Horizon Therapeutics plc Announces FDA Has Granted Priority Review of the Supplemental Biologics License Application (sBLA) for the Concomitant Use of KRYSTEXXA® (pegloticase injection) Plus Methotrexate for People Living With Uncontrolled Gout

March 7, 2022

-- sBLA seeks to expand the label to include KRYSTEXXA plus methotrexate to help more patients achieve a complete and durable response to therapy --

-- Application based on recent MIRROR randomized controlled trial results, which showed 71% of patients randomized to receive KRYSTEXXA plus methotrexate achieved a complete response --

DUBLIN--(BUSINESS WIRE)--Mar. 7, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that the U.S. Food and Drug Administration (FDA) granted priority review of the supplemental Biologics License Application (sBLA) to expand the label for KRYSTEXXA plus methotrexate, an immunomodulator commonly prescribed by rheumatologists. The Prescription Drug User Fee Act (PDUFA) action date is July 7, 2022.

KRYSTEXXA is indicated for the treatment of chronic gout in adult patients refractory to conventional therapies, also known as uncontrolled gout.[1] As the first and only biologic treatment approved for uncontrolled gout, KRYSTEXXA has changed the course of the treatment journey for people living with uncontrolled gout by substantially reducing the physical burden of the disease.[2] Some patients treated with KRYSTEXXA develop anti-drug antibodies, which can limit the effectiveness of treatment.[1] Emerging data has suggested that treatment with KRYSTEXXA in combination with methotrexate can help to prevent these anti-drug antibodies, helping more patients achieve a durable response to therapy.[3]

“People living with uncontrolled gout face a significant impact on their daily lives, as well as a higher risk of comorbidities, emphasizing the need to urgently lower the urate burden in this patient population,” said Tim Walbert, chairman, president and chief executive officer, Horizon. “Horizon has invested significantly in clinical research to improve the efficacy of KRYSTEXXA therapy and help ensure more uncontrolled gout patients can benefit from therapy. Today's announcement is an important milestone in our journey, and we remain committed in our efforts to help evolve the standard of care in uncontrolled gout.”

The sBLA is based on the MIRROR randomized controlled trial (*Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXX*A trial), which showed 71.0% of patients (71 of 100) who were randomized to receive KRYSTEXXA plus methotrexate achieved a complete serum uric acid (sUA) response, defined as sUA <6 mg/dL at least 80% of the time during Month 6. The trial demonstrated a 32.5-percentage point improvement compared to those randomized to KRYSTEXXA with placebo (38.5%; 20 of 52 patients) (p<0.0001). No new safety concerns were identified.[4]

These results reinforce what has been published in multiple case series, as well as the MIRROR open-label trial, showing improved treatment response rates through the use of KRYSTEXXA plus methotrexate.[5-7]

“With the case series, open-label and randomized controlled trials, we have substantial evidence that suggests using KRYSTEXXA with methotrexate gives uncontrolled gout patients a substantially better chance of responding to therapy,” said John K. Botson, M.D., R.Ph., C.C.D., president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. “The priority review of this sBLA highlights the urgent need to evolve the standard of care for this patient population, who otherwise have limited therapeutic options.”

About KRYSTEXXA

INDICATION AND USAGE

KRYSTEXXA (pegloticase injection) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Serum uric acid levels should be

monitored prior to infusions, and healthcare providers should consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Patients should be screened for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA should not be administered to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

CONGESTIVE HEART FAILURE

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Caution should be exercised when using KRYSTEXXA in patients who have congestive heart failure, and patients should be monitored closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Full Prescribing Information and Medication Guide for more information.

About Horizon

Horizon is focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our pipeline is purposeful: We apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives. For more information on how we go to incredible lengths to impact lives, visit www.horizontherapeutics.com and follow us on Twitter, LinkedIn, Instagram and Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential benefits of co-treatment of KRYSTEXXA with methotrexate for uncontrolled gout, Horizon's research and development plans and strategy and expected timing of the FDA's review of Horizon's sBLA submission. These forward-looking statements are based on management's expectations and assumptions as of the date of this press release and actual results may differ materially from those in these forward-looking statements as a result of various factors. These factors include, but are not limited to, risks regarding the timing and results of the FDA's review of the sBLA submission, whether or on what terms the FDA may approve the sBLA, whether additional data from clinical trials or other analyses will be required or consistent with prior data or Horizon's expectations and risks related to the adoption of co-treatment of KRYSTEXXA plus methotrexate for uncontrolled gout. For a further description of these and other risks facing Horizon, please see the risk factors described in Horizon's filings with the United States Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in those filings. Forward-looking statements speak only as of the date of this press release and Horizon undertakes no obligation to update or revise these statements, except as may be required by law.

References

1. KRYSTEXXA (pegloticase) [prescribing information] Horizon.
2. Schlesinger N, Edwards N, Khanna P, et al. Evaluation of Proposed Criteria for Remission and Evidence-Based Development of Criteria for Complete Response in Patients With Chronic Refractory Gout. *ACR Open Rheumatol.* 2019;1(4):236-243. doi: 10.1002/acr2.1025.
3. Strand V, Balsa A, Al-Saleh J, et al. *BioDrugs.* 2017;31:299-316.
4. Data on file. Horizon, October 2021.
5. Botson J, Tesser JHR, Bennett R, et al. Pegloticase in Combination With Methotrexate in Patients With Uncontrolled Gout: A Multicenter, Open-label Study (MIRROR). *J Rheumatol.* 2021;48(5):767-774. doi: 10.3899/jrheum.200460.
6. Albert J, Hosey T, LaMoreaux B. Increased Efficacy and Tolerability of Pegloticase in Patients With Uncontrolled Gout Co-Treated With Methotrexate: A Retrospective Study. *Rheumatol Ther.* 2020;7(3):639-648. doi: 10.1007/s40744-020-00222-7.
7. Botson JK, Peterson J. Pretreatment and Coadministration With Methotrexate Improved Durability of Pegloticase Response: An Observational, Proof-of-Concept Case Series. *J Clin Rheumatol*. 2022 Jan 1;28(1):e129-e134. doi:

10.1097/RHU.0000000000001639.

View source version on businesswire.com: https://www.businesswire.com/news/home/20220307005264/en/

Tina Ventura
Senior Vice President, Chief Investor Relations Officer
Investor-relations@horizontherapeutics.com

Erin Linnihan
Executive Director, Investor Relations
Investor-relations@horizontherapeutics.com

U.S. Media Contact:
Amanda Phraner
Director, Product Communications
media@horizontherapeutics.com

Ireland Media Contact:
Gordon MRM
Ray Gordon
ray@gordonmrm.ie

Source: Horizon Therapeutics plc