BioMarin, Pioneer in Rare Disease Treatments for Phenylketonuria (PKU), Receives FDA Approval of Label Expansion to Allow Maximum Dose of 60 mg for Palynziq® (pegvaliase-pqpz) Injection for Treatment of Adults with PKU

New Safety and Efficacy Data Out to 3 Years for First and Only Enzyme Therapy to Treat PKU Demonstrate Phe Lowering and Support Well-Characterized Safety Profile

BioMarin 15+ Years of Commitment to PKU Community Through Long-Term Study of Existing Approved Therapies and Ongoing Efforts to Develop New Treatments

SAN RAFAEL, Calif., Oct. 7, 2020 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) today announced that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) to increase the maximum allowable dose of 60 mg with Palynziq® (pegvaliase-pqpz) Injection for treatment of adults with Phenylketonuria (PKU). Previously, the maximum dose was 40 mg. In the Phase 3 PRISM studies, 19% of study participants required a 60 mg dose to achieve adequate response to Palynziq.

The label expansion includes the addition of longer-term efficacy data demonstrating sustained phenylalanine (Phe) lowering out to three years and over six years of data further supporting a well-characterized safety profile. The labeling was updated to allow individualized maintenance dosage to achieve blood Phe control (blood Phe concentrations less than or equal to 600 µmol/L), taking into account patient tolerability to Palynziq and dietary protein intake.

Palynziq is indicated to reduce blood Phe concentrations in adults with phenylketonuria (PKU), who have uncontrolled blood Phe concentrations greater than 600 µmol/L on existing management. Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme, is the first and only 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 serious condition. BioMarin also recently announced that the Company had dosed the first participant in the global Phearless Phase 1/2 study of BMN 307, an investigational gene therapy for people with PKU, and potentially its third approved treatment. BMN 307 has Fast Track Designation in the US, as well as Orphan Drug Designation in the U.S. and E.U.

This labeling long term data update is based on efficacy data from an open-label extension study out to three years demonstrating that two-thirds (66%) of the 86 participants treated for at least two years, had a blood Phe level ≤360 µmol/L consistent with the Phe target in American College of Medical Genetics and Genomics (ACMG) recommended guidelines, and 50% of participants had blood Phe levels ≤120 µmol/L at two years. Of the 77 participants treated for at least three years, 58 (75%), 51 (66%), and 37 (48%) had a blood Phe concentration less than or equal to 600, 360, and 120 µmol /L, respectively, at three years of treatment. Additional safety data with over six years of follow up remains consistent with the previous safety profile of Palynziq, irrespective of dose.

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 neuropsychological impairment, affecting a person's ability to think and problem solve, and can lead to depression, anxiety, and behavior disturbance impacting quality of life. 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. Individuals 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.

"BioMarin is pleased that the FDA has recognized the importance of including an additional dosing option to individuals with PKU. Consistent with the label in Europe, Palynziq is now available in the U.S. at doses of up to 60 mg," said Jean-Jacques Bienaimé, Chairman and Chief Executive Officer of BioMarin. "BioMarin remains committed to the PKU community and continues to build on our 15 plus years of research and development, which enabled us to deliver the first two PKU drug therapies. We continue our commitment to further understand the safety and efficacy of our treatments for PKU. We are grateful to the study participants, investigators, study staff and BioMarin employees who were essential to enable this label expansion."

"Adding a maximum dose of 60 mg allows more patients to optimize and achieve treatment goals to keep blood Phe levels within the range set in the medical guidelines or within normal range," said Cary Harding, M.D., professor at Oregon Health & Science University and Steering Committee Chair for the Palynziq program. "More than six years of long-term safety data further supports a well-characterized safety profile similar to the initial data and is important information to physicians considering a chronic therapy."

"It is essential to the PKU community to have treatment options that can control Phe levels and provide long term data on safety and efficacy as it becomes available. The additional information added to the Palynziq label, particularly the long-term safety follow-up demonstrates BioMarin's ongoing commitment to people with PKU," said Christine Brown, MS, executive director of the National PKU Alliance. "BioMarin's 15-year focus on innovative medical research to advance the standard of care in PKU with an existing treatment and for new treatments is transforming the way that the community thinks about this rare genetic disease."

BioMarin's 15-Plus Year Commitment to PKU Research

For more than 15 years, BioMarin has been a pioneer in ongoing research to help improve the lives of PKU patients. BioMarin has developed therapies that have been used to treat approximately 7,000 PKU patients around the world. The company has two approved PKU therapies, and an investigational gene therapy BMN 307 is currently in development. BioMarin has conducted 41 clinical studies in PKU and has sponsored 44 external clinical studies. BioMarin researchers have authored 65 publications in medical and scientific journals on PKU and supported another 57 publications by external researchers.

