patient groups at risk (see section 4.4).

Monitoring after infusion
- Patients should be monitored for the first 10 days following infusion at the qualified treatment centre for signs and symptoms of CRS, neurologic events and other toxicities.
- After the first 10 days following infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection
There is no clinical experience in patients with active HIV, HBV or HCV infection. Screening for HBV, active HIV and active HCV must be performed before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV infection will not be accepted for Abecma manufacturing (see section 4.4).

Elderly
No dose adjustment is required in patients over 65 years of age (see section 5.1).

Paediatric population
The safety and efficacy of Abecma in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

Abecma is for intravenous use only.

Administration
- Do NOT use a leukodepleting filter.
- Ensure that tocilizumab or suitable alternatives, in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, and emergency equipment are available prior to infusion and during the recovery period.
- Central venous access may be utilised for the infusion of Abecma and is encouraged in patients with poor peripheral access.
- Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Abecma infusion bag and accompanying documentation. The total number of infusion bags to be administered must also be confirmed with the patient specific information on the release for infusion certificate (RfIC) (see section 4.4).

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Abecma, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

Autologous use

Abecma is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Abecma must not be administered if the information on the product labels and the release for infusion certificate (RfIC) do not match the patient's identity.

Rapidly progressing disease

Before selecting patients for Abecma treatment, physicians should consider the impact of high-risk cytogenetic abnormalities, Revised International Staging System (R-ISS) stage III, presence of extramedullary plasmacytoma or high tumour burden, particularly for patients who have rapidly progressing disease that may affect their ability to receive CAR T infusion in due time. For these patients, optimising bridging therapy may be particularly important. Some patients may not benefit from Abecma treatment due to potential increased risk of early death (see section 5.1).

Reasons to delay treatment

Due to the risks associated with Abecma treatment, infusion should be delayed 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 (including pneumonitis, myocarditis or hepatitis).
- Active graft-versus-host disease (GVHD).

Concomitant disease

Patients with active central nervous system (CNS) disorder or inadequate renal, hepatic, pulmonary or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Central nervous system pathology

There is no experience of use of Abecma in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS pathologies.

Prior allogeneic stem cell transplantation

It is not recommended that patients receive Abecma within 4 months after an allogeneic stem cell transplant (SCT) because of the potential risk of Abecma worsening GVHD. Leukapheresis for Abecma manufacturing should be performed at least 12 weeks after allogeneic SCT.

Prior treatment with an anti-BCMA therapy

There is limited experience with Abecma in patients exposed to prior BCMA directed therapy.

There is limited experience of retreating patients with a second dose of Abecma. Responses after Abecma retreatment were infrequent and less durable when compared to initial treatment. Additionally, fatal outcomes were observed in retreated patients.

Cytokine release syndrome

CRS, including fatal or life-threatening reactions occurred following Abecma infusion. Nearly all patients experienced some degree of CRS. In clinical studies, the median time to onset of CRS was 1 day (range: 1 to 17) (see section 4.8).

Monitoring and management of CRS
CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia and hypotension. CRS has been reported to be associated with findings of haemophagocytic lymphohistiocytosis/macrophage activation syndrome (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 guidelines.

One dose of tocilizumab per patient must be on-site and available for administration prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS. Patients should be monitored for the first 10 days following Abecma infusion at the qualified treatment centre for signs and symptoms of CRS. After the first 10 days following infusion, the patient should be monitored at the physician's discretion. Patients should be counselled to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur at any time.

At the first sign of CRS, treatment with supportive care, tocilizumab or tocilizumab and corticosteroids should be instituted, as indicated in Table 1. Abecma can continue to expand and persist following administration of tocilizumab and corticosteroids (see section 4.5).

Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.

If concurrent neurologic toxicity is suspected during CRS, the neurologic toxicity should be managed according to the recommendations in Table 2 and use the more aggressive intervention of the two reactions specified in Tables 1 and 2.

Earlier escalation (i.e. higher corticosteroid dose, alternative anticytokine agents, anti-T cell therapies) is recommended in patients with refractory CRS within 72 hours post Abecma infusion characterised by persistent fever, end-organ toxicity (e.g. hypoxia, hypotension) and/or HLH/MAS not improving in grade within 12 hours of first line interventions.

Table 1. CRS grading and management guidance

CRS grade[a]	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise).	If onset 72 hours or more after infusion, treat symptomatically. If onset less than 72 hours after infusion and symptoms not controlled by supportive care alone, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	–
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.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	Consider dexamethasone 10 mg IV every 12 to 24 hours.

CRS grade[a]	Tocilizumab	Corticosteroids
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.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	Administer dexamethasone (e.g. 10 mg IV every 12 hours).
For Grade 2 and 3: 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.		
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	Administer dexamethasone 20 mg IV every 6 hours.
For Grade 4: 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 to 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.		

[a] Lee et al, 2014.

Neurologic adverse reactions

Neurologic toxicities, such as aphasia and encephalopathy, which may be severe or life-threatening, occurred following treatment with Abecma. The median time to onset of the first event of neurotoxicity was 3 days (range: 1 to 317 days; one patient developed encephalopathy at Day 317 as a result of worsening pneumonia and *Clostridium difficile* colitis). Grade 3 parkinsonism has also been reported, with delayed onset. Neurologic toxicity may occur concurrently with CRS, after CRS resolution or in the absence of CRS (see section 4.8).

Monitoring and management of neurologic toxicities

Patients should be monitored for the first 10 days following Abecma infusion at the qualified treatment centre for signs and symptoms of neurologic toxicities. After the first 10 days following infusion, the patient should be monitored at the physician's discretion. Patients should be counselled to remain within proximity (within 2 hours of travel) of the qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs and symptoms of neurologic toxicities occur at any time.

If neurologic toxicity is suspected, manage according to the recommendations in Table 2. Other causes of neurologic symptoms should be ruled out. Intensive care supportive therapy should be provided for severe or life-threatening neurologic toxicities.

If concurrent CRS is suspected during the neurologic toxicity reaction, it should be managed according to the recommendations in Table 1 and the more aggressive intervention used for the two reactions specified in Tables 1 and 2.

Table 2. Neurologic toxicity grading and management guidance

Neurologic toxicity grade[a]	Corticosteroids and antiseizure medications
Grade 1 Mild or asymptomatic.	Start non-sedating, antiseizure medicines (e.g. levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, and symptoms not controlled by supportive care alone, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2 Moderate.	Start non-sedating, antiseizure medicines (e.g. levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2 to 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 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation; disabling.	Start non-sedating, 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 oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 to 2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.
Grade 4 Life-threatening.	Start non-sedating, 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 to 2 g, repeated every 24 hours if needed; taper as clinically indicated). Consider cyclophosphamide 1.5 g/m^2. If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 to 2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.

[a] NCI CTCAE v.4 criteria for grading neurologic toxicities.

Prolonged cytopenias

Patients may exhibit prolonged cytopenias for several weeks following lymphodepleting chemotherapy and Abecma infusion (see section 4.8). Blood counts should be monitored prior to and after Abecma infusion. Cytopenias should be managed with myeloid growth factor and blood transfusion support according to institutional guidelines.

Infections and febrile neutropenia

Abecma should not be administered to patients with active infections or inflammatory disorders. Severe infections, including life-threatening or fatal infections, have occurred in patients after receiving Abecma (see section 4.8). Patients should be monitored for signs and symptoms of infection before and after Abecma infusion and treated appropriately. Prophylactic, pre-emptive and/or therapeutic antimicrobials should be administered according to institutional guidelines.

Febrile neutropenia was observed in patients after Abecma infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, infection should be evaluated and managed with broad-spectrum antibiotics, fluids and other supportive care as medically indicated.

Viral reactivation

Cytomegalovirus (CMV) infection resulting in pneumonia and death have occurred following Abecma administration (see section 4.8). Patients should be monitored and treated for CMV infection according to clinical guidelines.

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against plasma cells (see section 4.8).

Screening for CMV, HBV, active HIV and active HCV must be performed before collection of cells for manufacturing (see section 4.2).

Hypogammaglobulinaemia

Plasma cell aplasia and hypogammaglobulinaemia can occur in patients receiving treatment with Abecma (see section 4.8). Immunoglobulin levels should be monitored after treatment with Abecma and managed per institutional guidelines including infection precautions, antibiotic or antiviral prophylaxis and immunoglobulin replacement.

