FDA Approves KRYSTEXXA® (pegloticase) Injection Co-Administered With Methotrexate, Expanding the Labeling to Help More People with Uncontrolled Gout Achieve a Complete Response to Therapy

July 8, 2022

-- Approval based on MIRROR randomized controlled trial, which showed significant improvement and sustained patient response to KRYSTEXXA with methotrexate compared to KRYSTEXXA alone --

-- Trial data showed a greater than 30 percentage-point increase in efficacy, and a significant reduction in infusion reactions from 31% to 4% --

-- Priority review was granted for the supplemental Biologics License Application (sBLA) in March, emphasizing the urgent need to address the burden of uncontrolled gout --

DUBLIN--(BUSINESS WIRE)--Jul. 8, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) expanding the labeling to include KRYSTEXXA® (pegloticase) injection co-administered with methotrexate, which will help more people with uncontrolled gout achieve a complete response to therapy.

"Today's approval for KRYSTEXXA with methotrexate is the culmination of more than five years of effort and demonstrates Horizon's commitment to working together with the gout community to improve the patient experience and outcomes," said Elizabeth H.Z. Thompson, Ph.D., executive vice president, research and development, Horizon. "Immunomodulatory therapies like methotrexate are often used with biologics to reduce the development of anti-drug antibodies and allow more patients to achieve a complete response. We anticipate this approval will encourage more physicians to recommend KRYSTEXXA with methotrexate to help their patients with uncontrolled gout receive the full benefits of KRYSTEXXA."

The expanded labeling for KRYSTEXXA with methotrexate is based on the results from the MIRROR randomized controlled trial in which adults living with uncontrolled gout were randomized to receive methotrexate (15 mg/week) or placebo for four weeks, and then treatment with KRYSTEXXA with methotrexate or KRYSTEXXA with placebo for 52 weeks. The primary endpoint was defined as the proportion of serum uric acid (sUA) responders during Month 6 (defined as sUA less than 6 mg/dL at least 80% of the time).[1]

"Uncontrolled gout carries serious, long-term consequences in the joints and throughout the body, as well as a significant impact on a person's daily life," said co-primary investigator John K. Botson, M.D., R.Ph., C.C.D., president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. "Through multiple in-practice case series, the open-label trial and the randomized controlled trial, the medical community has been actively engaged in finding ways to reduce the impact of uncontrolled gout by maximizing the use of KRYSTEXXA. The expanded labeling reflects robust data on this treatment approach, which can allow us to change outcomes for many uncontrolled gout patients, most of whom have no other treatment option."

The MIRROR randomized controlled trial results reinforced a substantial body of data supporting the use of KRYSTEXXA with methotrexate. Results included:

- **Greater than 30 percentage-point increase in patient response rate during Month 6 (p<0.0001):** 71% (71 of 100) of patients randomized to receive KRYSTEXXA with methotrexate vs 39% (20 of 52) of patients randomized to receive KRYSTEXXA with placebo achieved the primary endpoint (defined as sUA less than 6 mg/dL at least 80% of the time during Month 6).[1]
- **Improvement in the patient response rate remained nearly 30 percentage points higher during Month 12 (p<0.001):** 60% (60 of 100) of patients randomized to receive KRYSTEXXA with methotrexate achieved a complete response during Month 12 compared to 31% (16 of 52) of patients randomized to receive KRYSTEXXA with placebo. Complete response is defined as sUA less than 6 mg/dL at least 80% of the time during Month 12.[2]
- **Marked reduction in infusion reactions:** during the treatment period, 4% (4 of 96) of patients who received KRYSTEXXA with methotrexate experienced infusion reactions vs 31% (15 of 49) of patients who received KRYSTEXXA with placebo. No new safety signals were observed.[1]
- **Over a 22 percentage-point increase in the complete resolution of at least one tophus at Month 12 (p=0.048):** among patients with validated tophi at baseline, 54% (28 of 52) of patients randomized to receive KRYSTEXXA with methotrexate had complete resolution of at least one tophus, no new tophus and no single tophus showing progression at Week 52 vs 31% (9 of 29) of patients randomized to receive KRYSTEXXA with placebo.[1]

More information on KRYSTEXXA with methotrexate is available in the Prescribing Information and at KRYSTEXXAhcp.com. Patients with questions can speak to a Gout Nurse Advocate at 833-469-4688.

About MIRROR Randomized Controlled Trial

The co-administration of KRYSTEXXA with an immunomodulator like methotrexate has increasingly been employed for patients with uncontrolled gout to help reduce the development of anti-drug antibodies, which can affect treatment efficacy with biologics.[2,3] Following a series of community case studies and an open-label evaluation, the MIRROR randomized controlled trial (*Methotrexate to Increase Response Rates in Patients with*

Uncontrolled Gout Receiving KRYSTEXXA trial, NCT03994731) was conducted.[4-6] The trial evaluated differences in treatment response for KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA with placebo. The primary endpoint was defined as the proportion of serum uric acid (sUA) responders defined as sUA <6 mg/dL at least 80% of the time during Month 6 (weeks 20 - 24). The study's secondary endpoints included the proportion of sUA responders during Month 12 (weeks 48 - 52), defined as sUA <6 mg/dL at least 80% of the time, and the proportion of participants with complete resolution of at least one tophus, no new tophus and no single tophus showing progression (using digital photography) at Week 52 in subjects with tophi at baseline. A total of 152 participants were randomized 2:1 to run-in and treatment periods with oral methotrexate (15 mg/week) or placebo, followed by bi-weekly infusions of KRYSTEXXA (8 mg) with either methotrexate or placebo for 52 weeks. The trial demonstrated a 32 percentage-point improvement ($p<0.0001$) in treatment response rate, with 71% of patients (71 of 100) who were randomized to receive KRYSTEXXA with methotrexate achieving a sustained urate-lowering response during Month 6, compared to 39% (20 of 52) of those randomized to receive KRYSTEXXA with placebo.[1,2]

About KRYSTEXXA

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult 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.

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOMINEMIA

- **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 manifest within 2 hours of the infusion. Delayed 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 and closely monitored for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Serum uric acid levels should be monitored prior to each infusion and treatment discontinued if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency should be screened prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. 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 formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Caution should be exercised in patients who have congestive heart failure and patients should be closely monitored following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are

- **KRYSTEXXA co-administration with methotrexate trial:** gout flares, arthralgia, COVID-19, nausea and fatigue; **KRYSTEXXA alone:** gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reactions, pain in extremity, hypertension, and vomiting.
- **KRYSTEXXA pre-marketing placebo-controlled trials:** gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Full Prescribing Information, **including Boxed Warning**.

About Horizon

Horizon is a global biotechnology company 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 KRYSTEXXA co-administered with methotrexate for uncontrolled gout and the impact of the expanded labeling for KRYSTEXXA with methotrexate. 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 related to the adoption of co-administration of KRYSTEXXA with 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. Botson J, et al. OP0171 A Randomized, Double Blind, Placebo Controlled, Multicenter, Study Of Methotrexate Combined with Pegloticase in Patients with Uncontrolled Gout. *Annals of the Rheumatic Diseases* 2022;81:112-113.
2. KRYSTEXXA (pegloticase) [prescribing information] Horizon.
3. Strand V, Balsa A, Al-Saleh J, et al. *BioDrugs*. 2017;31:299-316.
4. 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.
5. 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.
6. 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/20220708005097/en/

Investors:
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:
Amanda Phraner
Senior Director, Product Communications
media@horizontherapeutics.com

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

Source: Horizon Therapeutics plc