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Summary of Investigation Results

Regenerative medical products containing CAR-expressing T-cells

March 5, 2025

Non-proprietary name

a. Axicabtagene ciloleucel
b. Idecabtagene vicleucel
c. Ciltacabtagene autoleucel
d. Tisagenlecleucel
e. Lisocabtagene maraleucel

Brand name (marketing authorization holder)

a. Yescarta Intravenous Drip Infusion (Gilead Sciences K.K.)
b. Abecma Intravenous Infusion (Bristol-Myers Squibb K.K.)
c. Carvykti Suspension for Intravenous Infusion (Janssen Pharmaceutical K.K.)
d. Kymriah Suspension for Intravenous Infusion (Novartis Pharma K.K.)
e. Breyanzi Suspension for Intravenous Infusion (Bristol-Myers Squibb K.K.)

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

a. to e.

Language concerning occurrences of lymphoid neoplasm of CAR-positive T-cell origin reported in patients treated with regenerative medical products containing CAR-expressing T-cells (hereinafter referred to as “CAR-T cell products”), as well as precautions concerning

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lymphoid neoplasm of T-cell origin, should be added to the Important Precautions section.

a., b., d., e.

Language concerning the occurrence of lymphoid neoplasm of CAR-positive T-cell origin reported in patients treated with another CAR-T cell product should be deleted from the Other Precautions section.

Investigation results and background of the revision

Cases involving lymphoid neoplasm of CAR-positive T-cell origin were evaluated. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary for the following reasons:

- Multiple cases have been confirmed in which lymphoid neoplasm of CAR-positive T-cell origin occurred after administration of ciltacabtagene autoleucel and tisagenlecleucel, although the causal relationship with the CAR-T cell products is not clear. Of note, for axicabtagene ciloleucel, idecabtagene vicleucel, and lisocabtagene maraleucel, no cases have been reported for which it was definitely determined that the occurrence of lymphoid neoplasm of CAR-positive T-cell origin was observed.
- Taking into account that multiple cases have been confirmed in which lymphoid neoplasm of CAR-positive T-cell origin occurred after administration of ciltacabtagene autoleucel and tisagenlecleucel, it is considered to be highly probable that cases to be judged as lymphoid neoplasm of CAR-positive T-cell origin will also be reported for other CAR-T cell products. Therefore, issuing common precautions for all CAR-T cell products was deemed to be appropriate.

Reference: Number of cases* and patient mortalities involving lymphoid neoplasm of CAR-positive T-cell origin reported in Japan and overseas

a. to e.

No cases have been reported in Japan to date.

a.

One case has been reported overseas to date. (A causal relationship between the product and the event could not be established for this case.)

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No patient mortalities have been reported overseas to date.

b., e.

No cases have been reported overseas to date.

c.

A total of 9 cases have been reported overseas to date. (A causal relationship between the product and the event could not be established for any of these cases.)

No patient mortalities have been reported overseas to date.

d.

A total of 2 cases have been reported overseas to date. (A causal relationship between the product and the event could not be established for any of these cases.)

One instance of patient mortality has been reported overseas to date. (A causal relationship between the product and the death subsequent to the event could not be established for this case.)

*Cases collected in the PMDA's database for defects or adverse events, etc. reports

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications or Performance
a.	Axicabtagene ciloleucel	Yescarta Intravenous Drip Infusion	Gilead Sciences K.K.	May 2022	The following relapsed or refractory large B-cell lymphoma: • Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high-grade B-cell lymphoma Yescarta should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
b.	Idecabtagene vicleucel	Abecma Intravenous Infusion	Bristol-Myers Squibb K.K.	April 2022	Relapsed or refractory multiple myeloma Abecma should be used only in patients meeting all of the following criteria: • Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy • Patients who have received at least 2 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD 38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy
c.	Ciltacabtagene autoleucel	Carvykti Suspension for Intravenous Infusion	Janssen Pharmaceutical K.K.	Before market launch	Relapsed or refractory multiple myeloma Carvykti must be used only in patients meeting both of the following criteria: • Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy • Patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and who have failed to respond to or have relapsed after the last therapy
d.	Tisagenlecleucel	Kymriah Suspension for Intravenous Infusion	Novartis Pharma K.K.	May 2019	1. Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy: • Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy • Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy • Patients who are ineligible for, or relapsed after, allogeneic haematopoietic stem cell transplantation 2. Relapsed or refractory diffuse large B-cell lymphoma

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	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications or Performance
					Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T cell infusion therapy and are ineligible for, or relapsed after, autologous haematopoietic stem cell transplantation: • Newly diagnosed patients who failed to achieve a complete response to ≥2 lines of chemotherapy; newly diagnosed patients who achieved a complete response to ≥2 lines of chemotherapy but subsequently relapsed; patients who received ≥1 line of chemotherapy after relapse but failed to achieve a complete response; or patients who received ≥1 line of chemotherapy after relapse and achieved a complete response but subsequently relapsed again • Patients with diffuse large B-cell lymphoma transformed from follicular lymphoma who failed to achieve a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation, or who achieved a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation but subsequently relapsed 3. Relapsed or refractory follicular lymphoma Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy: • Newly diagnosed patients who failed to achieve a response to ≥2 lines of systemic therapy; newly diagnosed patients who achieved a response to ≥2 lines of systemic therapy but subsequently relapsed; patients who received ≥1 line of systemic therapy after relapse but failed to achieve a response; or patients who received ≥1 line of systemic therapy after relapse and achieved a response but subsequently relapsed again
e.	Lisocabtagene maraleucel	Breyanzi Suspension for Intravenous Infusion	Bristol-Myers Squibb K.K.	May 2021	The following relapsed or refractory large B-cell lymphoma: • Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed low-grade non-Hodgkin's lymphoma, high-grade B-cell lymphoma Relapsed or refractory follicular lymphoma Breyanzi should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.

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