Secondary malignancies

Patients treated with Abecma may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Abecma. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), an excipient in Abecma. Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored prior to the start of

the infusion, approximately every ten minutes during the infusion and every hour, for 3 hours, after the infusion.

Transmission of an infectious agent

Although Abecma is tested for sterility and mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Abecma must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Interference with virological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to create Abecma and HIV, some HIV nucleic acid tests (NAT) may give a false positive result.

Blood, organ, tissue and cell donation

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

Long-term follow-up

Patients are expected to be enrolled in a registry in order to better understand the long-term safety and efficacy of Abecma.

Excipients

This medicinal product contains up to 33 mmol (752 mg) sodium per dose, equivalent to 37.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains up to 7 mmol (274 mg) potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The co-administration of agents known to inhibit T cell function has not been formally studied. The co-administration of agents known to stimulate T cell function has not been investigated and the effects are unknown.

Tocilizumab or siltuximab and corticosteroid use

Some patients required tocilizumab or siltuximab and/or corticosteroid for the management of CRS (see section 4.8). The use of tocilizumab or siltuximab and/or corticosteroids for CRS management was more common in patients with higher cellular expansion.

In the KarMMa-3 study, patients with CRS treated with tocilizumab or siltuximab had higher Abecma cellular expansion levels, as measured by 3.1-fold and 2.9-fold higher median C_{max} (N = 156) and $AUC_{0\text{-}28days}$ (N = 155), respectively, compared to patients who did not receive tocilizumab or siltuximab (N = 64 for C_{max} and N = 63 for $AUC_{0\text{-}28days}$). Patients with CRS treated with corticosteroids had higher Abecma cellular expansion levels, as measured by 2.3-fold and 2.4-fold higher median C_{max} (N = 60) and $AUC_{0\text{-}28days}$ (N = 60), respectively, compared to patients who did not receive corticosteroids (N = 160 for C_{max} and N = 158 for $AUC_{0\text{-}28days}$).

Similarly, in the KarMMa study, 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 $AUC_{0\text{-}28days}$).

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with Abecma has not been studied. As a precautionary measure, vaccination with live 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status for women of childbearing potential should be verified using a pregnancy test prior to starting treatment with Abecma.

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

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

Pregnancy

There are no data from the use of idecabtagene vicleucel in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with idecabtagene vicleucel to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if idecabtagene vicleucel has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including plasma cell aplasia or hypogammaglobulinaemia. Therefore, Abecma is not recommended for women who are pregnant or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Abecma therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels in newborn infants of mothers treated with Abecma should be considered.

Breast-feeding

It is unknown whether idecabtagene vicleucel cells are excreted in human milk or transferred to the breast-feeding child. A risk to the breast-fed infant cannot be excluded. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

Fertility

There are no data on the effect of idecabtagene vicleucel on fertility. Effects of idecabtagene vicleucel on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Abecma may have major influence on the ability to drive and use machines.

Due to the potential for neurologic adverse reactions, including altered mental status or seizures with Abecma, patients receiving Abecma should refrain from driving or operating heavy or potentially

dangerous machines for at least 8 weeks after Abecma infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect the exposure to Abecma in the KarMMa, CRB-401 and KarMMa-3 studies in which 409 patients with relapsed and refractory multiple myeloma received Abecma. In KarMMa (N = 128) and CRB-401 (N = 56), the median duration of follow-up (from Abecma infusion to data cutoff date) was 20.8 months. In KarMMa-3 (N = 225), the median duration of follow-up was 29.3 months.

The most common adverse reactions (≥ 20%) included CRS (84.6%), neutropenia (80.0%), anaemia (63.6%), thrombocytopenia (55.0%), infections - pathogen unspecified (43.8%), hypophosphataemia (33.3%), diarrhoea (33.0%), leukopenia (32.8%), hypokalaemia (32.0%), fatigue (29.8%), nausea (28.1%), lymphopenia (26.9%), pyrexia (24.7%), infections - viral (23.2%), headache (22.5%), hypocalcaemia (22.0%), hypomagnesaemia (21.3%), and arthralgia (20.0%); other common adverse events occurring at lower frequency and considered clinically important included hypotension (18.6%), upper respiratory tract infection (15.6%), hypogammaglobulinemia (13.7%), febrile neutropenia (11.2%), pneumonia (11.0%), tremor (5.6%), somnolence (5.6%), encephalopathy (3.4%), syncope (3.2%), and aphasia (2.9%).

Serious adverse reactions occurred in 57.2% of patients. The most common serious adverse reactions (≥ 5%) included CRS (10.3%), and pneumonia (7.1%); other serious adverse events occurring at lower frequency and considered clinically important include febrile neutropenia (4.2%), pyrexia (3.7%), neutropenia (2.7%), sepsis (2.7%), confusional state (2.4%), haemophagocytic lymphohistiocytosis (1.7%), thrombocytopenia (1.5%), encephalopathy (1.5%), dyspnoea (1.5%), seizure (1.0%), mental status changes (1.0%), hypoxia (0.7%) and disseminated intravascular coagulation (0.5%).

The most common Grade 3 or 4 adverse reactions (≥ 5%) were neutropenia (77.3%), anaemia (50.9%), thrombocytopenia (42.5%), leukopenia (31.5%), lymphopenia (25.9%), hypophosphataemia (19.8%), infections - pathogen unspecified (15.2%), febrile neutropenia (10.5%), infections - viral (7.6%), pneumonia (6.8%), hypertension (6.6%), hypocalcaemia (5.6%) and infections - bacterial (5.4%).

Grade 3 or 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (93.2%) compared to after 8 weeks post-infusion (58.1%). The most frequently reported Grade 3 or 4 adverse reactions reported within the first 8 weeks after infusion were neutropenia (75.8%), anaemia (47.4%), thrombocytopenia (38.6%), leukopenia (30.3%) lymphopenia (23.5%) and hypophosphataemia (18.3%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions observed in the clinical studies of 409 patients treated with Abecma within the allowed dose range of 150 to 540 x 10^6 CAR-positive T cells (see Table 6 in section 5.1 for the corresponding dose range of CAR-positive viable T cells in KarMMa). Adverse reactions are presented by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions observed in patients treated with Abecma

System organ class	Adverse reaction	All grades frequency
Infections and infestations[a]	Infections – bacterial	Very common
	Infections – viral	Very common
	Infections – pathogen unspecified	Very common
	Infections – fungal	Common
Blood and lymphatic system disorders	Neutropenia	Very common
	Leukopenia	Very common
	Thrombocytopenia	Very common
	Febrile neutropenia	Very common
	Lymphopenia	Very common
	Anaemia	Very common
	Disseminated intravascular coagulation	Common
Immune system disorders	Cytokine release syndrome	Very common
	Hypogammaglobulinaemia	Very common
	Haemophagocytic lymphohistiocytosis*	Common
Metabolism and nutrition disorders	Hypophosphataemia	Very common
	Hypokalaemia	Very common
	Hyponatraemia	Very common
	Hypocalcaemia	Very common
	Hypoalbuminaemia	Very common
	Decreased appetite	Very common
	Hypomagnesaemia	Very common
Psychiatric disorders	Insomnia	Very common
	Delirium[b]	Common
Nervous system disorders	Encephalopathy[c]	Very common
	Headache*	Very common
	Dizziness[d]	Very common
	Aphasia[e]	Common
	Ataxia[f]	Common
	Motor dysfunction[g]	Common
	Tremor	Common
	Seizure	Common
	Hemiparesis	Uncommon
Cardiac disorders	Tachycardia*	Very common
	Atrial fibrillation*	Common
Vascular disorders	Hypertension	Very common
	Hypotension*[h]	Very common
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Very common
	Cough	Very common
	Pulmonary oedema	Common
	Hypoxia*	Common
Gastrointestinal disorders	Vomiting	Very common
	Diarrhoea	Very common
	Nausea	Very common
	Constipation	Very common
	Gastrointestinal haemorrhage[i]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Common

System organ class	Adverse reaction	All grades frequency
General disorders and administration site conditions	Pyrexia* Fatigue*[j] Oedema[k] Chills* Asthenia	Very common Very common Very common Very common Common
Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased C-reactive protein increased*	Very common Very common Common Common

* Event that has been reported as a manifestation of CRS.

