UnitedHealthcare®
MEDICARE & RETIREMENT

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Tamara Syrek Jensen
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: Formal Request for National Coverage Determination for Chimeric Antigen Receptor T-Cell Therapies

Dear Ms. Syrek Jensen:

The FDA recently approved the initial chimeric antigen receptor (CAR) –T cell therapies. UnitedHealthcare (UHC) submits the request below for a National Coverage Determination for these therapies to clarify the circumstances under which the therapies will be covered and to create consistent patient access to the therapies across the country and financial sustainability in the Medicare Advantage program with regard to these therapies.

As UHC anticipates emerging clinical advances, including these CAR-T therapies, UHC has several concerns that while promising clinically, CAR-T therapies could create significant financial risks for CMS, both Original Medicare FFS and Medicare Advantage plans. As CMS is aware, Medicare Advantage plans cover services as they are covered under Original Medicare, including Part B drugs. For that reason, we believe there is an industry-wide need for a National Coverage Determination (NCD) to ensure a level playing field across Medicare Advantage plans, so that providers and members are better equipped to make treatment decisions. Absent a National Coverage Determination, providers and beneficiaries could get inconsistent treatment decisions and inconsistent MAC decisions, leading to inconsistent coverage determinations, depending on a beneficiary's location. Accordingly, United urges CMS to act expeditiously to issue the NCD discussed below.[1]

[1] For Medicare Advantage members and plans, these CAR-T therapies clearly meet the significant cost criterion set forth in 42 C.F.R. § 422.109(a), which allows the Medicare Advantage plan to have its members submit the claims to Original Medicare until the contract year for which Medicare Advantage plan payments are appropriately adjusted to take into account the cost of the NCD. Accordingly, we intend to share this NCD request with the CMS Medicare Advantage team to urge them to issue a formal determination that the CAR-T therapies meet the significant cost threshold criterion upon issuance of an NCD.

Statutory Benefit Category for CAR-T

CAR-T cell therapy is a medical service and other health service furnished by a provider of services and eligible for coverage under Medicare pursuant to Sections 1832 (a)(2)(B) and 1861 (s)(2)(A) and (B) of the Social Security Act.

Description of CAR-T

CAR-T cell therapy is a form of adoptive cell transfer that has shown promise in the treatment of certain hematologic malignancies. The first CAR-T cell therapies developed for clinical use target CD19, an antigen that is present in leukemias and lymphomas that arise from B-cells, a type of white blood cell. Each dose of CAR-T cell therapy is individually manufactured for the patient using their own T-cells, a type of white blood cell known as a lymphocyte. In a process similar to that used for autologous hematologic stem cell transplants, the patient's T-cells are collected (leukapheresis) at a specialized treatment center. The T-cells are sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia or lymphoma cells that have CD19 on the surface. Once the cells are modified, they are sent back to the treatment center to be infused into the patient to target the cancer cells.[2]

Two CAR-T products recently received FDA approval. Kymriah™ (Novartis) received Food and Drug Administration (FDA) approval for use in pediatric and young adult patients, age 3 to 25 years, with relapsed or refractory Acute Lymphoblastic Leukemia (ALL).[3] Yescarta™ (Kite/Gilead) was approved by the FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including Diffuse Large B-Cell Lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, after two or more lines of systemic therapy.[4]

NCD Requested and Supporting Scientific Evidence

ALL is a cancer of the bone marrow and blood. In the United States, ALL occurs at an annual rate of approximately 41 cases per 1 million people aged 0 to 14 years and approximately 17 cases per 1 million people aged 15 to 19 years. The incidence of new cases of pediatric ALL is approximately 3,100 in children and adolescents per year, with 80-85% being of B cell origin. Fortunately most patients are cured with chemotherapy or with an allogeneic Hematopoietic Stem Cell Transplant (HSCT). Approximately 10-15% of patients will fail to respond to or relapse after initial treatment. Currently the only cure for relapsed or refractory pediatric ALL is allogeneic HSCT. However, for HSCT to succeed the patient needs to be in complete remission, and preferably with Minimal Residual Disease (MRD). Current standard of care is investigator choice, but usually

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[2] CAR T Cells Encouraging for Diffuse Large B-Cell Lymphoma - Medscape - Jun 27, 2017; FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting July 12, 2017. BLA 125646 https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm566165.htm

[3] Kymriah [package insert]. East Hanover, NJ. Novartis Pharmaceutical Corporation; August 2017

