RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	TECARTUS™
Generic Name	brexucabtagene autoleucel
Drug Manufacturer	Kite Pharma, Inc.

New Drug Approval

TECARTUS™ was approved under the Accelerated Approval pathway and was granted Priority Review and Breakthrough Therapy designations. TECARTUS™ also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
TECARTUS™ should not be administered to patients with active infection or inflammatory disorders.
The TECARTUS™ application was reviewed using a cross-agency approach. The clinical review was coordinated by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination. The FDA remains committed to supporting safe and effective treatment options that have the potential of providing lifesaving results.
Because of the risk of CRS and neurologic toxicities, TECARTUS™ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta® and TECARTUS™ REMS Program. The required components of the Yescarta® and TECARTUS™ REMS Program are:

- Healthcare facilities that dispense and administer TECARTUS™ must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within two hours after TECARTUS™ infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer TECARTUS™ are trained in the management of CRS and neurologic toxicities.

FDA Approval Date: July 24,2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Mantle cell lymphoma (MCL), one of the B cell non-Hodgkin lymphomas (NHL), has a variable course. A minority of patients with this disorder may survive untreated for many years. However, more frequently, MCL assumes a more virulent character, akin to that of an aggressive NHL variant.
Although MCL usually responds well to initial treatment, patients do tend to relapse or become refractory.
The term “relapsed” refers to disease that reappears or grows again after a period of remission.
The term “refractory” is used to describe when the lymphoma does not respond to treatment (meaning that the cancer cells continue to grow) or when the response to treatment does not last very long.
For patients who relapse or become refractory, secondary therapies may be successful in providing another remission.
Like other forms of non-Hodgkin lymphomas (NHL), there is no consensus on the best treatment for relapsed or refractory MCL; however, there are an increasing number of treatment options available for these patients. The type of treatment recommended for any individual patient depends on several factors, including the timing of the relapse, the patient’s age, extent of disease, overall health, and prior therapies received.
MCL is relatively uncommon form of NHL, comprising 3-10% of NHL with an annual incidence of 0.5 to 1 case per 100,000 population. The exact international prevalence of MCL is difficult to estimate because of the lack of uniform classification and procedures used for diagnosis.

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Efficacy

A single-arm, open-label, multicenter trial (ZUMA-2; NCT02601313) evaluated the efficacy and safety of a single infusion of TECARTUS™ in adult patients with relapsed or refractory mantle cell lymphoma (MCL) who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib). Seventy-four patients were leukapheresed, five (7%) of whom did not begin conditioning chemotherapy or receive TECARTUS™: three (4%) experienced manufacturing failure, one (1%) died of progressive disease, and one (1%) withdrew from the study. One patient (1%) received lymphodepleting chemotherapy but did not receive TECARTUS™ due to ongoing active atrial fibrillation. Sixty-eight of the patients who were leukapheresed received a single infusion of TECARTUS™, and 60 of these patients were followed for at least six months after their first objective disease response, qualifying them as efficacy evaluable.

Among the 60 efficacy-evaluable patients, 2 × 106 CAR-positive viable T cells/kg were administered to 54 (90%). The remaining six (10%) patients received doses of 1.0, 1.6, 1.8, 1.8, 1.9, and 1.9 × 106 CAR-positive viable T cells/kg.Of the 60 efficacy-evaluable patients, the median age was 65 years (range: 38 to 79 years).
Among the 60 efficacy-evaluable patients, 14 (23%) had blastoid MCL. Following leukapheuresis and prior to administration of TECARTUS™, 21 (35%) of the 60 patients received bridging therapy. Sixteen (27%) were treated with a BTKi, 9 (15%) with a corticosteroid, and 4 (7%) with both a BTKi and a corticosteroid.
Among the 60 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 15 days (range: 11 to 28 days), and the median time from leukapheresis to product infusion was 27 days (range: 19 to 63 days). Among the 60 efficacy-evaluable patients, 14 (23%) had blastoid MCL. Following leukapheuresis and prior to administration of TECARTUS™, 21 (35%) of the 60 patients received bridging therapy. Sixteen (27%) were treated with a BTKi, 9 (15%) with a corticosteroid, and 4 (7%) with both a BTKi and a corticosteroid.
Among the 60 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 15 days (range: 11 to 28 days), and the median time from leukapheresis to product infusion was 27 days (range: 19 to 63 days).

The primary endpoint of objective response rate (ORR) per the Lugano Classification (2014) in patients treated with TECARTUS™ as determined by an independent review committee. The median time to response was 28 days (range: 24 to 92 days) with a median follow-up time for DOR of 8.6 months.

Safety

ADVERSE EVENTS

The most common non-laboratory adverse reactions (incidence greater than or equal to 20%) are: pyrexia, CRS, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection – pathogen unspecified, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspnea, rash, insomnia, pleural effusion, and aphasia.

WARNINGS & PRECAUTIONS

- Cytokine Release Syndrome: It includes life threatening reactions, occurred in patients receiving TECARTUS™. Do not administer TECARTUS™ to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities: It includes life-threatening reactions, occurred in patients receiving TECARTUS™, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with TECARTUS™. Provide supportive care and/or corticosteroids, as needed.

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- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion.
- Severe Infections: Monitor patients for signs and symptoms of infection; treat appropriately.
- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following TECARTUS™ infusion. Monitor complete blood counts.
- Hypogammaglobulinemia: Monitor and provide replacement therapy.
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with TECARTUS™.
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving TECARTUS™.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

TECARTUS™, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-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.

Dose & Administration

ADULTS

2x 10^6 CAR-positive viable T cells/kg of body weight, with a maximum of 2x 10^8 CAR-positive viable T cells in approximately 68 mL.

PEDIATRICS

The safety and efficacy of TECARTUS™ have not been established in pediatric patients.

GERIATRICS

No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.

RENAL IMPAIRMENT

Renal impairment study of TECARTUS™ was not conducted.

HEPATIC IMPAIRMENT

Hepatic impairment study of TECARTUS™ was not conducted.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

TECARTUS™ is available as a cell suspension for infusion.

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TECARTUS™ comprises a suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL.

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