Idecabtagene vicleucel (Abecma®) for the treatment of patients with relapsed and refractory multiple myeloma (MM)

General information

Drug description [1, 2]	Indication [3]
Idecabtagene vicleucel (ide-cel, bb2121) is a genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy and the first cell-based gene therapy to treat adult patients with multiple myeloma (MM). Each dose of idecabtagene vicleucel is created by collecting a patient's own T-cells and genetically modifying them so that they include a new gene that helps the body target and kills the myeloma cells. These modified immune cells are then infused back into the patient's blood.	Idecabtagene vicleucel is indicated for the treatment of adult patients with relapsed and refractory MM who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor (PI) and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Current treatment

- ❖ Relapsed or refractory MM is usually treated with combinations of drugs from two or three general classes. The main classes of drugs used to treat relapsed or refractory myeloma are:
  - Immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide)
  - PIs (bortezomib, carfilzomib, ixazomib)
  - Steroids (dexamethasone)
  - Antibodies that target myeloma cells (daratumumab, elotuzumab, isatuximab, belantamab mafodotin)
  - Nuclear export inhibitor (selinexor)
  - Histone deacetylase inhibitor (panobinostat)
  - Chemotherapy drugs (melphalan, cyclophosphamide) [4].

- ❖ Despite the development and approval of a range of new medicines for the treatment of MM over the past few years, there are limited therapeutic options for patients who have already received three major classes of drugs (immunomodulatory agents, PIs and monoclonal antibodies) and no longer respond to these medicines [2].

Regulatory status

EMA [3]	FDA [5]
Approval status for this indication: On 24 June 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Abecma®, intended for the treatment of relapsed and refractory MM. As Abecma® is an advanced therapy medicinal product the CHMP's positive opinion is based on an assessment by the Committee for Advanced Therapies. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 18/08/2021 [6] <u>The full indication is:</u> Abecma® is indicated for the treatment of adult patients with relapsed and refractory MM who have received at least three prior therapies, including an immunomodulatory agent, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. **Other indications**: none	**Approval status for this indication**: On 26 March 2021, the FDA approved idecabtagene vicleucel (Abecma®) for the treatment of adult patients with relapsed or refractory MM after four or more prior lines of therapy, including an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody. **Other indications:** none ✓ **First FDA-approved cell-based gene therapy for MM** ✓ **Breakthrough therapy designation** ✓ **Orphan drug designation**

✓ **Orphan status** ✓ **Advanced therapy medicinal product** ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation[1]**	

Costs

Currently, no cost information is available.

Posology and method of administration [7]

- ❖ 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.

Posology

- ❖ Abecma® is intended for autologous use only. Manufacture and release of Abecma® usually takes about 4-5 weeks.
- ❖ 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 106 CAR-positive viable T cells within a range of 260 to 500 x 106 CAR-positive viable T cells. See the release for infusion certificate for additional information pertaining to dose.
- ❖ **Pre-treatment (lymphodepleting chemotherapy)**
  - Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m² intravenously (IV) and fludarabine 30 mg/m² IV should be administered for 3 days.
  - 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 of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Abecma®.
- ❖ **Pre-medication**
  - To minimise the risk of infusion reactions, the patient should be pre-medicated with paracetamol (500 to 1,000 mg orally) and diphenhydramine (12.5 mg IV or 25 to 50 mg orally) or another H1-antihistamine, approximately 30 to 60 minutes before infusion of Abecma®.
  - 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.
- ❖ **Clinical assessment prior to infusion**
  - Abecma® treatment should be delayed in some patient groups at risk.
- ❖ **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.

Method of administration

- ❖ Abecma® is for intravenous use only.
- ❖ **Administration**
  - Do NOT use a leukodepleting filter.
  - Ensure that tocilizumab 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.
  - Confirm the patient's identity matches the patient identifiers on the Abecma infusion bag.

Special warnings and precautions for use [7]

- ❖ **Traceability**

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- 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 should be kept for a period of 30 years after the expiry date of the product.

❖ **Reasons to delay treatment**
- Due to the risks associated with Abecma® treatment, the infusion should be delayed up to 7 days if a patient has any of the following conditions:
  - Unresolved SAEs (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).

❖ **Autologous use**
- Abecma® is intended solely for autologous use and should under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Abecma® infusion bag, cassette and the release for infusion certificate. Abecma® must not be administered if the information on the patient-specific label does not match the intended patient.

❖ **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 the 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 that occurred following Abecma® infusion. Nearly all patients experienced some degree of CRS. The median time to onset of CRS was 1 day (range: 1 to 12).

