Product: KYMRIAH™

Proper Name: Tisagenlecleucel

Manufacturer: Novartis Pharmaceuticals Corporation

Indication:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
- Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Description:

KYMRIAH™ (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

BLA: STN 125646

Regulatory Milestone:

DATE	**MILESTONES**
Regulatory activity of KYMRIAH for treatment of DLBCL	

04/12/2017	Breakthrough Therapy Designation for DLBCL
08/04/2017	Pre-sBLA meeting for DLBCL indication
08/29/2017	Orphan Designation for DLBCL
10/30/2017	sBLA 125646/76 submission for DLBCL
11/21/2017	sBLA 125646/80 – submission for changes in manufacture
11/22/2017	sBLA 125646/76 – 30-day safety and efficacy update received
02/28/2018	sBLA 125646/76 – 120-day safety update received

PDUFA Goal Date: May 1, 2018

FDA approval date: August 30, 2017

EU approval: August 22, 2018

Health Canada approval: September 6, 2018

Japanese Ministry of Health, Labor and Welfare (MHLW) Approval: March 26, 2019

TGA approval: December 19, 2018

Package Insert: Package Insert-KYMRIAH

Summary Basis for Regulatory Approval: April 13, 2018 Summary Basis for Regulatory Action - KYMRIAH

European Public Assessment Report:

- June 28, 2018 Assessment report - KYMRIAH
- May 28, 2020 Assessment report for pediatric studies – KYMRIAH

Manufacturing Platform:

PARAMETER	DATA	REFERENCE

Manufacturer	Novartis Pharmaceuticals Corporation	
Transgene	CAR transgene	1
Indication	KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of: • Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. • Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	3
Virus & Serotype	CTL019 (murine) HIV-1 vector	2
Cell Substrate	1α (EF-1α) promoter	3
Manufacturing platform	**Viral vector:** It uses an upstream process (consisting of thawing of the working cell bank (WCB), expansion of the production cell bank, plasmid transfection, induction, and harvest), followed by a downstream purification process (consisting of filtration, chromatography, and nuclease treatment steps) to yield the 'vector substance' (purified bulk vector). The vector substance undergoes sterile filtration, concentration, and filling to obtain the vector product. **Transduced cells CTL019:** The manufacture of CTL019 starts with the acceptance and thawing of the leukapheresis material and ends with the cryopreservation of the CAR-positive T-cell containing product. Washed leukapheresis cells are enriched and are then transduced with the vector. After static incubation, the cells are eventually expanded in a bioreactor. At the end of the culture period the cells are washed and cryopreserved.	3
Dose in vial/final container	• **Pediatric and Young Adult B-cell ALL (up to 25 years of age)** A single dose of KYMRIAH contains 0.2 to 5.0 x 106 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 108 CAR-positive	1

	viable T cells for patients more than 50 kg, suspended in a patient-specific infusion bag for i.v. infusion. (3) • **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma** A single dose of KYMRIAH contains 0.6 to 6.0 x 108 CAR-positive viable T cells suspended in one or more patient-specific infusion bag(s) for i.v. infusion.	
Dose / patient	**Pediatric and Young Adult B-cell ALL (up to 25 years of age)** • For patients 50 kg or less, administer 0.2 to 5.0 x 106CAR-positive viable T cells per kg body weight intravenously. • For patients above 50 kg, administer 0.1 to 2.5 x 108 total CAR-positive viable T cells (non-weight based) intravenously. **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma.** • Administer 0.6 to 6.0 x 108 CAR-positive viable T cells intravenously.	1

1. Package insert: Package Insert-KYMRIAH
2. EPAR full: Kymriah
3. EPAR quality: Kymriah: EPAR - Public assessment report
4. FDA SBAR – quality: April 13, 2018, Summary Basis for Regulatory Action - KYMRIAH

Advisory Committee:

An ODAC meeting was held on July 12, 2017 to discuss the safety and efficacy of Biologics License Application (BLA) 125646, tisagenlecleucel for the treatment patients age 3-25 years of age with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). The committee discussed the safety profile of tisagenlecleucel, risk mitigation for the licensed product, pharmacovigilance. The voting question queried whether there is a favorable benefit-risk profile

with the appropriate risk mitigation for the treatment of R/R B-cell precursor ALL with tisagenlecleucel.

Safety: Not Available

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	TITLE	COUNTRIES
NCT02435849	2	80	Determine Efficacy and Safety of CTL019 in Pediatric Patients with Relapsed and Refractory B-cell ALL and High-Risk B-cell ALL at First Relapse. Determine Feasibility and Safety of CTL019 Therapy in Pediatric Patients with High Risk B-cell ALL That Relapsed < 6 Months Post All-HSCT.	United States, Italy, Australia, Austria, Belgium, Canada, France, Germany, Japan, Norway, Spain

European clinical trial numbers:

- 2017-005019-15
- 2016-002966-29
- 2014-001673-14
- 2017-004385-94
- 2016-001991-31
- 2013-003205-25
- 2017-002116-14
- 2014-003060-20

Publications:

- Childhood Hematopoietic Cell Transplantation (PDQ®) - PDQ Cancer Information Summaries - NCBI Bookshelf
- MedlinePlus Drug Information: Tisagenlecleucel Injection
- Dictionary of Cancer Terms - PDQ Cancer Information Summaries - NCBI Bookshelf
- Tisagenlecleucel for B-Cell acute lymphoblastic leukemia and diffuse large B-Cell lymphoma. Project protocol, clinical ..... Book - 2018
- Cell and gene therapies... Book - 2019
- Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., Bader, P., Verneris, M. R., Stefanski, H. E., Myers, G. D., Qayed, M., De Moerloose, B., Hiramatsu, H., Schlis, K., Davis, K. L., Martin, P. L., Nemecek, E. R., Yanik, G. A., Peters, C., Baruchel, A., … Grupp, S. A. (2018). **Tisagenlecleucel in Children and**

Young Adults with B-Cell Lymphoblastic Leukemia. The New England journal of medicine, 378(5), 439–448. https://doi.org/10.1056/NEJMoa1709866

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