[a] Infections and infestations system organ class adverse events are grouped by pathogen type and selected clinical syndromes.

[b] Delirium includes delirium, disorientation, agitation, hallucination, restlessness.

[c] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dyscalculia, dysgraphia, encephalopathy, incoherent, lethargy, memory impairment, mental impairment, mental status changes, metabolic encephalopathy, neurotoxicity, somnolence, stupor.

[d] Dizziness includes dizziness, presyncope, syncope, vertigo.

[e] Aphasia includes aphasia, dysarthria, slow speech, and speech disorder.

[f] Ataxia includes ataxia, dysmetria, gait disturbance.

[g] Motor dysfunction includes motor dysfunction, muscular spasms, muscular weakness, parkinsonism.

[h] Hypotension includes hypotension, orthostatic hypotension.

[i] Gastrointestinal haemorrhage includes gastrointestinal haemorrhage, gingival bleeding, haematochezia, haemorrhoidal haemorrhage, melaena, mouth haemorrhage.

[j] Fatigue includes fatigue, malaise.

[k] Oedema includes oedema, oedema peripheral, face oedema, generalised oedema, peripheral swelling.

Description of selected adverse reactions

Cytokine release syndrome

In the pooled studies (KarMMa, CRB-401 and KarMMa-3), CRS occurred in 84.6% of patients receiving Abecma. Grade 3 or higher CRS (Lee et al, 2014) occurred in 5.1% of patients, with fatal (Grade 5) CRS reported in 0.7% of patients. The median time-to-onset, any grade, was 1 day (range: 1 to 17) and the median duration of CRS was 4 days (range: 1 to 63).

The most common manifestations of CRS (≥ 10%) included pyrexia (82.6%), hypotension (29.1%), tachycardia (24.7%), chills (18.8%), hypoxia (15.9%), headache (11.2%) and increased C-reactive protein (10.5%). Grade 3 or higher events that may be observed in association with CRS included atrial fibrillation, capillary leak syndrome, hypotension, hypoxia and HLH/MAS.

Of the 409 patients, 59.7% of patients received tocilizumab; 37.2% received a single dose while 22.5% received more than 1 dose of tocilizumab for treatment of CRS. Overall, 22.7% of patients received at least 1 dose of corticosteroids for treatment of CRS. Of the 92 patients in KarMMa and CRB-401 who received the target dose of 450 x 10^6 CAR-positive T cells, 54.3% of patients received tocilizumab and 22.8% received at least 1 dose of corticosteroids for treatment of CRS. Of the 225 patients in KarMMa-3 who received Abecma infusion, 71.6% of patients received tocilizumab and 28.4% received at least 1 dose of corticosteroids for the treatment of CRS. See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions

In the pooled studies, of the 409 patients, independent of investigator attribution of neurotoxicity, the most frequent neurologic or psychiatric adverse reactions (≥ 5%) included headache (22.5%), dizziness (12.5%), confusional state (11.0%), insomnia (10.3%), anxiety (5.9%), tremor (5.6%), and somnolence (5.6%). Other neurological adverse reactions occurring at a lower frequency and considered clinically important included encephalopathy (3.4%) and aphasia (2.9%).

Neurotoxicity identified by the investigators, which was the primary method of assessing CAR T cell associated- neurotoxicity in the KarMMa and KarMMa-3 studies, occurred in 57 (16.1%) of the 353 patients receiving Abecma, including Grade 3 or 4 in 3.1% of patients (with no Grade 5 events). The

median time to onset of the first event was 3 days (range: 1 to 317; one patient developed encephalopathy at Day 317 as a result of worsening pneumonia and *Clostridium difficile* colitis). The median duration was 3 days (range: 1 to 252; one patient developed neurotoxicity [highest Grade 3] 43 days after ide-cel infusion which resolved after 252 days). Overall, 7.1% of patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity.

In KarMMa, across the target dose levels, 7.8% of patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity, while at the target dose of 450 x 10^6 CAR-positive T cells, 14.8% of patients received at least 1 dose of corticosteroids.

In KarMMa-3, across all patients who received Abecma infusion at the target dose range, 6.7% of patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity.

Of the 353 patients in the KarMMa and KarMMa-3 studies, the most common manifestations of investigator identified neurotoxicity (≥ 2%) included confusional state (8.5%), encephalopathy (3.4%), somnolence (2.8%), aphasia (2.5%), tremor (2.3%), disturbance in attention (2.0%) and dysgraphia (2.0%). See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
In the pooled studies, infections occurred in 62.8% of patients. Grade 3 or 4 infections occurred in 23.2% of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 15.2%, viral infections in 7.6%, bacterial infections in 4.6% and fungal infections in 1.2% of patients. Fatal infections of unspecified pathogen were reported in 2.0% of patients, 0.7% of patients had fatal fungal or viral infection and 0.2% of patients had fatal bacterial infection. See section 4.4 for monitoring and management guidance.

Febrile neutropenia (Grade 3 or 4) was observed in 10.8% of patients after Abecma infusion. Febrile neutropenia may be concurrent with CRS. See section 4.4 for monitoring and management guidance.

Prolonged cytopenia
Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and Abecma infusion. In the pooled studies, 38.2% of the 395 patients who had Grade 3 or 4 neutropenia and 71.3% of the 230 patients who had Grade 3 or 4 thrombocytopenia during the first month following Abecma infusion had not resolved by last assessment during the first month. Among the 151 patients with neutropenia not resolved by month 1, 88.7% recovered from Grade 3 or 4 neutropenia with a median time to recovery from Abecma infusion of 1.9 months. Of the 164 patients with thrombocytopenia not resolved by month 1, 79.9% recovered from Grade 3 or 4 thrombocytopenia with the median time to recovery of 2.0 months. See section 4.4 for monitoring and management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 13.7% of patients treated with Abecma in the pooled studies with a median time to onset of 90 days (range 1 to 326). See section 4.4 for monitoring and management guidance.

Immunogenicity

Abecma has the potential to induce anti-CAR antibodies. In clinical studies, humoral immunogenicity of Abecma was measured by determination of anti-CAR antibody in serum pre- and post-administration. In the pooled studies of KarMMa, CRB-401 and KarMMa-3, 3.2% of patients tested positive for pre-infusion anti-CAR antibodies and post-infusion anti-CAR antibodies were detected in

56.2% 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data regarding overdose with Abecma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XL07.

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.

Clinical efficacy and safety

KarMMa-3
KarMMa-3 was an open-label, multicentre, randomised, controlled study that evaluated the efficacy and safety of Abecma, compared to standard regimens, in adult patients with relapsed and refractory multiple myeloma who had received two to four prior antimyeloma regimens including an immunomodulatory agent, a proteasome inhibitor, and daratumumab, and were refractory to the most recent prior antimyeloma regimen. A standard regimen was assigned to each patient prior to randomisation, contingent upon the patient's most recent antimyeloma treatment. The standard regimens consisted of daratumumab, pomalidomide, dexamethasone (DPd), daratumumab, bortezomib, dexamethasone (DVd), ixazomib, lenalidomide, dexamethasone (IRd), carfilzomib, dexamethasone (Kd), or elotuzumab, pomalidomide, dexamethasone (EPd). In patients randomised to the Abecma arm, the assigned standard regimen was to be used as bridging therapy, if clinically indicated.

The study included patients who achieved a response (minimal response or better) to at least 1 prior treatment regimen and had ECOG performance status of 0 or 1. The study excluded patients with CNS involvement of myeloma, history of CNS disorders (such as seizures), prior allogeneic SCT or prior treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy, ongoing treatment with immunosuppresants, serum creatinine clearance < 45 mL/min, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal, and left ventricular ejection fraction (LVEF) < 45%. Patients were also excluded if absolute neutrophil count < 1000/μL and platelet count < 75,000/μL in patients in

whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/μL in patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells.

Patients were randomised 2:1 to receive either Abecma (N = 254) or standard regimens (N = 132) for relapsed and refractory multiple myeloma. Randomisation was stratified by age, number of prior antimyeloma regimens and high-risk cytogenetics abnormalities. Patients receiving standard regimens were allowed to receive Abecma upon confirmed disease progression.