❖ **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 2 days (range: 1 to 10 days). Neurologic toxicity may occur concurrently with CRS, after CRS resolution or in the absence of CRS.

❖ **Prolonged cytopenias**
- Patients may exhibit prolonged cytopenias for several weeks following lymphodepleting chemotherapy and Abecma® infusion. 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®. 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 and may be concurrent with CRS. In the event of febrile neutropenia, the 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. 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.
- Screening for CMV, HBV, active HIV and active HCV must be performed before collection of cells for manufacturing.

❖ **Hypogammaglobulinaemia**
- Plasma cell aplasia and hypogammaglobulinaemia can occur in patients receiving treatment with Abecma®. 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.
- **Interference with serological testing**
  - HIV and the lentivirus used to make Abecma® have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received Abecma®.
- **Blood, organ, tissue and cell donation**
  - Patients treated with Abecma® should not donate blood, organs, tissues and cells for transplantation.
- **Long-term follow-up**
  - Patients are expected to be enrolled in a registry and will be followed in the 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.

Study characteristics [2, 8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KarMMa NCT03361748	128	idecabtagene vicleucel target doses of 150 × 10^6, 300 × 10^6, or 450 × 10^6 CAR-positive (CAR+) T cells.	-	overall response (partial response or better)	single-group, phase 2 study	-	bluebird bio and Celgene, a Bristol-Myers Squibb company	[2]

Efficacy (I vs. C)

At a median follow-up of 13.3 months
Response: 73% (95% CI, 66-81); p<0.001
Complete or stringent complete response: 33%
Very good partial response or better: 52%

At the target doses of 150 × 10^6, 300 × 10^6, and 50 × 10^6 CAR+ T cells:
Response in 50%, 69% and 81%, respectively,
Complete response or better in 25%, 29% and 39%, respectively.

Safety (I vs. C)

Grade 3 or 4 AEs: n=127 (99%)
Total deaths[2]**:** n=44 (34%)
Cytokine release syndrome[3]**:** n=107 (84%)

[2] Most deaths (n=27) attributed by the investigator to complications of myeloma progression. 2% of patients died within 8 weeks after ide-cel infusion from ide-cel–related AEs (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, and cytokine release syndrome). 1 patient (1%) died between 8 weeks and 6 months from an ide-cel–related AE (cytomegaloviral pneumonia). 5 patients (4%) died after 6 months from unrelated AEs, and an additional 8 patients (6%) died after disease progression.

[3] Mostly of grade 1 and 2; 4% had grade 3 cytokine release syndrome, <1%) had grade 4, and <1% had grade 5.

Of the 42 patients with a complete or stringent complete response, 79% also had **MRD-negative status** at a sensitivity level of 10^{-5}, corresponding to 26% (95% CI, 19-34) of the treated population; the remaining 21% could not be evaluated for MRD. **Median time to first response**: 1.0 month (range: 0.5-8.8) **Median time to a complete response or better**: 2.8 months (range: 1.0-11.8) **Kaplan–Meier estimate for median duration of response**: 10.7 months (95% CI, 9.0-11.3) overall; and 11.3 months (95% CI, 10.3-11.4) at the 450×10^6 dose. **Median response duration in patients having a best response of partial response**: 4.5 months (95% CI, 2.9-6.7) **Median response duration in patients having a very good partial response**: 10.4 months (95% CI, 5.1-11.3) **Median response duration in patients having a complete or stringent complete response**: 19.0 months (95% CI, 11.3-could not be estimated) **Kaplan–Meier estimated median PFS**: 8.8 months overall (95% CI, 5.6-11.6), 12.1 months (95% CI, 8.8-12.3) at the 450×10^6 dose, and 20.2 months (95% CI, 12.3-could not be estimated) in patients having a complete or stringent complete response. **Kaplan–Meier estimated median OS**: 19.4 months (95% CI, 18.2-could not be estimated), with an OS of 78% at 12 months Data on OS are **immature**, with data for 84 patients (66%) censored. **Retreated with ide-cel after disease progression**: 28 patients; 21% had a second response, with durations of response ranging from 1.9-6.8 months; all the patients who had a response were retreated at a dose higher than their initial dose.	

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	unclear[4]	yes

Overall risk of bias: low risk

First published: 07/2021
Last updated: 09/2021

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CMV=Cytomegalovirus, CNS=central nervous system, CRS=cytokine release syndrome, DMSO=dimethyl sulfoxide, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GVHD= graft-versus-host disease, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenous. MG=median gain, MM=multiple myeloma, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SCT= stem cell transplant, ST=standard treatment

[4] Primary analysis data, KarMMa trial is ongoing.

References:

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