Chiesi Global Rare Diseases and Protalix BioTherapeutics Announce Validation of Variation Submission by European Medicines Agency for pegunigalsidase alfa

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- *Application to label a less frequent dosing regimen at a dose of 2 mg/kg body weight administered every four weeks in adult patients with Fabry disease in European Union*

PARMA, Italy and CARMIEL Israel, Dec. 9, 2024 /PRNewswire/ -- Chiesi Global Rare Diseases, a business unit of the Chiesi Group established to deliver innovative therapies and solutions for people living with rare diseases, and Protalix BioTherapeutics, Inc. (NYSE American: PLX), a biopharmaceutical company focused on the development, production and commercialization of recombinant therapeutic proteins produced by its proprietary ProCellEx® plant cell-based protein expression system, today announced that the European Medicines Agency (EMA) has validated the Variation Submission for pegunigalsidase alfa ▼ to label a less frequent dosing regimen at a dose of 2 mg/kg body weight administered every four weeks in adult patients with Fabry disease. The currently approved dose of pegunigalsidase alfa is 1 mg/kg administered every two weeks.

The variation application is supported by a revised Population-PK model and new exposure-response analyses and by the clinical data on pegunigalsidase alfa 2 mg/kg E4W from the completed Phase 3 study PB-102-F50 (BRIGHT) and its ongoing extension study CLI-06657AA1-03 (formerly known as PB-102-F51), that have investigated the 2 mg/kg every four weeks dosing regimen in adult patients with Fabry disease who were previously treated with agalsidase-alfa or -beta administered every two weeks. Results of the completed study PB-102-F50 were recently published in the *Journal of Inherited Metabolic Disease*.

"The validation of this variation application is an important milestone in our efforts to reduce the burden of treatment for some adult patients living with Fabry disease who continue to experience unmet medical needs," said ***Giacomo Chiesi, Executive Vice President of Chiesi Global Rare Diseases****. "We are committed to delivering innovative therapies and solutions for people living with Fabry disease, their families and caregivers."*

"Based on study results, we believe in the potential of pegunigalsidase alfa 2 mg/kg administered every four weeks to be a beneficial, alternative dosing option for some adults living with Fabry disease," said ***Dror Bashan, Protalix's President and Chief Executive Officer****. "Together with Chiesi, we remain committed to meeting the needs of people with Fabry disease and bringing additional therapeutic options to market. We look forward to continuing to work closely with the agency in the months ahead."*

Indication and Important Safety Information for Elfabrio® (pegunigalsidase alfa-iwxj)

Indication

Elfabrio® (pegunigalsidase alfa-iwxj) is indicated for the treatment of adults with confirmed Fabry disease.

Important Safety Information

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Patients treated with Elfabrio have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Elfabrio administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Elfabrio immediately and initiate appropriate medical treatment. In patients with severe hypersensitivity reaction, a desensitization procedure to Elfabrio may be considered.

Prior to Elfabrio administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Inform patients and caregivers of the signs and symptoms of hypersensitivity reactions and infusion-associated reactions (IARs) and instruct them to seek medical care immediately if such symptoms occur.

- If a severe hypersensitivity reaction (including anaphylaxis) or severe IAR occurs, immediately discontinue Elfabrio administration and initiate appropriate medical treatment.
- If a mild to moderate hypersensitivity reaction or IAR occurs, consider slowing the infusion rate or temporarily withholding

the dose.

In clinical trials, 20 (14%) Elfabrio-treated patients experienced hypersensitivity reactions. Four Elfabrio-treated patients (3%) experienced anaphylaxis reactions that occurred within 5 to 40 minutes of the start of the initial infusion. The signs and symptoms of hypersensitivity reactions and anaphylaxis included headache, nausea, vomiting, throat tightness, facial and oral edema, truncal rash, tachycardia, hypotension, rigors, urticaria, intense pruritus, moderate upper airway obstructions, macroglossia, and mild lip edema.

In clinical trials, 41 (29%) Elfabrio-treated patients experienced one or more infusion-associated reactions, including hypersensitivity, nausea, chills, pruritus, rash, chest pain, dizziness, vomiting, asthenia, pain, sneezing, dyspnea, nasal congestion, throat irritation, abdominal pain, erythema, diarrhea, burning sensation, neuralgia, headache, paresthesia, tremor, agitation, increased body temperature, flushing, bradycardia, myalgia, hypertension, and hypotension.

A case of membranoproliferative glomerulonephritis with immune depositions in the kidney was reported during clinical trials. Monitor serum creatinine and urinary protein-to-creatinine ratio. If glomerulonephritis is suspected, discontinue treatment until a diagnostic evaluation can be conducted.

