PRESS RELEASE

MHRA Grants Marketing Authorisation for Elfabrio®▼(pegunigalsidase alfa) for the treatment of adult patients with Fabry Disease in Great Britain

MANCHESTER, UK, 15 August 2023 – Chiesi, the international research-focused biopharmaceutical and healthcare group, today announced that the UK Medicines and Healthcare products Regulatory Agency (MHRA) has granted marketing authorisation for Elfabrio® (pegunigalsidase alfa) in Great Britain for long-term enzyme replacement therapy (ERT) in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).[1]

"We are delighted to have received MHRA authorisation for pegunigalsidase alfa, bringing an additional licensed treatment option for Fabry patients across Great Britain," said Dr Kamran Iqbal, Head of Medical Affairs, Global Rare Diseases, Chiesi UK&I. *"As part of our goal to ensure equal access to innovative therapies for people living with rare diseases, we are working closely with health technology appraisal agencies to ensure that all eligible patients can access this new treatment as soon as possible."*

Pegunigalsidase alfa is the first and only PEGylated ERT for Fabry disease.[2] Pegunigalsidase alfa is produced in plant cells using recombinant DNA technology.[3]

The MHRA authorisation is based on an overall positive benefit/risk balance of pegunigalsidase alfa in the claimed indication as stated in the European Medicines Agency's (EMA) assessment report – which is based on the same evidence dossier submitted to the MHRA.[3]

The clinical development programme for pegunigalsidase alfa consists of 142 patients with Fabry disease (94 males and 48 females) of which 112 received pegunigalsidase alfa 1 mg/kg every other week.[4] These trials include the Phase 3 BALANCE (77 patients), BRIDGE (22 patients), and BRIGHT (30 patients) clinical trials, a one year Phase 1/2 clinical trial (18 patients), and four related extension studies (69, 29, 18 and 15 patients respectively).[3] These studies show that pegunigalsidase alfa is generally well tolerated, with the most common adverse reactions being infusion-related reactions (reported by 6.3% of patients), followed by hypersensitivity and asthenia (reported each by 5.6% of patients).[3,4,5]

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About Fabry Disease

It has been estimated that 1,150 people in England have symptomatic Fabry disease, a rare, progressive, X-linked inherited lysosomal storage disorder, caused by a genetic mutation which leads to an inherited deficiency of enzyme α-galactosidase A.[1,6,7] This is normally responsible for the breakdown of globotriaosylceramide (Gb_3).[8] The abnormal storage of Gb_3 increases with time and, accordingly, Gb_3 accumulates, primarily in the blood vessel and tissues.[6] The ultimate consequences of Gb_3 deposition range from episodes of pain and impaired peripheral sensation to end-organ failure.[3,8] Patients with Fabry disease may be treated by intravenous infusion with enzyme replacement therapy (ERT) to replace the function of the missing α-galactosidase A enzyme.[1,3,9] Alternatively, patients aged 12 and over with an amenable mutation may be treated with oral chaperone therapy.[10]

About Elfabrio® (pegunigalsidase alfa)

Elfabrio® (pegunigalsidase alfa) is a pegylated recombinant form of human α-galactosidase-A.[4] The amino acid sequence of the recombinant form is similar to the naturally occurring human enzyme.[4] Pegunigalsidase alfa supplements or replaces α-galactosidase-A, the enzyme that catalyses the hydrolysis of the terminal α-galactosyl moieties of oligosaccharides and polysaccharides in the lysosome, reducing the amount of accumulation of Gb_3 and globotriaosylsphingosine (Lyso-Gb_3).[4]

The efficacy and safety profile of pegunigalsidase alfa were evaluated in 142 patients (94 males and 48 females), of which 112 received pegunigalsidase alfa 1 mg/kg every other week.[4] These trials include the Phase 3 BALANCE (77 patients), BRIDGE (22 patients), and BRIGHT (30 patients) clinical trials, a one year Phase 1/2 clinical trial (18 patients), and four related extension studies (69, 29, 18 and 15 patients respectively).[3] These studies show that pegunigalsidase alfa is generally well tolerated, with the most common adverse reactions being infusion-related reactions (reported by 6.3% of patients), followed by hypersensitivity and asthenia (reported each by 5.6% of patients).[3,4,5]

