



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 10-13 June 2024 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 10-13 June 2024 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]² reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (24-27 June 2024) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available [guidance](#). Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

¹ Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

² The relevant EPITT reference number should be used in any communication related to a signal.



The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the [Questions and Answers on signal management](#).

1. Recommendations for update of the product information³

1.1. *Axicabtagene ciloleucel; brexucabtagene autoleucel; ciltacabtagene autoleucel; idecabtagene vicleucel; lisocabtagene maraleucel; tisagenlecleucel – Secondary malignancy of T-cell origin*

Authorisation procedure	Centralised
EPITT No	20040
PRAC Rapporteur	Ulla Wändel Liminga (SE)
Date of adoption	13 June 2024

Recommendation [see also section 3]

Product information

Having considered the available evidence in EudraVigilance, including the cumulative review and responses to the list of questions submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs of Abecma (Bristol-Myers Squibb Pharma EEIG), Breyanzi (Bristol-Myers Squibb Pharma EEIG), Carvykti (Janssen-Cilag International NV), Kymriah (Novartis Europharm Limited), Tecartus (Kite Pharma EU B.V.) and Yescarta (Kite Pharma EU B.V.) should submit a variation within 2 months from the publication of the PRAC recommendation to amend product information as described below (new text underlined, text to be deleted strikethrough)

Abecma

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T-cell origin

Patients treated with Abecma may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including Abecma. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. 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.

4.8 Undesirable effects

Table 3. Adverse reactions observed in patients treated with Abecma

Secondary malignancy of T-cell origin should be added into the Table of adverse reactions under the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps).

Frequency: rare

³ Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

Package leaflet

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

Warnings and precautions

Patients treated with Abecma may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Abecma and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

4. Possible side effects

Other side effects

Rare: may affect up to 1 in 1,000 people

- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

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

Educational programme

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:

risk of secondary malignancy of T-cell origin

Breyanzi

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T-cell origin

Patients treated with Breyanzi may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including Breyanzi. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. 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 tumour samples for testing.

4.8 Undesirable effects

Table 3: Adverse drug reactions identified with Breyanzi

Secondary malignancy of T-cell origin should be added under the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps). Frequency: Uncommon

Package leaflet

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

Warnings and precautions

Patients treated with Breyanzi may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Breyanzi and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

4. Possible side effects

Other possible side effects

Uncommon: may affect up to 1 in 100 people

- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

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

Educational programme

HCP Educational programme

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

- risk of secondary malignancy of T-cell origin

Carvykti

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T-cell origin

Patients treated with CARVYKTI may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including CARVYKTI. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. A case of CAR positive T cell lymphoma has been reported in an ongoing study. Patient should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

4.8 Undesirable effects

Table 4: Adverse reaction in patients with multiple myeloma treated with CARVYKTI (~~N=396~~)

Secondary malignancy of T-cell origin should be added under the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps). Frequency uncommon

Package leaflet

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

Warnings and precautions

Patients treated with CARVYKTI may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with CARVYKTI and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

Tell your doctor before you are given CARVYKTI if you have: [...]

4. Possible side effects

Other side effects

Uncommon (may affect up to 1 in 100 people):

- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

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

Educational programme: Prior to the launch of CARVYKTI in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational programme

The MAH shall ensure that in each Member State where CARVYKTI is marketed, all HCPs who are expected to prescribe, dispense, and administer CARVYKTI shall be provided with guidance:

- risk of secondary malignancy of T-cell origin

Kymriah

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T-cell origin

Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including Kymriah. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. They Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

4.8 Undesirable effects

Tabulated list of adverse reactions

The adverse reactions described in this section were identified in 79, 115 and 97 patients in the ongoing multicentre pivotal clinical studies (CCTL019B2202, CCTL019C2201 and CCTL019E2202), as well as 64 and 69 patients in the supportive studies (CCTL019B2205J and CCTL019B2001X), and from post marketing reporting. Adverse drug reactions ~~from these clinical studies~~ (Table 2) are listed by MedDRA system organ class.