When switching to Elfabrio from a prior enzyme replacement therapy, the risk of hypersensitivity reactions and infusion-associated reactions may be increased in certain patients with pre-existing anti-drug antibodies (ADAs). Consider monitoring IgG and IgE ADAs and clinical or pharmacodynamic response (eg, plasma lyso-Gb3 levels).

The most common adverse reactions (≥15%) were infusion-associated reactions, nasopharyngitis, headache, diarrhea, fatigue, nausea, back pain, pain in extremity, and sinusitis.

Please see Full Prescribing Information for Elfabrio.

About Chiesi Global Rare Diseases
Chiesi Global Rare Diseases is a business unit of the Chiesi Group established to deliver innovative therapies and solutions for people affected by rare diseases. As a family business, Chiesi Group strives to create a world where it is common to have a therapy for all diseases and acts as a force for good, for society and the planet. The goal of the Global Rare Diseases unit is to ensure equal access so as many people as possible can experience their most fulfilling life. The unit collaborates with the rare disease community around the globe to bring voice to underserved people in the health care system.

About Chiesi Group
Chiesi is a research-oriented international biopharmaceutical group that develops and markets innovative therapeutic solutions in respiratory health, rare diseases, and specialty care. The company's mission is to improve people's quality of life and act responsibly towards both the community and the environment.

By changing its legal status to a Benefit Corporation in Italy, the US, and France, Chiesi's commitment to create shared value for society as a whole is legally binding and central to company-wide decision-making. As a certified B Corp since 2019, we're part of a global community of businesses that meet high standards of social and environmental impact. The company aims to reach Net-Zero greenhouse gases (GHG) emissions by 2035.

With over 85 years of experience, Chiesi is headquartered in Parma (Italy), with 31 affiliates worldwide, and counts more than 7,000 employees. The Group's research and development centre in Parma works alongside 6 other important R&D hubs in France, the US, Canada, China, the UK, and Sweden.

About Protalix BioTherapeutics, Inc.
Protalix is a biopharmaceutical company focused on the development and commercialization of recombinant therapeutic proteins expressed through its proprietary plant cell-based expression system, ProCellEx®. It is the first company to gain FDA approval of a protein produced through plant cell-based in suspension expression system. This unique expression system represents a new method for developing recombinant proteins in an industrial-scale manner. Protalix's second product, pegunigalsidase alfa, was approved by both the FDA and the EMA in May 2023.

Protalix has partnered with Chiesi Farmaceutici S.p.A. for the global development and commercialization of pegunigalsidase alfa.

Protalix BioTherapeutics' Forward-Looking Statements
To the extent that statements in this press release are not strictly historical, all such statements are forward-looking, and are made pursuant to the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. The terms "expect," "anticipate," "believe," "estimate," "project," "may," "plan," "will," "would," "should" and "intend," and other words or phrases of similar import are intended to identify forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual future experience and results to differ materially from the statements made. These statements are based on Protalix's current beliefs and expectations as to such future outcomes. Drug discovery and development involve a high degree of risk and the final results of a clinical trial may be different than the preliminary findings for the clinical trial. Factors that might cause material differences include, among others: risks related to the commercialization of pegunigalsidase alfa (pegunigalsidase alfa-iwxj), Protalix's approved product for the treatment of adult patients with Fabry disease; risks relating to pegunigalsidase alfa market acceptance, competition, reimbursement and regulatory actions, including as a result of the boxed warning contained in the FDA approval received for the product; the possible disruption of Protalix's operations due to the war declared by Israel's security cabinet against the Hamas terrorist organization located in the Gaza Strip, the military campaign against the Hezbollah and other terrorist activities and armed conflict, including as a result of the disruption of the operations of certain regulatory authorities and of certain of Protalix's suppliers, collaborative partners, licensees, clinical trial sites, distributors and customers, and the risk that the current hostilities will result in a greater regional conflict; delays in the approval or potential rejection of any applications filed with the FDA, EMA or other health regulatory authorities for Protalix's product candidates, and other risks relating to the review process; the risk that the results of clinical trials will not support the applicable claims of safety or efficacy; risks related to the amount and sufficiency of our cash and cash equivalents; risks relating to changes to published interim, topline or preliminary data from clinical trials; the inherent risks and uncertainties in developing drug platforms and products of the type we are developing; the impact of development of competing therapies and/or technologies by other companies; and risks relating to changes in healthcare laws, rules and regulations in the United States or elsewhere; and other factors described in Protalix's filings with the U.S. Securities and Exchange Commission. The statements in this press release are valid only as of the date hereof and Protalix disclaims any obligation to update this information, except as may be required by law.

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