PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

18 July 2024

Abecma® ▼ (idecabtagene vicleucel), Breyanzi® ▼ (lisocabtagene maraleucel), Carvykti® ▼ (ciltacabtagene autoleucel), Kymriah® ▼ (tisagenlecleucel), Tecartus® ▼ (brexucabtagene autoleucel) and Yescarta® ▼ (axicabtagene ciloleucel)

(CD19- or BCMA-directed CAR T-cell therapies): Risk of secondary malignancy of T-cell origin

Dear Healthcare professional,

Bristol-Myers Squibb Pharma EEIG, Janssen-Cilag International NV, Novartis Europharm Limited and Kite Pharma EU B.V., in agreement with the European Medicines Agency and the Health Products Regulatory Authority, would like to inform you of the following:

Summary

- **Secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies, have been reported within weeks and up to several years following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy.**
- **Patients should be monitored life-long for secondary malignancies.**

Background on the safety concern

Currently approved CD19- or BCMA-directed CAR-T cell therapies cover a range of indications spanning from B-cell acute leukaemia, specific subtypes of B-cell lymphoma, and multiple myeloma.

Up to April 2024, approximately 42,500 patients have been treated with these medicinal products globally.

The European Medicines Agency (EMA) has evaluated 38 cases of T-cell malignancy that have been reported to occur after treatment with CAR T-cell therapies up to April 2024. These cases related to

different types of T-cell lymphoma and of T-cell lymphocytic leukaemia and were observed within weeks and up to several years after administration. There have been fatal outcomes.

Among the cases included in this review, further testing regarding the presence of the CAR-construct in the secondary malignancy had been undertaken for less than half of the reported T-cell malignancies. In 7 cases, the CAR-construct was detectable. This suggests that the CAR T-cell therapy was involved in disease development and insertional mutagenesis could have occurred. While other mechanisms may also be possible, further investigation is desirable to better understand and identify underlying mechanisms and contributing factors. Therefore, testing of T-cell malignancy tissue samples from patients is one important step for such investigations.

Since approval, the product information has advised that patients treated with these products may develop secondary malignancies. The product information will be updated to include the new information concerning secondary malignancy of T-cell origin. Patients treated with CAR T-cell products should be monitored life-long for secondary malignancies.

Call for reporting

▼These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information.

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie. Reports of suspected adverse reactions can also be made to the companies, contact details below.

Please report the product name and batch details.

Company contact point

If you have any questions, or if you require any further information, please contact the medical information service of the relevant Marketing Authorisation Holder:

Marketing Authorisation Holder	**Product /name**	**Email Address**	**Phone number**
Bristol-Myers Squibb Pharmaceuticals Limited	Idecabtagene vicleucel (Abecma®) Lisocabtagene maraleucel (Breyanzi®)	medical.information@bms.com	+353 1 800 749 749
Janssen-Cilag International NV	Ciltacabtagene autoleucel (Carvykti®)	medinfo@its.jnj.com	1 800 709 122
Novartis Ireland Ltd on behalf of Novartis Europharm Limited	Tisagenlecleucel (Kymriah®)	medinfo.dublin@novartis.com	+353 1 220 4100
Kite Pharma EU B.V.	Brexucabtagene autoleucel (Tecartus®) Axicabtagene ciloleucel (Yescarta®)	KiteMedInfo.EU@gilead.com	+353 214 825 999

Yours faithfully,

DocuSigned by Paula Williams
Paula Williams | I approve this document July 11, 2024 | 7:27:33 AM PDT
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Paula Williams
Medical Lead, Haematology
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Bristol-Myers Squibb Pharmaceuticals Limited

DocuSigned by Myles Leavy
Myles Leavy | I approve this document July 9, 2024 | 11:32:24 AM PDT
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Myles Leavy, PhD
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Janssen Sciences Ireland

DocuSigned by Ruth Connaughton
Ruth Connaughton | I approve this document July 10, 2024 | 1:40:57 PM IST
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Ruth Connaughton, Ph.D.
Medical Lead, Oncology
Novartis Ireland Ltd on behalf
of Novartis Europharm Limited

DocuSigned by Julian Cole
I approve this document July 9, 2024 | 8:55:31 PM BST
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Dr Julian Cole
Country Medical Director
Kite Pharma EU B.V.