Horizon Therapeutics plc Increases Peak U.S. Annual Net Sales Expectations for Key Growth Drivers; Provides Update on Several Pipeline Programs

January 13, 2020

-- Increases KRYSTEXXA® (pegloticase injection) Peak U.S. Annual Net Sales Expectations to More Than $1 Billion --

-- Increases Teprotumumab Peak U.S. Annual Net Sales Expectations to More Than $1 Billion --

-- Announces 79 Percent of Patients Achieved a Complete Response in MIRROR Open-Label Pilot Study, Supporting KRYSTEXXA Immunomodulation Strategy to Optimize Treatment Outcomes --

-- Announces Two New Pipeline Programs --

DUBLIN--(BUSINESS WIRE)--Jan. 13, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) announced today that it is increasing the peak U.S. annual net sales expectations for its key growth drivers KRYSTEXXA and teprotumumab, as well as providing several pipeline updates.

"As we enter 2020, Horizon is in its strongest position ever," said Timothy Walbert, chairman, president and chief executive officer, Horizon. "We believe KRYSTEXXA and teprotumumab each has the potential for more than $1 billion in peak U.S. annual net sales. In addition, our strong balance sheet allows us to augment our pipeline to bolster long-term growth. Furthermore, we are evaluating ways to help more patients benefit from our medicines, including two new pipeline programs – one that explores more convenient delivery for KRYSTEXXA by significantly reducing infusion time, and the other for an additional indication for teprotumumab, specifically for the rare disease, diffuse cutaneous scleroderma."

Continued Strong KRYSTEXXA Growth Drives Higher Peak Net Sales Expectation; New Immunomodulation Study Data and Shorter-Infusion Duration Development Program Offer Potential to Benefit More Uncontrolled Gout Patients
Based on current strong performance, the Company is increasing its peak U.S. annual net sales expectation for KRYSTEXXA to more than $1 billion, from the previous expectation of more than $750 million. The Company continues to project KRYSTEXXA full-year 2019 net sales growth of more than 25 percent.

The Company also announced topline results from its MIRROR open-label pilot study, which evaluated the use of the immunomodulator methotrexate with KRYSTEXXA to increase the response rate of KRYSTEXXA. The results of the study demonstrated that 79 percent, or 11 of 14 patients, achieved a complete response, defined as the proportion of serum uric acid (sUA) responders (sUA < 6 mg/dL) at Month 6. The combination was also well tolerated. Detailed results from the study will be presented at a future medical meeting. The 79 percent response rate is significantly higher than the 42 percent response rate in the KRYSTEXXA Phase 3 clinical program, which evaluated KRYSTEXXA alone.

KRYSTEXXA has demonstrated rapid reduction in sUA levels for people with uncontrolled gout; however, treatment with biologic medicines can, in some patients, trigger the body's immune system to develop anti-drug antibodies. These anti-drug antibodies can reduce the effectiveness of the biologic therapy. Immunomodulators such as methotrexate, which is commonly used by rheumatologists, can help reduce this reaction.

The MIRROR open-label pilot study follows other studies that showed an improved response rate when KRYSTEXXA is co-administered with methotrexate. There is a growing body of data supporting the potential of KRYSTEXXA plus immunomodulation to become the standard therapy opposed to KRYSTEXXA therapy alone. This includes an independent case series presented at the Annual European Congress of Rheumatology meeting in June 2019 which demonstrated that the administration of KRYSTEXXA with methotrexate resulted in a 100 percent response (10 of 10 patients) as defined by >80 percent of sUA levels being maintained at goal (<6.0 mg/dL) during the treatment period. Further, a case series presented at the American College of Rheumatology meeting in November 2019 demonstrated an 80 percent response (8 of 10 patients) as defined by receiving ≥12 infusions without loss of sUA response.

The Company is currently conducting a separate, placebo-controlled MIRROR trial evaluating the use of KRYSTEXXA and methotrexate. The trial, with 135 randomized patients, is designed to enable the potential for submission of results to the U.S. Food and Drug Administration (FDA) for update to the label.

In addition, the Company is planning to evaluate the impact of administering KRYSTEXXA over a significantly shorter infusion duration. The initial proof-of-concept work will begin mid-2020. Currently, KRYSTEXXA is infused over a two-hour or longer timeframe. A shorter infusion duration could meaningfully improve the experience and convenience for patients, physicians and sites of care.