Disease substrate: Analyses of kidney biopsies from naïve patients treated with pegunigalsidase alfa in a phase 1/2 study exhibited a reduction of the Gb_3 substrate from the renal peritubular capillaries, measured with BLISS (Barisoni Lipid Inclusion Scoring System) of 68% in the overall population (including females, classic males and non-classic males exposed to different tested doses; n=13) after 6 months of treatment.[4] Additionally, 11 out of 13 subjects with available biopsies had substantial reduction (≥50%) in their BLISS score following 6 months of treatment.[4] Plasma Lyso-Gb_3 decreased by 49% after 12 months of treatment (n=16) and by 83% after 60 months of treatment (n=10).[4] In a phase 3 study, where patients were switching from agalsidase beta to pegunigalsidase alfa, plasma Lyso-Gb_3 values stayed stable after 24 months of treatment (+3.3 nM mean value, n=48).[4]

Renal function: The renal function was evaluated through the estimated glomerular filtration rate (eGFR – CKD-EPI equation) and its annualised measurement slope was the primary endpoint for efficacy in two phase 3 studies in previously ERT-treated adult Fabry patients: BALANCE (main study), a randomised, double blinded, head-to-head comparison with agalsidase beta, after switch from agalsidase beta at month 12 (primary analysis) and month 24, and an open label single arm study, after switch from agalsidase alfa, both followed by a long-term extension study.[4] No final conclusion on non-inferiority over agalsidase beta as measured by the annualised eGFR can be retrieved from the main study given that the data for the primary endpoint comparison at month 12 was not on its own sufficiently informative due to the design and size of the trial.[4] Nevertheless, the median eGFR slopes from baseline to month 24 of pegunigalsidase and the comparator agalsidase beta appeared close.[4] At month 12, the mean slopes for eGFR in the ITT population were -2.507 mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -1.748 for the agalsidase beta arm (difference -0.759 [-3.026, 1.507].[3] At month 24, the median slopes for eGFR were -2.514 [-3.788; -1.240] mL/min/1.73 m²/year for the pegunigalsidase alfa

arm and -2.155 [-3.805; -0.505] for the agalsidase beta arm (difference -0.359 [-2.444; 1.726]).[4]

Pegunigalsidase alfa is approved in the European Union, Northern Ireland, and Great Britain for long-term ERT in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).[1,4] Pegunigalsidase alfa is also approved in the United States for the treatment of patients with confirmed Fabry disease.[11] The Great Britain Summary of Product Characteristics for pegunigalsidase alfa can be found at https://mhraproducts4853.blob.core.windows.net/docs/97703775fb45191a2ee987d696eca8e011df3d4e and the Northern Ireland Summary of Product Characteristics for pegunigalsidase alfa can be found at: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=80daa939-ce64-44a0-be07-a57ec24a1c45&type=smpc.

Protalix, a biopharmaceutical company focused on the development and commercialisation of recombinant therapeutic proteins expressed through its proprietary plant cell-based expression system, ProCellEx® and Chiesi are parties to a license and collaboration agreement. Under this agreement, Protalix granted Chiesi the exclusive right to develop and commercialise pegunigalsidase alfa for the treatment of Fabry disease.

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 an international, research-focused biopharmaceuticals 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), operates in 31 countries, and counts more than 6,500 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.

Media Contacts

Yasmin Ghariani, Chiesi UK
Head of External Communications
Phone: (+44) 161 488 5555
Email: y.ghariani@chiesi.com

Donna Caslin, Chiesi UK

Senior PR and Communications Manager
Phone: (+44) 161 488 5555
Email: d.caslin@chiesi.com

Sarah Pollard, M+F Health
Account Director
Phone: (+44) 793 9002465
Email: sarah.pollard@mandfhealth.com

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