# European Commission Approves Palynziq® (pegvaliase injection) for Treatment of Phenylketonuria (PKU) in Patients Aged 16 Years or Older

**First Enzyme Substitution Therapy Approved in Europe to Treat the Underlying Cause of PKU in Patients Aged 16 Years or Older at Doses up to 60 mg**
**Treatment Lowers Phe and Suggestive of Beneficial Effects on Inattention and Mood Symptoms**
**More than 18,000 Patients Aged 16 and Older Affected by PKU in Europe and the Middle East**

SAN RAFAEL, Calif., May 6, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) today announced that the European Commission (EC) has granted marketing authorization for Palynziq® (pegvaliase injection) at doses of up to 60 mg once daily, to reduce blood phenylalanine (Phe) concentrations in patients with phenylketonuria (PKU) aged 16 and older, who have inadequate blood Phe control (blood Phe levels greater than 600 micromol/L) despite prior management with available treatment options. Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme, is the first enzyme substitution therapy approved in Europe to target the underlying cause of PKU by helping the body to break down Phe. In addition, the EC acknowledged that the Phase 3 trial and extension study is suggestive of an improvement in inattention and mood symptoms.

On March 1, 2019 BioMarin announced that the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), adopted a positive opinion for the company's Marketing Authorization Application (MAA) for Palynziq. This is BioMarin's second approved treatment for this rare genetic disease.

PKU is a rare genetic disease that manifests at birth and results in a variety of cumulative toxic effects on the brain and is marked by an inability to break down Phe, an amino acid that is found in most forms of protein. PKU affects approximately 50,000 diagnosed patients in the developed world, and in Europe, approximately 1 in every 10,000 newborn babies are affected by this disease.[I] Approximately 18,000 patients aged 16 and older are affected by PKU in Europe and the Middle East. Left untreated, high levels of Phe become toxic to the brain and may lead to serious neurological and neuropsychiatric-related issues, affecting the way a person thinks, feels, and acts. Due to the seriousness of these symptoms, in many countries, infants are screened at birth to ensure early diagnosis and treatment to avoid intellectual disability and other complications. According to EU treatment guidelines, PKU patients should maintain lifelong control of their Phe levels.

"The approval of Palynziq is the latest milestone after more than 15 years of an ongoing commitment to the PKU community. BioMarin has brought the only two approved therapies for PKU to patients around the world, and we will continue to draw on our expertise in PKU to advance the standard of care in this serious rare disease," said Jean-Jacques Bienaimé, chairman and chief executive officer of BioMarin. "Today would not be possible without the efforts of our employees, partners in Europe, patients, families and clinicians. We thank the European Commission for recognizing the vast potential benefits of Palynziq for patients affected by PKU."

"Palynziq is a new and promising treatment for the PKU community," said Dr. Amaya Bélanger-Quintana, Head of the Metabolic Department of the University Hospital Ramon y Cajal, Madrid, Spain. "Many adult PKU patients struggle daily with their special diet, leading many of them to relax or stop their treatment despite knowing the negative consequences this will have on to their well-being. Palynziq provides a new opportunity for adult PKU patients to attain the metabolic control their doctors and they want for themselves."

On May 24, 2018, the U.S. Food and Drug Administration (FDA) approved Palynziq® (pegvaliase-pqpz) Injection to reduce blood Phe concentrations in adult patients with PKU, who have uncontrolled blood Phe concentrations greater than 600 µmol/L on existing management.

The Palynziq EC approval was based on the totality of data from the Palynziq clinical development program including a Phase 3 pivotal study, PRISM-2, which showed that a group of patients taking either 20 mg or 40 mg of Palynziq maintained mean blood Phe levels at 553.0 µmol/L and 566.3 µmol/L respectively after eight weeks, compared to their baseline in the randomized discontinuation trial (RDT) of 596.8 µmol/L and 410.9 µmol/L. The corresponding 20 mg and 40 mg placebo treated groups mean blood Phe levels returned to pre-treatment baseline levels of 1509.0 µmol/L and 1164 µmol/L compared to their RDT baselines of 563.9 µmol/L and 508.2 µmol/L respectively, the EU Summary of Product Characteristics (SmPC) allows for daily doses up to 60mg. The 8-week PRISM-2 double-blind, placebo-controlled, randomized drug discontinuation trial (RDT) consisted of 86 patients who were randomized to either remain on Palynziq or receive matching placebo.

