BioMarin Receives Standard Approval for Palynziq™ (pegvaliase-pqpz) Injection for Treatment of Adults with Phenylketonuria (PKU), a Rare Genetic Disease

First Enzyme Therapy to Treat PKU
Palynziq Significantly and Substantially Reduced Blood Phenylalanine Levels Confirmed by a Phase 3 Placebo-Controlled Randomized Withdrawal Study
Palynziq Approval Comes During National PKU Awareness Month
Conference Call and Webcast to be Held May 24 at 6 PM Eastern

SAN RAFAEL, Calif., May 24, 2018 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) today announced that BioMarin received standard approval from the U.S. Food and Drug Administration (FDA) for Palynziq™ (pegvaliase-pqpz) Injection to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria (PKU), who have uncontrolled blood Phe concentrations greater than 600 micromol/L on existing management. Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme, is the first approved enzyme substitution therapy to target the underlying cause of PKU by helping the body to break down Phe. Palynziq is BioMarin's second approved treatment for this important condition.

PKU is a rare genetic disease that manifests at birth and results in a variety of cumulative toxic effects on the brain. PKU affects approximately 1 in 12,500 live births in the United States each year. PKU is marked by an inability to break down Phe, an amino acid that is found in all forms of protein. Left untreated, high levels of Phe become toxic to the brain and may lead to serious neurological and neuropsychiatric-related issues, impacting the way a person thinks, feels, and acts. Due to the seriousness of these symptoms, infants are screened at birth to ensure that they are diagnosed early and treated to avoid intellectual disability and other complications. Patients living with PKU require life-long management, including adherence to a challenging and severely restrictive daily diet of medical foods and formula that avoids the ingestion of Phe that is present in most foods.

The approval of Palynziq in the United States marks an important milestone for adults living with PKU who will now have access to an effective new treatment option for controlling their blood Phe.

The approval of Palynziq comes during National PKU Awareness Month. During National PKU Awareness Month, local patient organizations are encouraged to organize events to spread PKU awareness and raise funds for academic research.

"BioMarin is thrilled to be able to offer this important new therapy to adults with PKU who are unable to control their Phe levels with existing options. The approval of Palynziq is the culmination of more than a decade of perseverance by BioMarin employees dedicated to bringing treatments to PKU adult patients," said Jean-Jacques Bienaimé, chairman and chief executive officer of BioMarin. "We are proud of this medical achievement and appreciate the FDA's thoughtful review of our application. We also are grateful to the PKU patients and medical communities for their continued partnership and participation in the clinical program that led to the approval of this effective therapy."

"The goal in treating PKU is to keep blood Phe levels within the range set in the medical guidelines, as

elevation of Phe can be toxic and damaging to the brain. Palynziq provides another much needed tool for us to help adult patients control their Phe levels, which previously had not been achievable for many adults living with the condition," said Cary Harding, M.D., professor at Oregon Health & Science University and investigator for the Phase 3 studies.

"Palynziq has the potential to be a game-changing therapy for adults in the PKU community who have struggled throughout their lives to control their Phe levels, despite rigorous management," said Christine Brown, MS, executive director of the National PKU Alliance. "BioMarin has provided unwavering support for the PKU community and continues innovative medical research to advance treatment options for this rare genetic disease."

Palynziq is expected to be available in the United States by the end of June, and BioMarin will begin the promotion of Palynziq immediately. Palynziq is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Palynziq REMS.

BioMarin is also committed to bringing Palynziq to adult PKU patients outside of the United States. In March 2018, the European Medicines Agency accepted BioMarin's submission of a Marketing Authorization Application for Palynziq.

Clinical Trial Results

Palynziq significantly and substantially reduced blood Phe levels as demonstrated in the pivotal Phase 3 PRISM-2 study, which met the primary endpoint of change in blood Phe compared with placebo ($p<0.0001$). During the PRISM-2 double-blind, placebo-controlled, randomized withdrawal period trial (RWP), participants were randomized in a 2:1 ratio to either continue their maintenance Palynziq dosage (20 mg once daily or 40 mg once daily) or to receive matching placebo for a total of 8 weeks. Palynziq-treated patients maintained their blood Phe concentrations as compared to their randomized withdrawal baseline, whereas patients randomized to matching placebo returned to their pretreatment baseline blood Phe concentrations.

In the Phase 3 program, 57% of patients were taking medical food at baseline and 16% were on a protein-restricted diet at baseline (defined as receiving greater than 75% of total protein intake from medical food).

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, the strict diet is difficult for most adult patients to adhere to 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 ACMG Guidelines

Practice guidelines issued by the American College of Medical Genetics and Genomics (ACMG) support the

need for lifelong management of Phe levels in patients with phenylketonuria or PKU. The new diagnosis and management guidelines were published online in Genetics In Medicine's Advance Online Publication (AOP) service.

The guidelines state that treatment of PKU should be initiated as early as possible and must be continued throughout adulthood and "lifelong," with a goal of maintaining blood levels of Phe for all patients between 120 to 360 micromol/L. Patients treated from the early weeks of life with initial good metabolic control, but who lose that control in later childhood or adult life, may experience both reversible and irreversible neurocognitive and neuropsychiatric consequences.

According to the guidelines "the primary goal of therapy is to lower blood Phe, and any interventions, including medications, or combination of therapies that help to achieve that goal in an individual, without other negative consequences, should be considered appropriate therapy." Evidence for the guidelines are drawn from two previous independent review processes from the National Institutes of Health (2001) and the Agency for Health Research and Quality (2012). The guidelines can be accessed here.

Conference Call and Webcast to be Held May 24 at 6 PM Eastern

Interested parties may access a live webcast that will accompany the conference call by going here. A replay of the call will be archived on the site for one week following the call.

U.S. / Canada Dial-in Number: (866) 502-9859
International Dial-in Number: (574) 990-1362
Conference ID: 4298742

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 4298742

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. Treatment is individualized to the lowest effective and tolerated dosage. Prescribers may consider increasing to a maximum of 40 mg once daily in patients who have not achieved a response with 20 mg once daily for at least 24 weeks. Prescribers are instructed to discontinue treatment in patients who have not responded after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily. 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.

To reach a BioMarin RareConnections® case manager, please call, toll-free, 1-866-906-6100 or e-mail support@biomarin-rareconnections.com. For more information about Palynziq, please visit www.palynziq.com. For additional information regarding this product, please contact BioMarin Medical Information at medinfo@bmrn.com.

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 (site will be live within 24 hours) 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, which will be available in 24 hours.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening rare disorders. The company's portfolio consists of seven commercialized products and multiple clinical and pre-clinical product candidates.

For additional information, please visit www.BMRN.com. Information on BioMarin's website is not incorporated by reference into this press release.

Forward-Looking Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including, without limitation, statements about: expectations regarding the potential impact of this therapy in the PKU community; the expectations about the availability of Palynziq in the United States by the end of June; BioMarin's ability to support the launch of a new product and ship to specialty pharmacies; BioMarin's development programs for Palynziq generally; and the potential approval of Palyniziq in jurisdictions outside of the U.S., including the EU. 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: actions by regulatory agencies other than the FDA, results and timing of current and planned clinical trials of BioMarin's products, the risks related to the commercialization of Palynziq, our ability to manufacture sufficient quantities of Palynziq for clinical trials and the commercial launch of Palynziq in the U.S., the market potential for Palynziq as a treatment for PKU in adults; 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 Annual Report on Form *10-Q for the quarter ended March 31, 2018*, 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. BioMarin® is a registered trademark, and Palynziq™ is a trademark of BioMarin Pharmaceutical Inc.

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