



## Data Presented on KRYSTEXXA® (pegloticase injection) Co-Prescribed with an Immunomodulator Adds to Growing Body of Evidence for this Treatment Approach

June 3, 2020

-- MIRROR open-label trial demonstrates 79 percent of patients achieved a complete response using KRYSTEXXA with methotrexate --

-- Additional data presentations highlight the effect of co-therapy for KRYSTEXXA with two other commonly used immunomodulators, supporting flexible options for patients and physicians --

-- Oral presentation provides insights on real-world use of KRYSTEXXA with immunomodulators --

-- Horizon will host an investor webcast on June 4, 2020, at 3 p.m. ET --

DUBLIN--(BUSINESS WIRE)--Jun. 3, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) announced today a series of data presentations that demonstrate KRYSTEXXA® (pegloticase injection) can be co-prescribed with three commonly used immunomodulators in rheumatology to potentially help more people with chronic gout refractory to conventional therapies – also known as uncontrolled gout – achieve complete and durable response to therapy. Presentations during the [European League Against Rheumatism \(EULAR\) European E-Congress of Rheumatology 2020](#) (EULAR E-Congress 2020) include new data from the MIRROR open-label trial of KRYSTEXXA with methotrexate, as well as in-practice cases and an investigator-initiated trial for two other immunomodulators with KRYSTEXXA, all of which show high response rates. An analysis of real-world use of KRYSTEXXA with immunomodulators will also be discussed in an oral presentation on June 4, 2020.

“Uncontrolled gout has been increasingly linked to a range of complications, including cardiovascular and renal risks, making it crucially important that we continue to gather more insight on how physicians can best treat this disease,” said Jeffrey D. Kent, M.D., FACG, FACP, executive vice president, medical affairs and outcomes research, Horizon. “It is encouraging to see the rheumatology community embracing opportunities to further improve outcomes for patients with trusted immunomodulators like methotrexate, as ongoing data generation continues to support KRYSTEXXA as an important tool for treating uncontrolled gout.”

While KRYSTEXXA has been traditionally used as a biologic monotherapy with a clinically demonstrated impact on uncontrolled gout, recent literature suggests that using an immunomodulator such as methotrexate has the potential to increase the durability of response to KRYSTEXXA.<sup>1</sup> Reducing the burden of urate is critical to improving overall outcomes and quality of life.

“Multiple studies presented at EULAR show that we may be on the cusp of a paradigm shift toward immunomodulatory co-therapy with KRYSTEXXA and further support the 80 to 100 percent response rates shown using KRYSTEXXA with methotrexate in previously presented data,” said John K. Botson, M.D., R.Ph., C.C.D., president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. “I am also encouraged by data on KRYSTEXXA with other commonly used immunomodulators showing high percentages of people who were able to complete a full course of therapy. Given individual patient comorbidities, it is imperative that physicians have the flexibility to select from a range of immunomodulators that could be co-prescribed with KRYSTEXXA and have the potential to provide similar efficacy for the overall response and durability of response to therapy.”

New data from the *Methotrexate to Increase Response Rates in Patients With Uncontrolled GOut Receiving KRYSTEXXA* (MIRROR OL, [NCT03635957](#)) open-label trial showed that when treated with oral methotrexate (15 mg/week) prior to and throughout the KRYSTEXXA treatment period, 78.6 percent of patients (11 of 14 patients) achieved a complete response, defined as the proportion of serum uric acid (sUA) responders (sUA < 6 mg/dL) during Month 6. All patients tolerated methotrexate and no new safety concerns were identified. [*Pegloticase response improvement by co-treatment with methotrexate: results from the MIRROR open-label clinical trial in patients with uncontrolled gout*]

Additional data presented during the EULAR E-Congress 2020 indicate the benefit of this enhanced therapeutic approach may extend to other commonly used immunomodulators, helping to prevent the development of anti-drug antibodies with biologics:

- **Methotrexate addition to KRYSTEXXA allowed most patients to complete therapy and achieve a full therapeutic response.** Based on experience in a community rheumatology practice between 2017 and 2019, this chart review included 10 patients treated with a combination of KRYSTEXXA and methotrexate. Most were treated with subcutaneous methotrexate. All 10 patients experienced a rapid decrease in serum uric acid and 80.0 percent (8 of 10 patients) were complete responders. Two patients discontinued treatment before infusion 12; one due to a mild infusion reaction and one lost to follow-up. A gout flare was reported in one patient and no new safety concerns were identified. [*Pegloticase response rate in uncontrolled gout patients co-treated with methotrexate: experience in a community rheumatology practice*]
- **Leflunomide as an immunomodulator showed high response rates with KRYSTEXXA.** This in-practice case series shows 70.0 percent (7 of 10 patients) achieved a complete response when co-treated with KRYSTEXXA and leflunomide. Three patients discontinued or were lost to follow-up. The findings indicated that low-to-moderate immunomodulation could minimize or prevent the formation of anti-drug antibodies and increase the number of patients who gain the full benefit of a

course of treatment, with no new safety concerns. *[Leflunomide co-therapy with pegloticase in uncontrolled gout]*

- **Azathioprine with KRYSTEXXA could increase the frequency of patients experiencing long-term lowering of serum urate.** The interim data for this investigator-initiated open-label trial of 12 uncontrolled gout patients showed that at the time of data publication 60.0 percent (6 of 10 patients) achieved a complete response; two patients were still receiving treatment with persistent urate-lowering. No adverse events related to azathioprine were reported and gout flares were noted in six patients. *[Companion Immunosuppression with Azathioprine Increases the frequency of Persistent Responsiveness to pegloticase in patients with chronic refractory gout]*

In addition to the above, an oral presentation on real-world use of KRYSTEXXA with immunomodulators will be held [on June 4, 2020 at 10:35 a.m. CET](#). This analysis uses claims data to understand the portion of patients prescribed an immunomodulator (methotrexate or azathioprine) with KRYSTEXXA. *[Immunomodulation co-therapy with pegloticase: database trends 2014-2019]*

On June 4, 2020, at 3 p.m. ET, Horizon [will host an investor webcast](#) to discuss data presented at the EULAR E-Congress 2020 on the range of immunomodulators used to increase the durability of response to KRYSTEXXA, as well as provide an overview of immunomodulation and the Company's immunomodulation strategy for KRYSTEXXA.

## 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](http://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 in treating uncontrolled gout and the potential benefits of using immunomodulators with KRYSTEXXA. 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 additional clinical trials will be consistent with results of prior trials or Horizon's expectations, and the risks associated with clinical development. 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 and Peterson J. *Ann Rheum Dis*. 2019; 78: A1289 and Bessen SY, et al. *Semin Arthritis Rheum*. 2019;49:56-61.

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