The approval was also based on data from an ongoing open-label extension study at 36 months, where patients being treated with Palynziq showed a sustained reduction in mean blood Phe over time, durability of response and an increase

in participants reaching important blood Phe thresholds. Mean blood phenylalanine levels reduced from 1233 micromol/l at baseline to 565 micromol/l at Month 12 (n=164) and 345 micromol/l at Month 24 (n =90), and these reductions in mean blood phenylalanine levels were maintained through Month 36 (341 micromol/l; n =48). At 36 months, 66% reached Phe levels of ≤360 µmol/L and 72% reached Phe levels of ≤600 µmol/L (the recommended treatment target in the EU). These results were observed concurrent with a median increase in protein intake from intact food of 25g over baseline after 36 months on treatment. In addition, the data collected in the Phase 3 trial and extension study was suggestive of an improvement in inattention and mood symptoms as measured by the inattention subscale of the investigator-rated Attention Deficient Hyperactivity Disorder Rating Scale (ADHD-RS IV) and the Profile of Mood States (POMS) tool that was modified to be specific to PKU (PKU-POMS).

**Phase 3 Study Design**

The Phase 3 program consists of two studies. PRISM-1 study was a Phase 3 open-label, randomized, multi-center study that enrolled 261 patients, and its primary objective was to characterize the safety and tolerability of Palynziq during induction, titration, and maintenance dosing. The secondary objective of the study was to evaluate blood Phe levels during induction, titration, and maintenance dosing to achieve a target dose of Palynziq 20mg/day or 40mg/day.

215 patients who completed PRISM-1 or PAL-003 (Phase 2 long term extension) enrolled into PRISM-2, which included a randomized, double-blind, placebo-controlled discontinuation study to evaluate the efficacy and safety of subcutaneous injections of Palynziq self-administered by adults with PKU, followed by an open-label extension. The primary efficacy endpoint is change from the RDT baseline in blood Phe at eight weeks.

Patients who reached a target dose and achieved ≥20% decrease in blood Phe from PRISM-1 baseline were randomized into the RDT portion of the PRISM-2 study to either continue their Palynziq dose or to start matching placebo. Those participants not reaching a ≥20% reduction in blood Phe from PRISM-1 baseline did not match the inclusion criteria for the RDT and enrolled into the open label extension portion of the study. In the open-label extension, physicians were allowed to modify dose based on blood Phe response using a range of doses from 5 mg/day to 60 mg/day. Patients were evaluated for safety, changes in Phe levels and neurocognitive assessments focused on inattention and mood symptoms.

**About Phenylketonuria**

PKU, or PAH deficiency, is a genetic disorder affecting approximately 50,000 diagnosed patients in the regions of the world where BioMarin operates and is caused by a deficiency of the enzyme PAH. This enzyme is required for the metabolism of Phe, an essential amino acid found in most protein-containing foods. If the active enzyme is not present in sufficient quantities, Phe accumulates to abnormally high levels in the blood and becomes toxic to the brain, resulting in a variety of complications including severe intellectual disability, seizures, tremors, behavioral problems and psychiatric symptoms. As a result of newborn screening efforts implemented in the 1960s and early 1970s, virtually all individuals with PKU under the age of 40 in countries with newborn screening programs are diagnosed at birth and treatment is implemented soon after. PKU can be managed with a Phe-restricted diet, which is supplemented by low-protein modified foods and Phe-free medical foods; however, it is difficult for most adult patients to adhere to the strict diet to the extent needed for achieving adequate control of blood Phe levels.