About Phenylketonuria

PKU, or phenylalanine hydroxylase (PAH) deficiency, is a genetic disorder affecting approximately 70,000 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 severe Phe-restricted diet, which is supplemented by low-protein modified foods and Phe-free medical foods; however, it is difficult for most patients to adhere to the life-long strict diet to the extent needed to achieve adequate control of blood Phe levels. Dietary control of Phe in childhood can prevent major developmental neurological toxicities, but poor control of Phe in adolescence and adulthood is associated with a range of neurocognitive disabilities with significant functional impact.

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 ACMG support the need for lifelong management of Phe levels in patients with PKU. The 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.

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 from 20 mg to 40 mg in patients who have been on 20 mg once daily continuously for at least 24 weeks and who have not achieved blood Phe control. Prescribers may increase dosage to a maximum of 60 mg once daily

in patients who have been on 40 mg once daily continuously for at least 16 weeks and who have not achieved blood Phe control. Prescribers are instructed to discontinue treatment in patients who have not responded after 16 weeks of continuous treatment with the maximum dosage of 60 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) is a phenylalanine (Phe)-metabolizing enzyme indicated to reduce blood Phe levels in adult patients with phenylketonuria who have uncontrolled blood Phe levels greater than 600 micromol/L on existing management.

BOXED WARNING: RISK OF ANAPHYLAXIS

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment**
- **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**
- **Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during PALYNZIQ treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after PALYNZIQ administration, should be able to administer auto–injectable epinephrine, and call for emergency medical support upon its use**
- **Prescribe auto-injectable epinephrine. 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 PALYNZIQ treatment

- **PALYNZIQ is available only through a restricted program called PALYNZIQ REMS (Risk Evaluation and Mitigation Strategy). Further information, including a list of qualified pharmacies, is available at www.PALYNZIQREMS.com or by telephone at 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 PALYNZIQ treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after PALYNZIQ administration, 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 PALYNZIQ treatment. Prior to the first dose, instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, 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 PALYNZIQ dose titration 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 PALYNZIQ administration based upon individual patient tolerability

Other Hypersensitivity Reactions

- Hypersensitivity reactions other than anaphylaxis have been reported in 204 of 285 (72%) patients treated with PALYNZIQ in clinical trials
- 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, 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 reactions lasting at least 14 days, nausea, abdominal pain, vomiting, cough, oropharyngeal pain, pruritus, diarrhea, nasal congestion, fatigue, dizziness, and anxiety
- Of the 285 patients exposed to PALYNZIQ in an induction/titration/maintenance regimen in clinical trials, 44 (15%) 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), 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 (15% 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 hypersensitivity reactions (14% of patients), arthralgia (13% of patients), anaphylaxis (4% of patients), and injection site reactions (4% of patients)
- Angioedema and serum sickness: In clinical trials, 22 out of 285 (8%) patients experienced 45 episodes of angioedema (symptoms included: pharyngeal edema,

swollen tongue, lip swelling, mouth swelling, eyelid edema, and face edema) occurring independent of anaphylaxis. In clinical trials, serum sickness was reported in 7 out of 285 (2%) patients

Blood Phenylalanine Monitoring and Diet

- Obtain blood Phe levels every 4 weeks until a maintenance dosage is established. Periodically monitor blood Phe levels during maintenance therapy
- Counsel patients to monitor dietary protein and Phe 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, two patients receiving concomitant injections of medroxyprogesterone acetate suspension (a formulation containing PEG 3350) experienced a hypersensitivity reaction. One of the two patients 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 including anaphylaxis

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

- PALYNZIQ may cause fetal harm when administered to a pregnant woman
- Advise women who are exposed to PALYNZIQ during pregnancy or who become pregnant within one month following the last dose of PALYNZIQ that there is a pregnancy surveillance program that monitors pregnancy outcomes. Healthcare providers should report PALYNZIQ exposure and encourage these patients to report their pregnancy to BioMarin (1-866-906-6100)
- Monitor blood Phe levels in breastfeeding women treated with PALYNZIQ

Pediatric Use

- The safety and effectiveness 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 suspected adverse reactions to BioMarin at 1-866-906-6100, or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

Please see accompanying full Prescribing Information, including Boxed Warning.

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 six 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 Palynziq in the PKU community; the updated Palynziq label allowing individualized maintenance dosage to achieve blood Phe control (blood Phe concentrations less than or equal to 600 micromol/L), taking into account patient tolerability to Palynziq and dietary protein intake; new data supporting Phe lowering and a well-characterized safety profile; the Company's Phase 1/2 Phearless study of BMN 307, including BMN 307 potentially becoming BioMarin's third approved treatment for PKU; and BioMarin's development programs for PKU and BioMarin's ongoing commitment to patients with PKU generally. 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, 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; 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 June 30, 2020*, and future filings and reports by the Company. Stockholders are urged not to place undue reliance on forward-looking statements contained in this press release, which speak only as of the date hereof. BioMarin is under no obligation, and expressly disclaims any obligation, to update or alter any forward-looking statement, whether as a result of new information, future events, changes in its expectations or otherwise.

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