Drug Monograph

Drug/Drug Class:	**Yescarta® (axicabtagene ciloleucel) suspension for infusion/ Chemotherapy Agents**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Yescarta® is available as a cell suspension for infusion. A single dose of Yescarta® contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 ml suspension in an infusion bag. Kite Pharma, Inc., Santa Monica, CA 90404
Summary of Findings:	Efficacy for Yescarta® was established in a single-arm, open-label, multicenter trial in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Of the 101 patients that received Yescarta®, 73 of them had an objective response rate. Of those 73, 52 patients achieved complete remission and 21 patients achieved partial remission. The median duration of response was 9.2 months, with the higher duration of response demonstrated in patients achieving complete remission.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in adults. NHLs are cancers that begin in certain cells of the immune system and can be either fast-growing or slow-growing. Approximately 72,000 new cases of NHL are diagnosed in the U.S. each year, and DLBCL represents approximately one in three newly diagnosed cases.

Dosage Form(s) [1]

Yescarta® is available as a cell suspension for infusion. A single dose of Yescarta® contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 ml suspension in an infusion bag.

Manufacturer [1]

Kite Pharma, Inc., Santa Monica, CA 90404

Indication(s) [1]

Yescarta® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Yescarta® binds to CD-19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacokinetics:

Following infusion of Yescarta®, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after infusion.

Relapsed or Refractory Large B-Cell Lymphoma

STUDY DESIGN	Single-arm, open-label, multicenter trial
INCLUSION CRITERIA	Adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year about autologous hematopoietic stem cell transplantation (HSCT).
EXCLUSION CRITERIA	Patients with prior allogeneic HSCT, any history or central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 ml/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50% or active serious infection.
TREATMENT REGIMEN	Following lymphodepleting chemotherapy, Yescarta® was administered as a single intravenous infusion at a target dose of 2 x 10^6 CAR-positive T cells/kg (maximum permitted dose: 2 x 10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV, both given on the fifth, fourth, and third day before Yescarta®. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for a minimum of 7 days after Yescarta® infusion.
RESULTS	Of 111 who underwent leukapheresis, 101 received Yescarta®. 72% of patients had an objective response rate. 51% of patients achieved complete remission, while 21% of patients achieved partial remission. The median duration of response for the responders was 9.2 months. The duration of response was longer in patients who achieved complete remission versus partial remission.
SAFETY	The most common adverse events (≥ 20%) experienced in the clinical trial included cytokine releasing syndrome (CRS), fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- CRS, including fatal or life-threating reactions, occurred following treatment with Yescarta®
- Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with

Yescarta®

- Because of the risk of CRS and neurologic toxicities, Yescarta® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)
- Allergic reactions may occur with infusion
- Severe or life-threatening infections may occur
- Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Yescarta® infusion
- B-cell aplasia and hypogammaglobulinemia can occur
- Patients treated with Yescarta® may develop secondary malignancies
- Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Yescarta® are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion. Patients should refrain from driving and engaging in hazardous occupations or activities during this initial period.

Adverse Effects [(1)]

Most common, ≥ 10%	Any Grade (%)	Grade 3 or Higher (%)
Tachycardia	57	2
Arrhythmia	23	7
Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
Abdominal pain	14	1
Dry mouth	11	0
Fever	86	16
Fatigue	46	3
Chills	40	0
Edema	19	1
Cytokine release syndrome	94	13
Hypogammaglobulinemia	15	0
Infections-pathogen unspecified	26	16
Viral infection	16	4
Bacterial infections	13	9
Decreased appetite	44	2

Weight decreased	16	0
Dehydration	11	3
Motor dysfunction	19	1
Pain in extremity	17	2
Back pain	15	1
Muscle pain	14	1
Arthralgia	10	0
Encephalopathy	57	29
Headache	45	1
Tremor	31	2
Dizziness	21	1
Aphasia	18	6
Delirium	17	6
Hypoxia	32	11
Cough	30	0
Dyspnea	19	3
Pleural effusion	13	2
Renal insufficiency	12	5
Hypotension	57	15
Hypertension	15	6
Thrombosis	10	1

Drug Interactions [(1)]

- None specified

Dosage and Administration [(1)]

Yescarta® is for autologous use only. The patient's identity must match the patient identifiers on the Yescarta® cassette and infusion bag.

Each single infusion bag contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 ml. The target dose is 2 x 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2 x 10^8 CAR-positive viable T cells.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	COST/ INFUSION BAG**
Axicabtagene ciloleucel	Yescarta	Kite	$373,000

** Maximum Allowable Cost

Conclusion

Yescarta® is a chimeric antigen receptor (CAR) T cell therapy indicated to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. It is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin lymphoma. Each dose of Yescarta® is a customized treatment created using a patient's own immune system to help fight the lymphoma. The patients T-cells are collected and genetically modified to include a new gene that targets and kills the lymphoma cells. Once the cells are modified, they are infused back into the patient. The safety and efficacy of Yescarta® were established in a multicenter trial of 101 adults with refractory or relapsed large B-cell lymphoma. The objective response rate was 72% with 51% of patients achieving complete remission. Treatment with Yescarta® has the potential to cause severe side effects. It carries a box warning for CRS, which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and for neurologic toxicities. Both CRS and neurologic toxicities can be fatal or life-threatening. Patients are monitored in the hospital for 7 days following infusion for adverse reactions.

Recommendation

The Division recommends adding this drug as a Clinical edit.

References

1) Yescarta. Retrieved 5/29/2018 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59&audience=consumer
2) FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma. Retrieved 5/29/2018 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm

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