To learn more about PKU and PAH deficiency, please visit www.PKU.com. Information on this website is not incorporated by reference into this press release.

**About Palynziq**

**Palynziq** substitutes the deficient phenylalanine hydroxylase (PAH) enzyme in PKU with the PEGylated version of the enzyme phenylalanine ammonia lyase to break down Phe. **Palynziq** is administered using a dosing regimen designed to facilitate tolerability; Palynziq's safety profile consists primarily of immune-mediated responses, including anaphylaxis, for which robust risk management measures effective in clinical trials are in place.

The dosing and administration of Palynziq follows an induction, titration, and maintenance paradigm. Periodic blood Phe monitoring is recommended, and patients should be counseled on how to adjust their dietary intake, as needed, based on blood Phe concentrations.

**U.S. FDA-Approved Indication**

PALYNZIQ® (pegvaliase-pqpz) Injection is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 µmol/L on existing management.

**Important Safety Information**

**BOXED WARNING: RISK OF ANAPHYLAXIS**

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment with PALYNZIQ.**
- **Administer the initial dose of PALYNZIQ under the supervision of a healthcare provider**

**equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection. Prior to self-injection, confirm patient competency with self-administration, and patient's and observer's (if applicable) ability to recognize signs and symptoms of anaphylaxis and to administer auto-injectable epinephrine, if needed.**

- **Prescribe auto-injectable epinephrine to all patients treated with PALYNZIQ. Prior to the first dose, instruct the patient and observer (if applicable) on its appropriate use. Instruct the patient to seek immediate medical care upon its use. Instruct patients to carry auto-injectable epinephrine with them at all times during treatment with PALYNZIQ.**
- **PALYNZIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALYNZIQ REMS.** Further information, including a list of qualified pharmacies, is available at www.PALYNZIQREMS.com or by telephone 1-855-758-REMS (1-855-758-7367).

**WARNINGS AND PRECAUTIONS**

**Anaphylaxis**

- Signs and symptoms of anaphylaxis reported include syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, tongue), throat tightness, skin flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, diarrhea).
- Anaphylaxis generally occurred within 1 hour after injection; however, delayed episodes occurred up to 48 hours after PALYNZIQ administration.
- Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during treatment with PALYNZIQ. If an adult observer is needed, the observer should be present during and for at least 60 minutes after administration of PALYNZIQ, and should be able to administer auto-injectable epinephrine and call for emergency medical support upon its use.
- Anaphylaxis requires immediate treatment with auto-injectable epinephrine. Prescribe auto-injectable epinephrine to all patients receiving PALYNZIQ and instruct patients to carry auto-injectable epinephrine with them at all times during treatment with PALYNZIQ. Prior to the first dose, instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, on how to properly administer auto-injectable epinephrine, and to seek immediate medical care upon its use. Consider the risks associated with auto-injectable epinephrine use when prescribing Palynziq. Refer to the auto-injectable epinephrine prescribing information for complete information.
- Consider the risks and benefits of readministering PALYNZIQ following an episode of anaphylaxis. If the decision is made to readminister PALYNZIQ, administer the first dose under the supervision of a healthcare provider equipped to manage anaphylaxis and closely observe the patient for at least 60 minutes following the dose. Subsequent dose titration of PALYNZIQ should be based on patient tolerability and therapeutic response.
- Consider premedication with an $H_1$-receptor antagonist, $H_2$-receptor antagonist, and/or antipyretic prior to administration of PALYNZIQ based upon individual patient tolerability.

**Other hypersensitivity reactions**

- Hypersensitivity reactions other than anaphylaxis have been reported in 196 of 285 (69%) patients treated with PALYNZIQ.
- Consider premedication with an $H_1$-receptor antagonist, and/or antipyretic prior to PALYNZIQ administration based upon individual patient tolerability.
- Management of hypersensitivity reactions should be based on the severity of the reaction, recurrence of the reaction, and the clinical judgment of the healthcare provider, and may include dosage adjustment, temporary drug interruption, drug discontinuation, or treatment with antihistamines, antipyretics, and/or corticosteroids.