Patients randomised to Abecma were to receive lymphodepleting chemotherapy consisting 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. Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd anticancer therapy for disease control (bridging therapy) was permitted between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

Of the 254 patients randomised to Abecma, 249 (98%) patients underwent leukapheresis, and 225 (88.6%) patients received Abecma. Of the 225 patients, 192 (85.3%) patients received bridging therapy. Twenty-nine patients did not receive Abecma due to death (n = 4), adverse event (n = 5), patient withdrawal (n = 2), physician decision (n = 7), failure to meet lymphodepleting chemotherapy treatment criteria (n = 8) or manufacturing failure (n = 3).

The allowed dose range was 150 to 540 x 10^6 CAR-positive T cells. The median actual received dose was 445.3 x 10^6 CAR-positive T cells (range: 174.9 to 529.0 x 10^6 CAR-positive T cells). The median time from leukapheresis to product availability was 35 days (range: 24 to 102 days) and the median time from leukapheresis to infusion was 49 days (range: 34 to 117 days).

Of the 132 patients randomised to standard regimens, 126 (95.5%) patients received treatment. Six patients discontinued without receiving treatment due to disease progression (n = 1), patient withdrawal (n = 3), or physician decision (n = 2). Patients receiving standard regimens were allowed to receive Abecma at investigator's request, upon confirmed disease progression by the independent review committee (IRC) based on the International Myeloma Working Group (IMWG) criteria and confirmed eligibility. Of the eligible patients, 69 (54.8%) underwent leukapheresis and 60 (47.6%) received Abecma.

Table 4 summarises the baseline patient and disease characteristics in KarMMa-3 study.

Table 4. Baseline demographic/disease characteristics for patients in KarMMa-3 study

Characteristic	Abecma (N = 254)	Standard regimens (N = 132)
Age (years)		
Median (min, max)	63 (30, 81)	63 (42, 83)
≥ 65 years, n (%)	104 (40.9)	54 (40.9)
≥ 75 years, n (%)	12 (4.7)	9 (6.8)
Gender, male, n (%)	156 (61.4)	79 (59.8)
Race, n (%)		
Asian	7 (2.8)	5 (3.8)
Black	18 (7.1)	18 (13.6)
White	172 (67.7)	78 (59.1)
ECOG performance status, n (%)[a]		
0	120 (47.2)	66 (50.0)
1	133 (52.4)	62 (47.0)
2	0	3 (2.3)

3	1 (0.4)	1 (0.8)
Patients with extramedullary plasmacytoma, n (%)	61 (24.0)	32 (24.2)
Time since initial diagnosis (year) n median (min, max)	 251 4.1 (0.6, 21.8)	 131 4.0 (0.7, 17.7)
Prior stem cell transplant, n (%)	214 (84.3)	114 (86.4)
Baseline cytogenetic abnormality, n (%)[b]		
High risk[c]	107 (42.1)	61 (46.2)
Non-high risk	114 (44.9)	55 (41.7)
Not evaluable/Missing	33 (13.0)	16 (12.1)
Revised ISS stage at baseline (derived)[d], n (%)		
Stage I	50 (19.7)	26 (19.7)
Stage II	150 (59.1)	82 (62.1)
Stage III	31 (12.2)	14 (10.6)
Unknown	23 (9.1)	10 (7.6)
Distribution of prior anti-myeloma regimens, n (%)		
2	78 (30.7)	39 (29.5)
3	95 (37.4)	49 (37.1)
4	81 (31.9)	44 (33.3)
Refractory status to prior classes of therapy, n (%)		
IMiD	224 (88.2)	124 (93.9)
Proteasome inhibitor (PI)	189 (74.4)	95 (72.0)
Anti-CD38 antibodies	242 (95.3)	124 (93.9)
Triple refractory[e], n (%)	164 (64.6)	89 (67.4)

ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; ISS = International Staging System; max = maximum; min = minimum

[a] All subjects had ECOG score 0 or 1 at screening, but the ECOG score may be >1 at baseline.

[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, cytogenic abnormality and serum lactate dehydrogenase.

[e] Triple refractory is defined as refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.

The primary efficacy endpoint was progression free survival (PFS) according to the IMWG Uniform Response Criteria for Multiple Myeloma as determined by an Independent Review Committee (IRC). Other efficacy measures included overall response rate (ORR), overall survival (OS) and patient-reported outcomes. At a pre-specified interim analysis at 80% information fraction with a median follow up time of 18.6 months, Abecma demonstrated a statistically significant improvement in PFS compared to the standard regimens arm; HR = 0.493 (95% CI: 0.38, 0.65, two-sided p-value < 0.0001). The results of the subsequent primary analysis (shown in Table 5 and Figure 1), with a median follow-up time of 30.9 months, were consistent with the interim analysis.

Table 5. Summary of efficacy results from KarMMa-3 (intent-to-treat population)

	Abecma arm (N = 254)	**Standard regimens arm (N = 132)**
Progression free survival		
Number of events, n (%)	184 (72.4)	105 (79.5)
Median, months [95% CI][a]	13.8 [11.8, 16.1]	4.4 [3.4, 5.8]
Hazard ratio [95% CI][b]	0.49 [0.38, 0.63]	
Overall response rate		
n (%)	181 (71.3)	56 (42.4)
95% CI (%)[c]	(65.7, 76.8)	(34.0, 50.9)
CR or better (sCR+CR)	111 (43.7)	7 (5.3)
sCR	103 (40.6)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	45 (17.7)	15 (11.4)
PR	25 (9.8)	34 (25.8)
DOR if best response is CR		
N	**111**	**7**
Median, months [95% CI]	15.7 [12.1, 22.1]	24.1 [4.6, NA]
DOR if best response is PR		
N	**181**	**56**
Median, months [95% CI]	16.5 [12.0, 19.4]	9.7 [5.4, 15.5]
MRD-negative status by NGS and ≥ CR		
MRD negativity rate, n (%)[d]	57 (22.4)	1 (0.8)
95% CI (%)[c]	(17.3, 27.6)	(0.0, 2.2)

CI=confidence interval; CR=complete response; DOR=duration of response; MRD=minimal residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

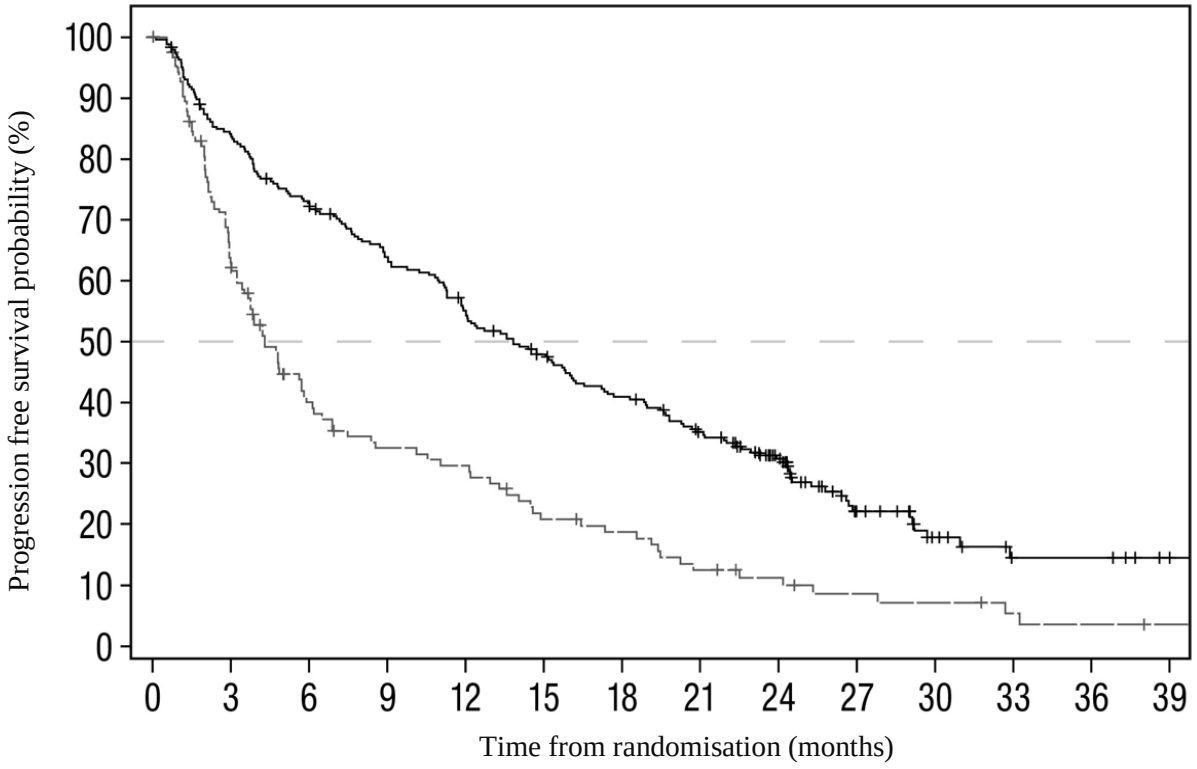
[a] Kaplan-Meier estimate.

