25 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 Ltd, Novartis Pharmaceuticals UK Limited and Kite Pharma EU B.V., in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA), 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 MHRA recently conducted a review of the signal for secondary T-cell malignancies following CAR T-cell therapy and sought advice from the independent Commission on Human Medicines. The MHRA also considered a review by the EMA, which 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

Abecma® ▼, Breyanzi® ▼, Carvykti® ▼, Kymriah® ▼, Tecartus® ▼ and Yescarta® ▼ are subject to additional monitoring. This will allow quick identification of new safety information.

Healthcare professionals should report ANY suspected adverse drug reactions (ADRs) associated with the use of these CAR T-cell products to the MHRA through the Yellow Card scheme.

Please report:

- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼
- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

Please include in your report the product name and batch/lot details.

You can report via:

- the Yellow Card website: www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, timing onset, treatment dates, and product brand name.

The non-identical nature of biological medicines and vaccines means it is very important that safety surveillance is carried out on a brand/product-specific basis. When reporting a suspected ADR to a biological medicine (such as blood products, antibodies and advanced therapies [such as gene and tissue therapy]) or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch-number.

Additionally, when providing patients with details of the vaccine or biological medicine administered, it is good practice to give them details of the brand and batch number. This will allow patients and carers to more accurately report suspected ADRs to the Yellow Card scheme.

Healthcare professionals can find further details on the testing process for T-cell secondary malignancies by contacting the Marketing Authorisation Holders using the medical information contact information.

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	0800 731 1736
Janssen-Cilag Ltd	Ciltacabtagene autoleucel (Carvykti®)	medinfo@its.jnj.com	+44 (0)1494567444
Novartis Pharmaceuticals UK Limited	Tisagenlecleucel (Kymriah®)	medinfo.uk@novartis.com	+44 (0)1276 698370
Kite Pharma EU B.V.	Brexucabtagene autoleucel (Tecartus®) Axicabtagene ciloleucel (Yescarta®)	KiteMedInfo.EU@gilead.com	0800 0113 700

Yours faithfully,

DocuSigned by Paula Williams
Paula Williams
I approve this document
July 17, 2024 | 7:42:38 AM PDT
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Paula Williams
Medical Lead, Haematology
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Mohamed Lockhat
Medical Director Haematology
Janssen-Cilag Ltd

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I approve this document
July 17, 2024 | 2:07:35 PM GMT
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Gerrit Zijlstra, Ph.D.
Chief Medical Officer
Novartis Pharmaceuticals UK Limited

DocuSigned by Julian Cole
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Dr Julian Cole
Country Medical Director
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