**ADVERSE REACTIONS**

- The most common adverse reactions (at least 20% of patients in either treatment phase) were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reaction lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue.
- Of the 285 patients exposed to PALYNZIQ in an induction/titration/maintenance regimen in clinical trials, 31 (11%) patients discontinued treatment due to adverse reactions. The most common adverse reactions leading to treatment discontinuation were hypersensitivity reactions (6% of patients)—including anaphylaxis (3% of patients) and angioedema (1% of patients)—arthralgia (4% of patients), generalized skin reactions lasting at least 14 days (2% of patients), and injection site reactions (1% of patients)
- The most common adverse reactions leading to dosage reduction were arthralgia (14% of patients), hypersensitivity reactions (9% of patients), injection site reactions (4% of patients), alopecia (3% of

patients), and generalized skin reactions lasting at least 14 days (2% of patients)
- The most common adverse reactions leading to temporary drug interruption were arthralgia (13% of patients), hypersensitivity reactions (13% of patients), anaphylaxis (4% of patients), and injection site reactions (4% of patients)

**Blood Phenylalanine Monitoring and Diet**

- Obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established.
- After a maintenance dosage is established, periodically monitor blood phenylalanine concentrations.
- Counsel patients to monitor dietary protein and phenylalanine intake, and adjust as directed by their healthcare provider.

**DRUG INTERACTIONS**

**Effect of PALYNZIQ on other PEGylated products**

- In a single dose study of PALYNZIQ in adult patients with PKU, 2 patients receiving concomitant injections of medroxyprogesterone acetate suspension (a formulation containing PEG 3350) experienced hypersensitivity reactions, and 1 of the 2 patients also experienced anaphylaxis.
- The clinical effects of concomitant treatment with different PEGylated products is unknown. Monitor patients treated with PALYNZIQ and concomitantly with other PEGylated products for hypersensitivity reactions.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy and Lactation**

- PALYNZIQ may cause fetal harm when administered to a pregnant woman.
- If PALYNZIQ is administered during pregnancy, or if a patient becomes pregnant while receiving PALYNZIQ or within 1 month following the last dose of PALYNZIQ, healthcare providers should report PALYNZIQ exposure by calling 1-866-906-6100.
- Monitor blood phenylalanine concentrations in breastfeeding women treated with PALYNZIQ.

**Pediatric use**

- The safety and efficacy of PALYNZIQ in pediatric patients have not been established.

**Geriatric Use**

- Clinical studies of PALYNZIQ did not include patients aged 65 years and older.

**You are encouraged to report side effects to report suspected adverse events to BioMarin at 1-877-695-8826 and the FDA at 1-800-FDA-1088 or** www.fda.gov/medwatch**.**
Please see full Prescribing Information, including Boxed Warning, at PALYNZIQ.com/hcp.

**About BioMarin**

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The company's portfolio consists of seven commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.biomarin.com. Information on such website is not incorporated by reference into this press release.

**Forward-Looking Statement**

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about: the potential benefits and commercial availability of Palynziq® (pegvaliase injection), BioMarin continuing to advance the standard of care in PKU and the data collected in the Phase 3 trial and extension study being suggestive of an improvement in inattention and mood symptoms. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others, risks related to: uncertainties inherent in research and development, including unfavorable new clinical data and additional analyses of existing clinical data; the results and timing of current and future clinical trials related to Palynziq; the risks related to commercialization of Palynziq and our ability to manufacture sufficient quantities of Palynziq; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission (SEC) filings including the Current Report on Form 10-Q for the quarter ended March 31, 2019, and future filings and reports by the Company. The Company undertakes no duty or obligation to update any forward-looking statements contained in this Current Report on Form 8-K as a result of new information, future events or changes in its expectations.

[I] van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12(1):162. Published 2017 Oct 12. https://doi.org/10.1186/s13023-017-0685-2. Last accessed: May 2019

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