[b] Based on stratified univariate Cox proportional hazards model.

[c] Two-sided Wald confidence interval.

[d] MRD negativity was defined as the proportion of all patients in the ITT population who achieved CR or stringent CR and are MRD negative at any timepoint within 3 months prior to achieving CR or stringent CR until the time of progression or death. Based on a threshold of 10^{-5} using ClonoSEQ, a next-generation sequencing (NGS) assay.

Figure 1. Kaplan-Meier plot of progression-free survival based on IRC assessment in KarMMa-3 study (intent-to-treat population)



Number of subjects at risk

—— Abecma

254 206 177 153 131 111 94 77 54 25 14 7 7 2

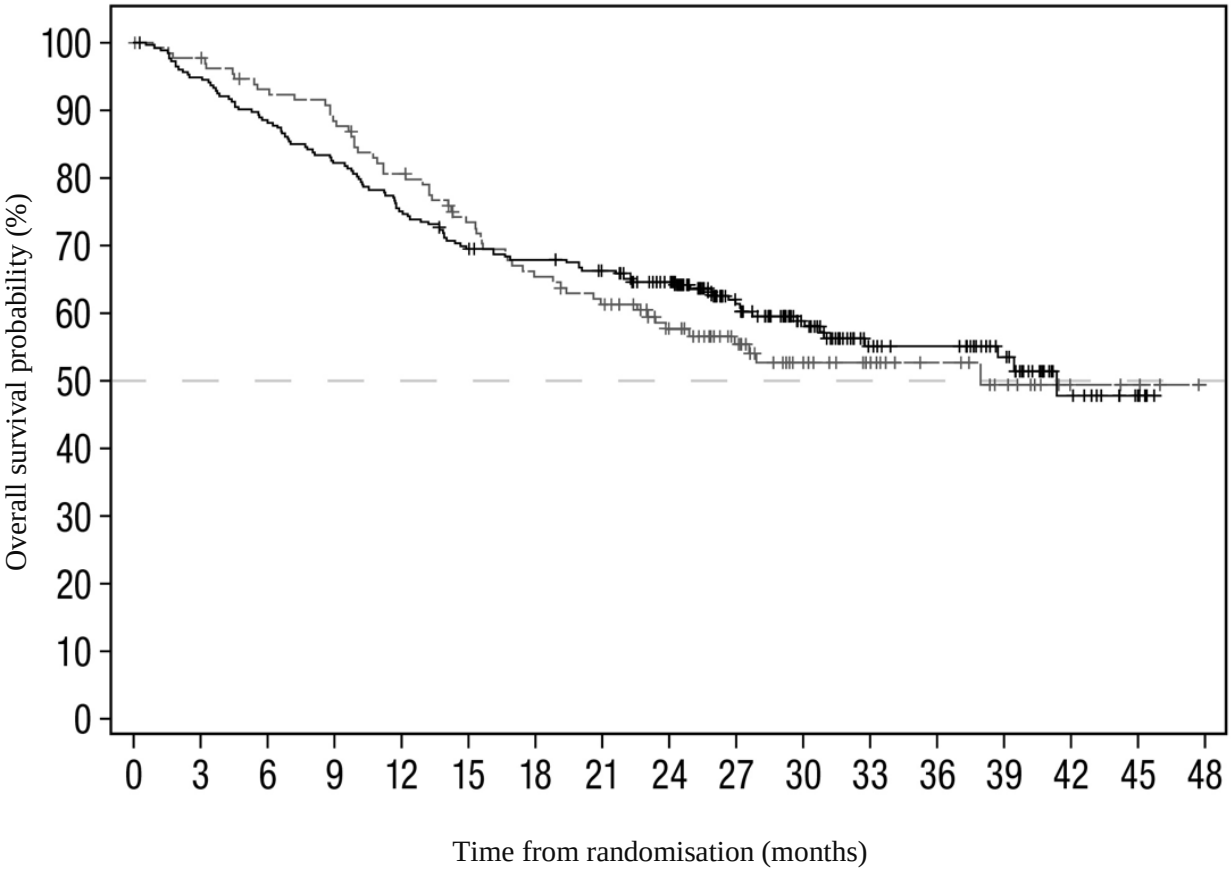
- - - - Standard regimens

132 76 43 34 31 21 18 12 9 6 5 3 2 1

At the time of the final analysis for PFS, 74% of planned OS events were reached. Patients receiving standard regimens were allowed to receive Abecma upon confirmed disease progression; the OS data are therefore confounded by 74 (56.1%) patients from the standard regimen arm who received Abecma as a subsequent therapy. The median OS for Abecma was 41.4 months (95% CI: 30.9, NR) versus standard regimens 37.9 months (95% CI: 23.4, NR); HR = 1.01 (95% CI: 0.73, 1.40). Figure 2 shows the Kaplan-Meier curve for OS in the intent-to-treat population (not corrected for cross-over).

Compared to the standard regimens arm (9/132; 6.8%), a higher proportion of patients experienced death within 6 months after randomisation in the Abecma arm (30/254; 11.8%). Of the 30 patients with an early death event in the Abecma arm, 17 patients never received Abecma treatment, and 13 of these 17 died of disease progression. High-risk factors such as high-risk cytogenetic abnormalities, R-ISS stage III, presence of extramedullary plasmacytoma or high tumour burden (see section 4.4 on rapidly progressing disease) are associated with higher risk of early death.

Figure 2. Kaplan-Meier plot of overall survival based on IRC assessment in KarMMa-3 study (intent-to-treat population)



Number of subjects at risk

——— Abecma

254 240 223 208 190 175 169 161 143 103 75 48 44 30 13 4 0

- - - - Standard regimens

132 128 120 114 103 91 81 75 59 45 32 24 18 11 4 3 0

KarMMa

KarMMa was an open-label, single-arm, multicentre study that evaluated the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and who were refractory to the last treatment regimen. Patients with CNS involvement of myeloma, a history of other BCMA targeting therapies, allogeneic SCT or prior gene therapy based or other genetically modified T cell therapy were excluded. Patients with a history of CNS disorders (such as seizures), inadequate hepatic, renal, bone marrow function, cardiac, pulmonary function or ongoing treatment with immunosuppressants were excluded.

The study consisted of pre-treatment (screening, leukapheresis and bridging therapy [if needed]); treatment (lymphodepleting chemotherapy and Abecma infusion); and posttreatment (ongoing) for a minimum of 24 months following Abecma infusion or until documented disease progression, whichever was longer. The lymphodepleting chemotherapy 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 hospitalised for 14 days after infusion of Abecma to monitor and manage potential CRS and neurotoxicity.

Of the 140 patients who were enrolled (i.e. underwent leukapheresis), 128 patients received the Abecma infusion. Out of the 140 patients, only one 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.

Anticancer therapy for disease control (bridging) was permitted between apheresis and lymphodepletion with the last dose being administered at least 14 days prior to initiation of lymphodepleting chemotherapy. Of the 128 patients treated with Abecma, most patients (87.5%) received anticancer therapy for disease control at the discretion of the investigator.

The doses targeted in the clinical study were 150, 300 or 450 x 10^6 CAR-positive T cells per infusion. The allowed dose range was 150 to 540 x 10^6 CAR-positive T cells. Table 6 below shows the target dose levels used in the clinical study based on total CAR-positive T cells and the corresponding range of actual dose administered defined as CAR-positive viable T cells.