Increasing Teprotumumab Peak Net Sales Expectation; Evaluating an Additional Indication for Diffuse Cutaneous Scleroderma, a Rare Disease with No Treatment Options
The FDA is currently evaluating a Biologics License Application (BLA) for teprotumumab for the treatment of Thyroid Eye Disease (TED) under Priority Review, with a Prescription Drug User Fee Act (PDUFA) action date of March 8, 2020. On Dec. 13, 2019, the Dermatologic and Ophthalmic Drugs Advisory Committee of the FDA voted unanimously (12-0) in favor of teprotumumab. Teprotumumab is a fully human monoclonal antibody that targets and blocks the insulin-like growth factor 1 receptor (IGF-1) with the potential to be the first and only medicine approved for this rare eye disease.

TED is a serious, progressive, vision-threatening rare autoimmune disease in which the muscles and fatty tissue behind the eye become inflamed and expand, which can lead to proptosis (eye bulging) and diplopia (double vision) and seriously impact activities of daily living and patients' quality of life.

Based on an improved understanding of the TED landscape informed by market research and launch preparation activities as well as the dramatic results achieved in the teprotumumab Phase 3 OPTIC trial, the Company is increasing its peak U.S. annual net sales expectation to more than $1 billion, from the previous expectation of more than $750 million.

The Company is evaluating additional indications for teprotumumab and is initiating an exploratory study in diffuse cutaneous scleroderma, a rare fibrotic disease with no treatment options. Diffuse cutaneous scleroderma is a subtype of scleroderma in which excess collagen production causes skin thickening and hardening, or fibrosis, over large areas of the body, usually the fingers, hands, arms, anterior trunk, legs and face. There can be significant associated organ damage, including to the gastrointestinal tract, kidneys, lungs and heart. Literature suggests that the mechanism of action of teprotumumab, which is to block the IGF-1 receptor, could have an impact on fibrotic processes, such as those that are relevant to diffuse cutaneous scleroderma. The Company expects to conduct an exploratory trial beginning in the first half of 2020 to evaluate objective biomarker and clinical endpoints to inform potential subsequent larger and longer duration clinical trials.

“We are extremely pleased to be one step closer to bringing teprotumumab to the thousands of patients with Thyroid Eye Disease who have been waiting for a treatment for this debilitating, painful and vision-threatening disease,” said Shao-Lee Lin, M.D., Ph.D., executive vice president, head of research and development and chief scientific officer, Horizon. “Understanding the potential of our medicines for additional diseases is also important. We believe teprotumumab may impact underlying mechanisms of fibrosis and could demonstrate utility beyond thyroid eye disease, including diffuse cutaneous scleroderma, a rare autoimmune disease with central characteristics of inflammation and fibrosis.”

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 patients 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 Teprotumumab

Teprotumumab is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the IGF-1R. Teprotumumab has received Priority Review, Orphan Drug, Fast Track and Breakthrough Therapy designations from the FDA. The clinical development program for teprotumumab in the treatment of TED includes statistically significant results from both the Phase 2 clinical study, which were published in The New England Journal of Medicine, as

well as from the Phase 3 OPTIC confirmatory clinical trial. Both trials were conducted at leading centers in the U.S., Germany and Italy, with co-principal investigators Raymond Douglas, M.D., Ph.D., Cedars-Sinai Medical Center and George Kahaly, M.D., Ph.D., Johannes Gutenberg University Medical Center. Horizon is also conducting the OPTIC-X extension trial to gather further insight into the long-term efficacy and safety of teprotumumab.

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, but not limited to, statements related to expected financial performance and operating results in future periods, including potential growth in net sales of certain of Horizon's medicines; plans with respect to product development efforts; potential market opportunity for, regulatory approval of and benefits of Horizon's medicines and medicine candidates; statements regarding the timing of an FDA decision on the teprotumumab BLA; expectations regarding the review of the BLA and the potential benefits of teprotumumab to patients; and business and other statements that are not historical facts. These forward-looking statements are based on Horizon's current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks that Horizon's actual future financial and operating results may differ from its expectations or goals; Horizon's ability to grow net sales from existing medicines and successfully launch new medicines; the availability of coverage and adequate reimbursement and pricing from government and third-party payers; risks relating to Horizon's ability to successfully implement its business strategies; risks inherent in developing novel medicine candidates and existing medicines for new indications; risks associated with regulatory approvals; risks in the ability to recruit, train and retain qualified personnel; competition, including potential generic competition; the ability to protect intellectual property and defend patents; regulatory obligations and oversight, including any changes in the legal and regulatory environment in which Horizon operates and those risks detailed from time-to-time under the caption "Risk Factors" and elsewhere in Horizon's filings and reports with the SEC. Horizon undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information.

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