

Company

Mirum Pharmaceuticals, Inc.

Drug or Device Name

LIVMARLI® (maralixibat) oral solution

Category

Pharmaceutical

Compound/Technical Name

Maralixibat

Trade Name

LIVMARLI® (maralixibat) oral solution

Date of Approval

09/29/2021

Therapeutic Categories

Alagille syndrome, cholestasis, liver disease, pediatrics

Indications

LIVMARLI® (maralixibat) oral solution is approved by the United States Food and Drug Administration for the treatment of cholestatic pruritus in patients with Alagille syndrome, three months of age and older.

Background

LIVMARLI® (maralixibat) oral solution is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor and the first and only FDA-approved medication in Alagille syndrome (ALGS), a cholestatic liver disease affecting 2,000-2,500 people in the United States. LIVMARLI works by re-directing bile acids so that more are excreted in the feces, leading to lower circulating levels (of bile acids) thereby addressing many clinical impacts of cholestasis. ALGS is a rare, genetic, multisystem disease that causes abnormalities in bile ducts leading to severe symptomatic burden and progressive liver disease. Malformed or reduced bile ducts cause cholestasis, the accumulation of bile acids in the liver, which leads to inflammation and liver injury, and prevents the liver from working properly. Cholestasis in ALGS is associated with pruritus which is among the most common indications for liver transplant in ALGS. Symptoms of ALGS typically start early in life and caregivers have reported noticing itch as early as infancy. This intractable itch can lead to red marks, bleeding, and scarring, and can cause severe disruption and impact to both the child and their family's quality of life. The approval of LIVMARLI in the U.S. is based on the pivotal ICONIC study as well as five years of data from supportive studies. Data from ICONIC demonstrated statistically significant reductions in pruritus, which was maintained through four years.

Development

LIVMARLI was initially developed by Lumena, and following the acquisition of the company by Shire, the LIVMARLI development program was deprioritized. During the time that Shire was considering out-licensing or discontinuing the program, Mirum co-founders (including the former Lumena CEO) recognized the impact LIVMARLI was having in its clinical program. Through relationships with the Alagille Syndrome Alliance, an ALGS advocacy group, the potential for patients and urgency to bring LIVMARLI forward was clear. This was confirmed when the landmark ICONIC study topline data were analyzed and showed a positive result, highlighting the role of LIVMARLI as a future standard of care in ALGS. Mirum acquired LIVMARLI and rapidly advanced conversations with FDA for an approval based on the Phase 2b ICONIC data. This study showed pronounced and durable improvements in pruritus, serum bile acids and other cholestatic manifestations. Based on the striking data, Mirum was granted breakthrough designation for LIVMARLI in Alagille syndrome and the company applied for approval which was granted in September 2021. The clinical program for LIVMARLI in ALGS has a unique advantage of years of long-term follow-up which has recently allowed for evaluating long-term event-free survival and drivers of long-term outcomes. Mirum has collaborated with an academic consortium that led to an analysis of the LIVMARLI clinical data compared to natural history of a matched pool of patients in a large database. Again, these results showed the striking impact of LIVMARLI with a 70% reduction in event risk over the 6-year analysis. Mirum has continued to build on the learnings from the transformative program in ALGS with an ongoing randomized study in biliary atresia and regulatory approval submissions to the FDA and EMA for the PFIC indication following groundbreaking data from its phase 3 study last year. Since its FDA approval, the EMA has since approved LIVMARLI for the same indication in ALGS, 2 months and older. Mirum is also building on these findings in the pediatric indications with a broad program in adult liver disease with volixibat, its second program.

Innovation

ALGS is a complex rare liver disease with pruritus being one of the most burdensome symptoms. The severe and unrelenting itch can be debilitating for patients. The itch can lead to sleepless nights and can cause a significant impact to not only the lives of patients but their families. Further, the intractable itch can have a mutilative effect causing excessive bleeding and scarring. This itch is also known to be a cause of liver transplantation in patients with ALGS. In some cases since launch, physicians were able to take some patients off of the liver transplant list based on their response to LIVMARLI. In ALGS, cholestasis drives dangerous accumulations of bile acids systemically and in the liver. LIVMARLI works by blocking bile acid absorption in the intestines, thereby reducing the levels of excess bile acids and improving clinical manifestations of cholestasis. In addition to a reduction in itch and serum bile acids, data from more than six years of LIVMARLI studies have also shown to improve growth and quality of life, and reduce xanthomas, which are all effects of ALGS. A particular advantage of the innovation of LIVMARLI in this devastating disease is that the medication is minimally absorbed, meaning it was designed to act only in the gut and not enter the bloodstream. Prior to LIVMARLI's approval, there were no approved treatments to address pruritus in ALGS and many children would

cycle through off-label medications and ultimately require major surgical interventions such as liver transplantation. The approval of LIVMARLI signifies a shift in the treatment paradigm for ALGS and gives hope to children and their families living with this devastating disease. Further, LIVMARLI's success in treating ALGS, a cholestatic liver disease, provides an analog for how LIVMARLI and other IBAT inhibitors may provide benefit in treating other cholestatic liver diseases affecting children and adults.

Pubmed

Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. Gonzales E, Hardikar W, Stormon M, Baker A, Hierro L, Gliwicz D, Lacaille F, Lachaux A, Sturm E, Setchell KDR, Kennedy C, Dorenbaum A, Steinmetz J, Desai NK, Wardle AJ, Garner W, Vig P, Jaecklin T, Sokal EM, Jacquemin E. *Lancet*. 2021 Oct 30;398(10311):1581-1592. doi: 10.1016/S0140-6736(21)01256-3. Epub 2021 Oct 28. PMID: 34755627 Clinical Trial. <https://pubmed.ncbi.nlm.nih.gov/34755627/> Maralixibat: First Approval. Shirley M. *Drugs*. 2022 Jan;82(1):71-76. doi: 10.1007/s40265-021-01649-0. PMID: 34813049 Free PMC article. Review. <https://pubmed.ncbi.nlm.nih.gov/34813049/>

Attachments

- 1656523239HANSEN-1.PDF
- 1656523252Kamath_et_al_2021_(NASPGHAN)_GI_tolerability_of_maralixibat_in_patients_with_ALGS_an_integrated_analysis_of_short_and_long_term_treatmer
- 1656523263Raman_et_al_2021_(EASL)_An_integrated_analysis_of_long-term_clinical_safety_in_maralixibat-treated_participants_with_ALGS.pdf
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