Table 2 Adverse drug reactions ~~observed in clinical studies~~

The following should be added to the Table of adverse drug reactions:

Secondary malignancy of T-cell origin; SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps). Frequency: rare

Anaphylactic reaction; SOC Immune system disorders; Frequency: unknown

Neurotoxicity; SOC Nervous system disorders; Frequency: unknown

~~Post marketing experience~~

~~The following adverse drug reactions have been derived from post marketing experience with Kymriah via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration studies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to tisagenlecleucel exposure.~~

~~Frequency unknown: Anaphylactic reaction/infusion related reaction, neurotoxicity.~~

Package leaflet

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

Warnings and precautions

Kymriah is made from your own white blood cells and should only be given to you.

Patients treated with Kymriah may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Kymriah and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

4. Possible side effects

Other possible side effects

Rare (may affect up to 1 in 1,000 people)

- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

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

Educational programme

HCP Educational programme

The MAH shall ensure that in each Member State where KYMRIAH is marketed, all HCPs who are expected to prescribe, dispense ~~and~~ and administer KYMRIAH shall be provided with a guidance document to:

- risk of secondary malignancy of T-cell origin

Tecartus

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T cell origin

Patients treated with Tecartus may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CART-cell therapy. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes.

Patients must be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

4.8 Undesirable effects

Description of selected adverse reactions from ZUMA-2 and ZUMA-3 (n=182), and from post marketing reporting

[...]

Secondary malignancies

There have been cases of the following adverse effect(s) reported after treatment with other CAR T-cell products, which might also occur after treatment with Tecartus: secondary malignancy of T-cell origin.

Package leaflet

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

Warnings and precautions

Tecartus is made from your own white blood cells and must only be given to you (autologous use).

Patients treated with Tecartus may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with other similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

4. Possible side effects

[...]

A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin) has been reported for other similar medicines.

Reporting of side effects
[...]

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

Educational program

HCP Educational program

The MAH shall ensure that in each Member State where Yescarta is marketed, all HCPs who are expected to prescribe, dispense, and administer Yescarta shall be provided with a guidance document to:

- [...] risk of secondary malignancy of T-cell origin

Yescarta

Summary of product characteristics

4.4 Special warnings and precautions for use

Secondary malignancies including of T-cell origin

Patients treated with Yescarta may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including Yescarta. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. Patients are to be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T-cell origin occurs, the company is to be contacted to obtain instructions on patient samples to collect for testing.

4.8 Undesirable effects

Table 3: Adverse drug reactions identified with Yescarta*

Secondary malignancy of T-cell origin should be added under the SOC *Neoplasms benign, malignant and unspecified (including cysts and polyps)*. Frequency: rare

~~* Adverse drug reactions were identified from a pooled analysis of 397 adult patients treated with Yescarta in ZUMA-1, ZUMA-5, and ZUMA-7 and from post-marketing experience~~

Package leaflet

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

Warnings and precautions

Yescarta is made from your own white blood cells and must only be given to you (autologous use).

Patients treated with Yescarta may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Yescarta and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

4. Possible side effects

Rare (may affect up to 1 in 1,000 people)

- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

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

Educational program

HCP Educational program

The MAH shall ensure that in each Member State where Yescarta is marketed, all HCPs who are expected to prescribe, dispense, and administer Yescarta shall be provided with a guidance document to:

[...]

risk of secondary malignancy of T-cell origin

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Roxadustat	Thrombocytopenia (20079)	Anna Mareková (SK)	Assess in the next PSUR (submission by 25 August 2024)	Astellas Pharma Europe B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel; idecabtagene vicleucel; lisocabtagene maraleucel; ciltabtagene autoleucel; tisagenlecleucel; brexucabtagene autoleucel	Secondary malignancy of T-cell origin (20040)	Ulla Wändel Liminga (SE)	<ul style="list-style-type: none"> · See section 1.1 · Update the risk management plan · Provide new information in upcoming PSURs · Distribute a joint direct healthcare professionals communication (DHPC) 	Bristol-Myers Squibb Pharma EEIG, Janssen-Cilag International NV, Novartis Europharm Limited, Kite Pharma EU B.V.
Medroxyprogesterone acetate	Meningioma (20030)	Bianca Mulder (NL)	Respond to list of questions (submission by 3 July 2024)	Orion Corporation, Pfizer Limited
Valaciclovir	Acute hepatitis (20047)	Jana Lukačičinová (CZ)	Monitor in PSUR	MAHs of valaciclovir containing products