Table 6. Total CAR-positive T cells dose with the corresponding dose range of CAR-positive viable T cells (x10^6) - KarMMa study

Target dose based on total CAR-positive T cells, including both viable and non-viable cells (x10^6)	CAR-positive viable T cells (x10^6) (min, max)
150	133 to 181
300	254 to 299
450	307 to 485

Table 7 summarises the baseline patient and disease characteristics for the enrolled and treated population in study.

Table 7. Baseline demographic/disease characteristics for study population - KarMMa study

Characteristic	Total enrolled (N = 140)	Total treated (N = 128)
Age (years)		
Median (min, max)	60.5 (33, 78)	60.5 (33, 78)
≥ 65 years, n (%)	48 (34.3)	45 (35.2)
≥ 75 years, n (%)	5 (3.6)	4 (3.1)
Gender, male, n (%)	82 (58.6)	76 (59.4)
Race, n (%)		
Asian	3 (2.1)	3 (2.3)
Black	8 (5.7)	6 (4.7)
White	113 (80.7)	103 (80.5)
ECOG performance status, n (%)		
0	60 (42.9)	57 (44.5)
1	77 (55.0)	68 (53.1)
2[a]	3 (2.1)	3 (2.3)
Patients with extramedullary plasmacytoma, n (%)	52 (37.1)	50 (39.1)
Time since initial diagnosis (years), median (min, max)	6 (1.0, 17.9)	6 (1.0, 17.9)
Prior stem cell transplant, n (%)	131 (93.6)	120 (93.8)
Baseline cytogenetic high risk[b,c]	46 (32.9)	45 (35.2)

Revised ISS stage at baseline (derived)[d], n (%)		
Stage I	14 (10.0)	14 (10.9)
Stage II	97 (69.3)	90 (70.3)
Stage III	26 (18.6)	21 (16.4)
Unknown	3 (2.1)	3 (2.3)
Number of prior anti-myeloma therapies[e], median (min, max)	6 (3, 17)	6 (3, 16)
Triple refractory[f], n (%)	117 (83.6)	108 (84.4)
Creatinine clearance (mL/min), n (%)		
< 30	3 (2.1)	1 (0.8)
30 to < 45	9 (6.4)	8 (6.3)
45 to < 60	13 (9.3)	10 (7.8)
60 to < 80	38 (27.1)	36 (28.1)
≥ 80	77 (55.0)	73 (57.0)

max = maximum; min = minimum

[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 LD 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, cytogenic abnormality and serum lactate dehydrogenase.

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

[f] Triple refractory is defined as refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.

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). The median actual dose received across all doses targeted in the clinical study was 315.3 x 10^6 CAR-positive T cells (range 150.5 to 518.4).

Efficacy was assessed on the basis of overall response rate (ORR), complete response (CR) rate and duration of response (DOR), as determined by an independent review committee. Other efficacy endpoints included minimal residual disease (MRD) using next-generation sequencing (NGS).

Efficacy results across doses targeted in the clinical study (150 to 450 x 10^6 CAR-positive T cells) are shown in the Table 8. Median follow-up was 19.9 months for all Abecma treated patients.

Table 8. Summary of efficacy based on the KarMMa study

	Enrolled[a]	**Treated population Target dose of Abecma (CAR-positive T cells)**			
	(N = 140)	**150 x 10^{6b} (N = 4)**	**300 x 10^6 (N = 70)**	**450 x 10^6 (N = 54)**	**Total 150 to 450 x 10^6 (N = 128)**
Overall response rate (sCR+CR+VGPR+PR), n (%)	**94 (67.1)**	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**
95% CI[c]	59.4, 74.9	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1
CR or better, n (%)	**42 (30.0)**	**1 (25.0)**	**20 (28.6)**	**21 (38.9)**	**42 (32.8)**
95% CI[c]	22.4, 37.6	0.6, 80.6	18.4, 40.6	25.9, 53.1	24.7, 40.9

	Enrolled[a] (N = 140)	Treated population Target dose of Abecma (CAR-positive T cells)			
		150 x 10^{6}[b] (N = 4)	300 x 10^{6} (N = 70)	450 x 10^{6} (N = 54)	Total 150 to 450 x 10^{6} (N = 128)
VGPR or better, n (%)	**68 (48.6)**	**2 (50.0)**	**31 (44.3)**	**35 (64.8)**	**68 (53.1)**
95% CI[c]	40.3, 56.9	6.8, 93.2	32.4, 56.7	50.6, 77.3	44.5, 61.8
MRD-negative status[d] and ≥ CR					
Based on treated patients	**–**	**4**	**70**	**54**	**128**
n (%)	–	1 (25.0)	17 (24.3)	14 (25.9)	32 (25.0)
95% CI	–	0.6, 80.6	14.8, 36.0	15.0, 39.7	17.8, 33.4
Time to response, n	**94**	**2**	**48**	**44**	**94**
Median (months)	1.0	1.0	1.0	1.0	1.0
Min, max	0.5, 8.8	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8
Duration of response (PR or better)[e], n	**94**	**2**	**48**	**44**	**94**
Median (months)	10.6	15.8	8.5	11.3	10.6
95% CI	8.0, 11.4	2.8, 28.8	5.4, 11.0	10.3, 17.0	8.0, 11.4

CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; MRD = minimal residual disease; NE = not estimable; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] All patients who underwent leukapheresis.

[b] The 150 x 10^{6} CAR-positive T cell dose is not part of the approved dose range.

[c] For "Total (Treated population" and "Enrolled population"): Wald CI; for individual target dose levels: Clopper-Pearson exact CI.

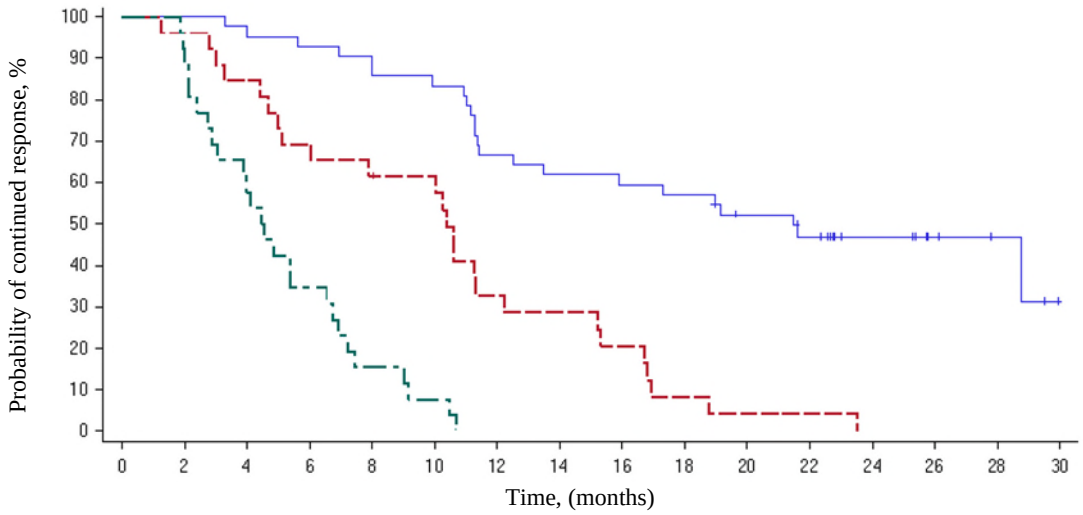
[d] Based on a threshold of 10^{-5} using a next-generation sequencing assay. 95% CI for percentage of MRD negativity use Clopper-Pearson exact CI for individual target dose levels as well as for Treated population.

[e] Median and 95% CI are based on the Kaplan-Meier approach.

Note: The target dose is 450 x 10^{6} CAR-positive T cells within a range of 150 to 540 × 10^{6} CAR-positive T cells. The 150 x 10^{6} CAR-positive T cell dose is not part of the approved dose range.

The Kaplan-Meier curve of duration of response by best overall response is shown in Figure 3.

