

Company

Jazz Pharmaceuticals

Drug or Device Name

Rylaze®

Category

Biotechnology

Compound/Technical Name

JZP458

Trade Name

Rylaze®

Date of Approval

06/30/2021

Therapeutic Categories

N/A

Indications

Rylaze® (asparaginase erwinia chrysanthemi (recombinant)-rywn) is approved for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in pediatric and adult patients one month and older who have developed hypersensitivity to E. coli-derived asparaginase.

Background

Acute lymphoblastic leukemia (ALL) is the most common cancer among children and the most frequent cause of death from cancer before 20 years of age. In the past several decades, a substantial improvement in the survival of patients with ALL and lymphoblastic lymphoma (LBL) was achieved due to the use of multi-agent chemotherapeutic regimens, with asparaginases being an important component of ALL and LBL therapy for over 40 years. The most common asparaginases are derived from E. coli, which can produce severe allergic reactions resulting in the need for treatment cessation. The inability to receive asparaginase has been associated with poor patient outcomes. These hypersensitivity reactions affect up to 30% of patients with ALL or LBL who are treated with E. coli-derived asparaginase, and data from a Children's Oncology Group retrospective analysis of over 8,000 patients found that patients who did not receive a full course of asparaginase treatment due to associated toxicity had significantly lower survival outcomes, with 50% increased risk of events such as relapse. Asparaginase Erwinia chrysanthemi (crisantaspase) is an effective treatment alternative for patients who develop a hypersensitivity. However, since 2016, there has been a worldwide shortage of crisantaspase due to ongoing manufacturing issues, which has resulted in consistent disruptions in product availability and prevented many pediatric patients from receiving all their planned doses of

asparaginase. Therefore, to ensure that patients who develop hypersensitivity to E. coli-derived asparaginases can complete their full treatment course, alternative preparations were needed. Since its approval, Rylaze has been a reliable treatment option for ALL and LBL patients who develop this type of hypersensitivity where there was a critical unmet need, providing patients with the opportunity to complete their full course of asparaginase therapy. Today, Rylaze is the only available option for those patients in the U.S.

Development

To create a reliable, high-quality supply of a non-E. coli based asparaginase and alleviate current market shortages, Jazz was committed to rapidly creating a reliable high-quality non-E. coli-derived asparaginase to address the immense patient need. Jazz identified novel technology and entered into a unique partnership to accelerate the development and approval process of Rylaze. Central to achieving this was a clinical trial collaboration with the Children's Oncology Group (COG), a large research organization with a vast network of pediatric oncology patients and research sites. Together, Jazz and COG developed and conducted the Phase 2/3 trial evaluating the administration of Rylaze in adult and pediatric patients with ALL and LBL who have developed hypersensitivity to an E. coli-derived asparaginase. By leveraging COG's expertise and strong connection to patients, the study had a brisk enrollment, despite occurring amidst COVID, and the best dosing of Rylaze for patients was quickly identified. This enabled an accelerated review and approval by the U.S. Food and Drug Administration (FDA) following a Fast Track designation by the Agency. The development program advanced quickly, from filing the IND in late 2018 and completing the Phase 1 study through to enrolling the first patient in the Phase 2/3 study in December 2019. This critical medication received approval in June of 2021 under the Real Time Oncology Review program, just 18 months after initiating the Phase 2/3 trial. Following approval, a rapid launch was deployed, leveraging a fully modern and scalable manufacturing process to ensure all patients who could benefit from the therapy could reliably secure access to Rylaze immediately. To avoid supply shortages, Jazz manufactured a year's supply of Rylaze at approval and have had sufficient safety stocks to ensure no shortages since then, even with strong clinical adoption.

Innovation

Unlike other asparaginase-based treatment options, Rylaze is a recombinant medication that uses a novel *Pseudomonas fluorescens* expression platform that produces an enzyme with no immunologic cross reactivity to E. coli-derived asparaginases. Rylaze contains an asparagine specific bacterial enzyme (L-asparaginase), which is a tetrameric enzyme with a similar amino acid sequence and consistent physiochemical properties to native asparaginase *Erwinia chrysanthemi*. Given the historical manufacturing issues for crisantaspase which affected product availability, an innovative approach to manufacturing was critical. Rylaze represents a significant advance through recombinant, modern manufacturing, supported by partnership with trusted manufacturers committed to the highest standards of production and quality control. Rylaze's modern manufacturing uses Pelican Expression Technology, a novel approach to recombinant protein production which helps to produce high yields of purified product in as little as 3 weeks. The efficient manufacturing process from start to finish results in a ready-to-use, high concentration formulation with reliable supply, ensuring uninterrupted therapy for patients. Since its approval, Jazz continues to advance research into Rylaze by putting patient and family needs at the center of its ongoing development. Recently, Jazz submitted two additional supplemental regulatory filings for Rylaze to the FDA, that support a three-day-a-week intramuscular dosing schedule and an intravenous administration option. These new options address an unmet patient need by providing alternative dosing schedules and routes of

administration, increasing flexibility and access to this important therapy for patients who need it. Through a unique, collaborative approach that brought this critical medication to market in an accelerated manner and through consistent, uninterrupted supply since its approval, Jazz is fulfilling its commitment to enabling people with rare forms of blood cancers to live longer, healthier lives.

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1American Cancer Society. Key Statistics for Childhood Leukemia. Available at <https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html>. Updated January 12, 2022. Accessed June 30, 2022. Salzer W, Bostrom B, Messinger Y et al. 2018. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leukemia & Lymphoma*. 59:8, 1797-1806, DOI: 10.1080/10428194.2017.1386305. Hijjiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2016;57(4):748–757. DOI: 10.3109/10428194.2015.1101098. National Cancer Institute. Adult Acute Lymphoblastic Leukemia Treatment (PDQ®)–Patient Version. Available at www.cancer.gov/types/leukemia/patient/adult-all-treatment-pdq. Updated November 19, 2021. Accessed June 30, 2022.

Attachments

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