[4] Yescarta [package insert]. Santa Monica, CA. Kite Pharma, Inc.; October 2017

includes combination chemotherapy to achieve remission with intent to proceed to HSCT if appropriate donor can be identified.[5]

The efficacy of Kymriah for the treatment of relapsed or refractory B-cell ALL was demonstrated in a phase 2 open-label trial in 63 patients. Among the 63 patients who received Kymriah, 52 (83%) achieved remission with MRD as determined by an independent review committee.[6] Approximately, 56% of patients who achieved remission with Kymriah were still in remission at last assessment prior to the data being censored. The estimated relapse-free rate among responders at six months was 75%.[7]

Non-Hodgkin Lymphomas (NHL) is the most common hematologic cancer in adults with approximately 72,000 new cases diagnosed in the U.S. each year. DLBCL is the most common type of NHL representing approximately one third of new cases. Initial therapy for advanced DLBCL includes combination chemotherapy plus rituximab with survival estimates surpassing 70% at 3 years. Relapsed or refractory disease is typically treated with high dose chemotherapy with intent to proceed with autologous HSCT. The treatment of patients who are not candidates for HSCT, who have failed to respond to second-line therapy, or who have relapsed after HSCT has generally been palliative, or investigational. An estimated 7,500 Americans with refractory DLBCL may be eligible for CAR-T cell therapy.

The efficacy of Yescarta for the treatment of relapsed or refractory large B-cell lymphoma was demonstrated in the phase 2 open-label ZUMA-1 trial in 101 patients who had refractory disease to their most recent therapy or had relapse within 1 year after autologous HSCT. Among the 101 patients who received Yescarta, 73 (72%) achieved an overall response and 52 (51%) achieved a complete response. Of the responders, the median duration of response was 9.2 months.[8] The median duration of response for those with a complete response to Yescarta has yet to be defined.

Treatment with CAR-T therapy has the potential to cause severe side effects. Kymriah™ and Yescarta™ both carry a boxed warning for life-threatening neurological toxicities and Cytokine Release Syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms. CRS occurred in 79% and 94% of patients who received Kymriah or Yescarta respectively. Neurologic toxicity occurred in 65% and 87% of patients who received Kymriah or Yescarta respectively. Because of the risk of CRS and neurological events, Kymriah and Yescarta were approved with a Risk Evaluation and Mitigation Strategy (REMS) in place. An aspect of the REMS program is that intravenous Actemra (tocilizumab), which is indicated for CRS, must be immediately available at the certified healthcare facility that administers CAR-T therapy. Since the CD19 antigen is also present on normal B-cells, and Kymriah can destroy those normal B cells that produce antibodies, there may be an increased risk of infections for a prolonged period of time. Patients may require supplemental immunoglobulin infusions to minimize risk of infections during this time.

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[5] Yescarta [package insert]. Santa Monica, CA. Kite Pharma, Inc.; October 2017

[6] Kymriah [package insert]. East Hanover, NJ. Novartis Pharmaceutical Corporation; August 2017

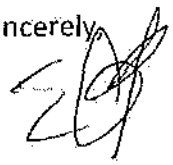
[7] FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting July 12, 2017. BLA 125646 https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm566165.htm

[8] Yescarta [package insert]. Santa Monica, CA. Kite Pharma, Inc.

Given the complexity of the therapy, treating patients with acute life-threatening disease requiring the manufacture of an individualized product, the potential for severe and also life-threatening side-effects necessitating specialized expertise to manage, and the high cost of the products and associated care required, a National Coverage Determination is essential to ensure that coverage is available to the Medicare population and that the criteria used to determine eligibility for coverage are evidence-based and are consistent regardless of the state of residence of the beneficiary. UHC proposes that coverage for CAR-T cell therapy be based upon the indications specified in the FDA labels. However, given that CAR-T cell therapy is an innovative therapy, and ongoing clinical trials are likely to identify new patient populations who may benefit, which may not all be reviewed by the FDA, we urge CMS to develop a process to update the NCD as new evidence emerges.

Thank you for your consideration of our request. Given the new CAR-T therapies in the pipeline -- which are also promising clinically but very expensive - we believe there is an opportunity to address national, consistent and thoughtful coverage criterion for Medicare beneficiaries to maximize the benefit of these new therapies. If you have any questions about the request, please do not hesitate to contact me or Dr. Jennifer Malin at (763) 283-2401.

Sincerely,



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