



Data from Uncontrolled Gout Case Series Supports Immunomodulation with KRYSTEXXA® (pegloticase injection) Strategy to Optimize Treatment Outcomes

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-- Horizon data at American College of Rheumatology Annual Meeting also cite the need for vigilance in treating gout among kidney transplant recipients --

DUBLIN--(BUSINESS WIRE)--Nov. 11, 2019-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the presentation of a patient case series at the American College of Rheumatology (ACR) Annual Meeting illustrating that the addition of methotrexate to a course of therapy with KRYSTEXXA® (pegloticase injection) may help more people with chronic gout refractory to conventional therapies – also known as uncontrolled gout – achieve response to treatment. In addition, Horizon will present data describing the inflammatory impact of uric acid on other organs, including the liver and kidney.

KRYSTEXXA has demonstrated rapid reduction in the serum uric acid level for people with uncontrolled gout; however, as with any biologic, the immune system can sometimes react to the therapeutic proteins, hindering a complete response. Immunomodulators, such as methotrexate, are often co-prescribed with biologics to help reduce this reaction.

The case series presented by John A. Albert, M.D. details his in-practice experience for 10 adult patients with uncontrolled gout who received KRYSTEXXA during or after treatment with methotrexate (either oral or subcutaneous). Methotrexate exposure varied (most received 25 mg of methotrexate subcutaneously every week and nine of the 10 patients started methotrexate prior to receiving KRYSTEXXA). Eight of the 10 patients were complete responders at 24 weeks of therapy. Two patients ceased therapy, one due to loss of response and a mild infusion reaction, and the other due to methotrexate injection-related issues. Treatment was well tolerated for the duration of therapy. Given the importance of this clinical concept, Horizon assisted with the analysis and compilation of the case series. The co-prescription of KRYSTEXXA and methotrexate is investigational and its safety and efficacy have not been established. (*Subcutaneous or oral methotrexate exposure and response to pegloticase in uncontrolled gout patients in a community rheumatology practice*, [Abstract 1236](#))

“Despite gout being the most common form of inflammatory arthritis, it is often not treated with urgency that reflects the impact on patients and its serious, chronic and systemic nature,” said John A. Albert, M.D., Rheumatic Disease Center, Glendale, WI. “In order to address the impact of gout for patients like mine, it is important we quickly and effectively decrease the uric acid burden. Adding methotrexate to KRYSTEXXA treatment for patients with uncontrolled gout employs a commonly used immunomodulation strategy by rheumatologists to minimize the immune response and strives to help more patients benefit from a full course of therapy. This case series demonstrates the significant improvement in response rate which can be achieved through this treatment strategy.”

These in-practice insights expand upon earlier clinical evidence of the immunomodulation strategy from independent investigators, presented during the ACR Annual Meeting in 2018¹ as well as the Annual European Congress of Rheumatology (EULAR) earlier in 2019.² Horizon is also evaluating the use of methotrexate to increase the response rate with KRYSTEXXA in its immunomodulation trials, the small MIRROR open-label pivotal study [initiated in 2018](#), and the larger MIRROR registrational clinical trial, which was [initiated](#) earlier this year.

Additional presentations deliver new insights on the systemic, inflammatory aspects of uric acid and its effects on multiple organ systems.

- **Inflammatory effects of uric acid on liver health in people living with gout:**

- *Improvement in Hepatic Fibrosis Estimated by Fibrosis-4 (FIB-4) Index in Subjects with Chronic Refractory Gout Treated with Pegloticase*, [Abstract 1231](#)

Prior research has described the link between hyperuricemia and non-alcoholic fatty liver disease (NAFLD). This study evaluates the hypothesis that lowering uric acid levels with KRYSTEXXA may improve the course of NAFLD for people living with gout.

- **The complex correlation between kidney transplantation and gout:**

- *Renal Transplant Complications in Patients with and without Gout*, [Abstract 335](#)

Gout is a known co-morbidity among people who have undergone renal transplantation. This evaluation has assessed whether the presence of gout contributes to greater complications after transplant, with the goal of elevating awareness of prompt gout screening and management strategies within this vulnerable population.

- *Incident Gout after Renal Transplantation in Gout-naïve Patients: Large Database Analysis*, [Abstract 332](#)

While evidence has described a clear link between renal transplantation and gout, important factors remain unclear about this link, such as the frequency of this occurrence and the timing of gout after renal transplant. This study quantifies the incidence of gout in gout-naïve patients undergoing renal transplantation, offering important insights to physicians to help properly identify and intervene to control the disease.

“Our research efforts are illustrating important indicators of the multi-organ impact of gout, particularly in the liver and kidneys, where uncontrolled gout can contribute to long-term health consequences,” said Jeffrey D. Kent, M.D., FACP, executive vice president, medical affairs and outcomes research, Horizon. “Combined with other insights at the ACR meeting, this research highlights the need for clinicians to look holistically at their care strategy for people with gout to ensure the disease is well controlled through appropriate treatment regimens.”

About Uncontrolled Gout

Gout is a chronic, progressive inflammatory form of arthritis that is caused by excess uric acid in the body and needs to be managed aggressively.³ Over time uric acid can build up and form deposits, called tophi, inside the body and joints, which can have harmful effects including causing damage to the underlying bone. Patients with uncontrolled gout continue to have abnormally high levels of uric acid and continued symptoms of gout despite the use of conventional therapies.⁴ KRYSTEXXA is the only biologic approved by the U.S. Food and Drug Administration (FDA) for the treatment of uncontrolled gout in adult patients.

About KRYSTEXXA

INDICATIONS 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 researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic 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, please visit www.horizontherapeutics.com, follow us [@HorizonNews](#) on Twitter, like us on [Facebook](#) or explore career opportunities on [LinkedIn](#).

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential benefits of KRYSTEXXA, including in combination with methotrexate and expectations regarding the MIRROR clinical trial. 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 whether results of the MIRROR trial will be consistent with results of prior trials or Horizon's expectations, and the risks associated with clinical development of drug candidates. 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. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective, observational, proof-of-concept, case series. [Poster presented at the 2018 Annual Scientific Meeting of the American College of Rheumatology \(ACR\)](#), Chicago, IL, USA; October 19–24, 2018.
2. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective, observational, proof-of-concept, case series. [Poster presented at the 2019 Annual European Congress of Rheumatology \(EULAR\)](#), Madrid, Spain; June 12-15, 2019.
3. Keuhn B. Chronic Disease Approaches Needed to Curb Gout's Growing Burden. *Journal of the American Medical Association*. 2018;319(13):1308-1309.
4. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63(10):3136-3141.

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