Figure 3. **Kaplan-Meier curve of duration of response based on independent response committee review according to IMWG criteria – by best overall response (Abecma-treated population - KarMMa study)**



CR or better	42	42	40	39	36	35	28	26	25	24	20	17	10	6	3	0
VGPR	26	25	22	18	16	15	8	7	5	2	1	1	0	0	0	
PR	26	23	15	9	4	2	0	0	0	0	0	0	0	0	0	

CR or better: Subjects: 42; Events: 23; Median: 21.45 (95% CI: 12.52, NE)
VGPR: Subjects: 26; Events: 25; Median: 10.38 (95% CI: 5.09, 12.22)
PR: Subjects: 26; Events: 26; Median: 4.50 (95% CI: 2.86, 6.54)

CI= confidence interval; IMWG = International Myeloma Working Group; NE = not estimable. Two patients with 150 x 10^6 CAR-positive T cell dose, which is not part of the approved dose range, are included in Figure 3.

Special populations

Elderly
In the clinical trials of Abecma, 163 (39.9%) patients were 65 years of age or older and 17 (4.2%) were 75 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Abecma in all subsets of the paediatric population in the treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following Abecma infusion, the CAR-positive T 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.

Abecma transgene levels were positively associated with objective tumour response (partial response or better). In patients who received Abecma in the KarMMa-3 study, the median C_{max} levels in responders (N = 180) were approximately 5.4-fold higher compared to the corresponding levels in non-responders (N = 40). Median $AUC_{0\text{-}28days}$ in responders (N = 180) was approximately 5.5-fold higher than non-responders (N = 38). In patients who received Abecma in the KarMMa study, 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).

Special populations

Renal and hepatic impairment
Hepatic and renal impairment studies of Abecma were not conducted.

Effects of age, weight, gender or race
Age (range: 30 to 81 years) had no impact on Abecma expansion parameters. The pharmacokinetics of Abecma in patients less than 18 years of age have not been evaluated.

Patients with lower body weight had higher cellular expansion. Due to high variability in pharmacokinetic cellular expansion, the overall effect of weight on the expanison parameters of Abecma is considered not to be clinically relevant.

Gender had no impact on Abecma expansion parameters.

Race and ethnicity had no significant impact on Abecma expansion parameters.

5.3 Preclinical safety data

Abecma comprises engineered human T cells, therefore there are no representative in vitro assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed. Genotoxicity assays and carcinogenicity studies were not conducted.

In vitro expansion studies from healthy donors and patients showed no evidence for transformation and/or immortalisation and no preferential integration near genes of concern in Abecma T cells.

Given the nature of the product, non-clinical studies on fertility, reproduction and development were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CryoStor CS10 (contains dimethyl sulfoxide)
Sodium chloride
Sodium gluconate
Sodium acetate trihydrate
Potassium chloride
Magnesium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

1 year.

Each bag must be infused within 1 hour from start of thaw. After thawing, the volume of the product intended for infusion should be kept at room temperature (20°C – 25°C).

6.4 Special precautions for storage

Abecma must be stored in the vapour phase of liquid nitrogen (≤ -130°C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product should not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ethylene vinyl acetate cryopreservation bag(s) with sealed addition tube containing 10-30 mL (50 mL bag), 30-70 mL (250 mL bag) or 55-100 mL (500 mL bag) of cell dispersion.

Each cryopreservation bag is individually packed in a metal cassette.

One individual treatment dose is comprised of one or more infusion bags of the same size and fill volume.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

Abecma must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Abecma must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Prior to Abecma infusion, it must be confirmed that the patient's identity matches the patient identifiers on the Abecma cassette(s), the infusion bag(s) and the release for infusion certificate (RfIC). The Abecma infusion bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient. The company must be contacted immediately if there are any discrepancies between the labels and the patient identifiers.

If more than one infusion bag has been received for treatment, thaw each infusion bag one at a time. The timing of thaw of Abecma and infusion should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Abecma is available for infusion when the patient is ready.

Thawing

- Remove the Abecma infusion bag from the cassette and inspect the infusion bag for any breaches of container integrity such as breaks or cracks before thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local guidelines on handling of waste of human-derived material.
- Place the infusion bag inside a second sterile bag.
- 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

- Prime the tubing of the infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Infuse Abecma within 1 hour from start of thaw as quickly as tolerated by gravity flow.
- After the entire content of the infusion bag is infused, rinse the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection at the same infusion rate to ensure all product is delivered.
- Follow the same procedure for all subsequent infusion bags for the identified patient.

Measures to take in case of accidental exposure
In case of accidental exposure, local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Abecma must be decontaminated with appropriate disinfectant.

Precautions to be taken for disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Abecma (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1539/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 2021
Date of latest renewal: 08 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Celgene Corporation
Building S12
556 Morris Avenue
Summit, NJ 07901
United States

Name and address of the manufacturer(s) responsible for batch release

Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification via the controlled distribution programme

The MAH will ensure that hospitals and their associated centres that dispense Abecma are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational programme

Prior to the launch of Abecma in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

HCP educational programme

All HCPs who are expected to prescribe, dispense and administer Abecma shall be provided with a healthcare professional guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions;
- management of the CRS and serious neurologic adverse reactions;
- adequate monitoring of CRS and serious neurologic reactions;
- provision of all relevant information to patients;
- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on-site;
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin;
- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided.

Patient educational programme

All patients who receive Abecma shall be provided with a patient card, which will contain the following key messages:

- the risks of CRS and serious neurologic adverse reactions associated with Abecma;
- the need to report the symptoms of suspected CRS and NT to their treating doctor immediately;
- the need to remain in the proximity of the location where Abecma was received for at least 4 weeks following Abecma infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency and a message for HCPs that the patient is using Abecma;
- fields to record contact details of the prescriber and batch number.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
In order to further characterise the long-term efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. Final report: Q1 2043

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

Abecma 260 - 500 x 10^6 cells dispersion for infusion
idecabtagene vicleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells genetically modified *ex vivo* using a lentiviral vector encoding a chimeric antigen receptor (CAR) that recognises BCMA.

Contains 260 - 500 x 10^6 CAR+ viable T cells.

3. LIST OF EXCIPIENTS

Also contains: CryoStor CS10 (contains dimethyl sulfoxide), sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
10-30 mL per bag
30-70 mL per bag
55 -100 mL per bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
Intravenous use.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
Properly identify intended recipient and product..

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen (≤ -130 °C).
Do not thaw the product until use.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1539/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

SEC:
First name:
Last name:
Patient DOB:
Aph ID/DIN:
JOIN:
Lot:
Bag ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT

Abecma 260 - 500 x 10^6 cells dispersion for infusion
idecabtagene vicleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells genetically modified *ex vivo* using a lentiviral vector encoding a chimeric antigen receptor (CAR) that recognises BCMA.
Contains 260 - 500 x 10^6 CAR+ viable T cells.

3. LIST OF EXCIPIENTS

Also contains: CryoStor CS10 (contains dimethyl sulfoxide), sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
10-30 mL per bag
30-70 mL per bag
55-100 mL per bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
Intravenous use.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen (≤ -130 °C).
Do not thaw the product until use.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1539/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

SEC:
First name:
Last name:
Patient DOB:
Aph ID/DIN:
JOIN:
Lot:
Bag ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE RELEASE FOR INFUSION CERTIFICATE (RfIC) INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Abecma 260 - 500 x 10^6 cells dispersion for infusion
idecabtagene vicleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells genetically modified *ex vivo* using a lentiviral vector encoding a chimeric antigen receptor (CAR) that recognises BCMA.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT AND DOSE OF THE MEDICINAL PRODUCT

Bag ID for administration	Actual fill volume (mL)*	Number of CAR+ viable T cells per bag
Bag ID:		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Bag ID: ☐ N/A		
Total number of bags for administration	Total dose volume	Dose (total number of CAR+ viable T cells)

*Actual volume is the volume of filled drug product within each bag and may not be the same as the target volume listed on the drug product bag label.

4. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

5. OTHER SPECIAL WARNING(S), IF NECESSARY

SAVE THIS DOCUMENT AND HAVE IT AVAILABLE WHEN PREPARING FOR ADMINISTRATION OF ABECMA.

For autologous use only.

6. SPECIAL STORAGE CONDITIONS

Not applicable.

7. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

Product and dose information

Manufactured by:	
Manufacture date:	
Expiration date:	
Cell viability percentage:	

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. BATCH NUMBER, DONATION AND PRODUCT CODES

Patient information

First name:		Last name:	
Date of birth:		Lot number:	
JOIN:		Country:	
APH ID/DIN:			
SEC:			

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

11. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1539/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Abecma 260 - 500 x 10^6 cells dispersion for infusion
idecabtagene vicleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- 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 hospital.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Abecma is and what it is used for

What Abecma is
Abecma is a type of medicine called a 'genetically modified cell therapy'. The active substance in the medicine is idecabtagene vicleucel, which is made from your own white blood cells, called T cells.

What Abecma is used for
Abecma is used to treat adults with multiple myeloma, which is a cancer of the bone marrow.
It is given when previous treatments for your cancer have not worked or the cancer has come back.

How Abecma works
The white blood cells are taken from your blood and are genetically modified so that they can target the myeloma cells in your body.
When Abecma is infused into your blood, the modified white blood cells will kill the myeloma cells.

2. What you need to know before you are given Abecma

You must not be given Abecma
- if you are allergic to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you are allergic to any of the ingredients in the medicines you will be given for lymphodepleting chemotherapy, which is used to prepare your body for Abecma treatment.

Warnings and precautions
Before you are given Abecma you should tell your doctor if:
- you have any lung or heart problems.
- you have low blood pressure.
- you have had a stem cell transplant in the last 4 months.
- you have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- you have an infection. The infection will be treated before you are given Abecma.
- you notice the symptoms of your cancer getting worse. In myeloma these might include fever, feeling weak, bone pain, unexplained weight loss.
- you have had cytomegalovirus (CMV) infection, hepatitis B or C or human immunodeficiency virus (HIV) infection.
- you have had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given Abecma.

Tests and checks
Before you are given Abecma your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given Abecma.
- Check if your cancer is getting worse.
- Check for CMV infection, hepatitis B, hepatitis C or HIV infection.

After you have been given Abecma
- There are serious side effects which you need to tell your doctor or nurse about straight away and which may require you to get immediate medical attention. See section 4 under ‘Serious side effects’.
- Your doctor will regularly check your blood counts as the number of blood cells may decrease.
- Stay close to the treatment centre where you had Abecma for at least 4 weeks. See sections 3 and 4.
- Do not donate blood, organs, tissues or cells for transplantation.

Children and adolescents
Abecma should not be given to children and adolescents below 18 years of age.

Other medicines and Abecma
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Medicines that affect your immune system
Before you are given Abecma, tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids. This is because these medicines may interfere with the effect of Abecma.

See section 3 for information about the medicines you will be given before having Abecma.

Vaccinations
You must not be given certain vaccines called live vaccines:
- in the 6 weeks before you are given a short course of chemotherapy (called lympodepleting 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.

Pregnancy and breast-feeding
If you 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 breast-fed child.

- If you 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.

Discuss pregnancy with your doctor if you have received Abecma.

Driving and using machines
Do not drive, use machines or take part in activities that need you to be alert for at least 8 weeks after treatment or until your doctor tells you that you have completely recovered. Abecma may make you feel sleepy, may cause confusion or fits (seizures).

Abecma contains sodium, potassium and dimethyl sulfoxide (DMSO)
This medicine contains up to 752 mg sodium (main component of cooking/ table salt) per dose. This is equivalent to 37.6% of the recommended maximum daily intake of sodium for an adult.

This medicine contains up to 274 mg potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

If you have not been previously exposed to DMSO you should be observed closely during the first minutes of the infusion period.

3. How Abecma is given

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

How Abecma is given

- 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

- 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 10 days to check if your treatment is working - and help you if you have any side effects. See sections 2 and 4.
- Do not donate blood, organs, tissues or cells for transplantation.

If you miss an appointment
Call your doctor or the treatment centre as soon as possible to make another appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor immediately if you get any of the following side effects after being given Abecma. They usually happen in the first 8 weeks after the infusion, but can also develop later:

- fever, chills, difficulty breathing, dizziness or light-headedness, nausea, headache, fast heartbeat, low blood pressure or fatigue - these may be symptoms of cytokine release syndrome or CRS, a serious and potentially fatal condition.
- 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. Symptoms of parkinsonism, such as tremor, slow movements and stiffness.
- any signs of an infection, which may include fever, chills or shivering, cough, shortness of breath, rapid breathing and rapid pulse.
- feeling very tired or weak or short 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.

Tell your doctor immediately if you get any of the side effects above, as you may need urgent medical treatment.

Other possible side effects

Very common: may affect more than 1 in 10 people
- lack of energy
- high blood pressure
- decreased appetite
- constipation
- swollen ankles, arms, legs and face
- joint pain
- difficulty sleeping
- low number of white blood cells (neutrophils, leucocytes and lymphocytes), which can increase your risk of infection
- infections including pneumonia or infections of the respiratory tract, mouth, skin, urinary tract or blood, which may be bacterial, viral or fungal
- laboratory test results showing low levels of antibodies, called immunoglobulins (hypogammaglobulinaemia) that are important in fighting infections
- laboratory test results showing decreased levels of calcium, sodium, magnesium, potassium, phosphate or albumin, which may cause fatigue, muscle weakness or cramps or an irregular heartbeat
- 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: may affect up to 1 in 10 people
- severe inflammation due to activation of your immune system which could lead to serious damage in the body
- muscle pain

- abnormal body movements or lack of coordination
- uneven or irregular heartbeat
- fluid in the lungs
- low oxygen level in the blood, which may cause shortness of breath, confusion or drowsiness.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Abecma

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the cassette label and infusion bag label after 'EXP'.

Stored and transport frozen in the vapour phase of liquid nitrogen (≤ -130°C). Do not thaw the product until it is ready to be used. Do not refreeze.

Do not use this medicine if the infusion bag is damaged or leaking.

6. Contents of the pack and other information

What Abecma contains
- The active substance is idecabtagene vicleucel. Each infusion bag of Abecma contains idecabtagene vicleucel cell dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-BCMA chimeric antigen receptor (CAR-positive viable T cells). One or more infusion bags contain a total of 260 to 500 × 10^6 CAR-positive viable T cells.
- The other ingredients (excipients) are Cryostor CS10, sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, water for injections. See section 2, "Abecma contains sodium, potassium and DMSO".

This medicine contains genetically modified human blood cells.

What Abecma looks like and contents of the pack
Abecma is a colourless cell dispersion for infusion, supplied in one or more infusion bags individually packed in a metal cassette. Each bag contains 10 mL to 100 mL of cell dispersion.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Abecma.

Precautions to be taken before handling or administering the medicinal product

- Abecma must be transported within the facility in closed, break-proof, leak-proof containers.
- This medicinal product contains human blood cells. Healthcare professionals handling Abecma must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation prior to administration

- Prior to Abecma infusion, it must be confirmed that the patient's identity matches the patient identifiers on the Abecma cassette(s), the infusion bag(s) and the release for infusion certificate (RfIC).
- The Abecma infusion bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient. The company must be contacted immediately if there are any discrepancies between the labels and the patient identifiers.
- If more than one infusion bag has been received for treatment, thaw each infusion bag one at a time. The timing of thaw of Abecma and infusion should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Abecma is available for infusion when the patient is ready.

Thawing

- Remove the Abecma infusion bag from the cassette and inspect the infusion bag for any breaches of container integrity such as breaks or cracks before thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local guidelines on handling of waste of human-derived material.
- Place the infusion bag inside a second sterile bag.
- 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.
- Intravenous infusion of Abecma should only be administered by a healthcare professional experienced with immunosuppressed patients and prepared to manage anaphylaxis.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- Central venous access may be utilised for the infusion of Abecma and is encouraged in patients with poor peripheral access.
- Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Abecma infusion bag and accompanying documentation. The total number of infusion bags to be administered must also be confirmed with the patient specific information on the release for infusion certificate (RfIC).

- Prime the tubing of the infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Infuse Abecma within 1 hour from start of thaw as quickly as tolerated by gravity flow.
- After the entire content of the infusion bag is infused, rinse the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection at the same infusion rate to ensure all product is delivered.
- Follow the same procedure for all subsequent infusion bags for the identified patient.

Measures to take in case of accidental exposure

- In case of accidental exposure, local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Abecma must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

- Unused medicinal product and all material that has been in contact with Abecma (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

ANNEX IV

CONCLUSIONS ON THE REQUEST FOR ONE-YEAR MARKETING PROTECTION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.