

BioMarin Receives Positive CHMP Opinion in Europe for Palynziq® (pegvaliase Injection) for Treatment of Patients with Phenylketonuria (PKU) Aged 16 and Older

**Decision on Marketing Authorization Application Expected Q2 '19
In Phase 3 Trial, Palynziq Substantially Reduced Blood Phenylalanine Levels, While Increasing Dietary Protein; Data 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., March 1, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq: BMRN) announced today that the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), has adopted a positive opinion for the company's Marketing Authorization Application (MAA) for Palynziq® (pegvaliase) Injection 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. In addition, the CHMP noted that the data collected in the Phase 3 trial and extension study was suggestive of an improvement in inattention and mood symptoms.

In May 2018, Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme, received regulatory approval from the U.S. Food and Drug Administration, making it the first approved enzyme substitution therapy to target the underlying cause of PKU by helping the body break down Phe.



"For more than a decade, BioMarin has been committed to providing meaningful new treatment options for the PKU community. Palynziq is the latest result of this commitment and represents the very first enzyme therapy for PKU; an important step forward in advancing the standard of care and in broadening available treatment options for PKU patients," said Hank Fuchs, M.D., President Worldwide Research and Development at BioMarin. "We thank the CHMP for recognizing the potential of Palynziq to make a difference for patients living with PKU and are grateful to the PKU community for their continued support and participation in the clinical program."

"People living with PKU have limited treatment options to manage their Phe levels. As a treating physician, I welcome the potential addition of a new option that could substantially lower Phe levels for more patients with this rare, genetic disease," said Professor Francjan van Spronsen, Head of Metabolic Diseases at Beatrix Children's Hospital, Center of Expertise for PKU and Tyrosinemia in The Netherlands. "This offers the potential to effectively control Phe levels in patients with PKU and allow for more normal nutritional intake."

The CHMP is a scientific committee composed of representatives from the 28-member states of the EU, and Iceland, Norway and Liechtenstein. The committee reviews medical product applications on their scientific and clinical merit and provides advice to the European Commission (EC), which has the authority to approve medicines for the EU. The EC, which typically adheres to the recommendation of the CHMP, is expected to make its final decision on Palynziq in Q2 2019.

The CHMP based its opinion 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, 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 increased to 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 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 CHMP also considered data from an ongoing open-label extension study at 36 months, where patients being treated with Palynziq showed durability and an increase in participants reaching blood Phe thresholds of physiologically normal (≤ 120 µmol/L), as well as thresholds recommended in the U.S. (≤ 360 µmol/L) and the European Union (E.U.) (≤ 600 µmol/L). At 36 months, 58% of the participants reached Phe levels of ≤ 120 µmol/L, 66% reached Phe levels of ≤ 360 µmol/L, and 72% reached Phe levels of ≤ 600 µmol/L. 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 CHMP noted that 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).

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 all 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 that they are diagnosed early and treated to avoid intellectual disability and other complications.

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 $\geq 20\%$ decrease in blood Phe from PRISM-1 baseline were randomized into the RDT portion of the study to either continue their Palynziq dose or to start matching placebo. Those participants not reaching a $\geq 20\%$ 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 10 mg/day to 60 mg/day. Patients were evaluated for safety, changes in Phe levels and neurocognitive assessments focused on inattention and mood symptoms.

Medical Guidelines Support Lifelong Therapy to Manage PKU

Medical guidelines in both the United States and Europe support the need for lifelong management of phenylalanine (Phe) levels in patients with phenylketonuria or PKU. In Europe in 2017, The *Lancet Diabetes & Endocrinology* published shortened medical guidelines, and the *Orphanet Journal of Rare Diseases* published a full version of the Guidelines stating that untreated blood Phe concentrations greater than 600 $\mu\text{mol/l}$ should be treated. Both publications can be accessed on the [website of the European Society for Phenylketonuria \(ESPKU\)](#).

In the U.S., the American College of Medical Genetics and Genomics (ACMG) issued guidelines in 2014, which 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 120-360 $\mu\text{mol/L}$. 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."

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 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, which in Europe is referred to as acute systemic hypersensitivity reactions, 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.

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 or contact BioMarin Medical Information at medinfo@bmrn.com.

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 H₁-receptor antagonist, H₂-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 H₁-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.biomin.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: regulatory filings for the commercial approval of Palynziq, including the expected timing of the EC's final decision on Palynziq and statements about 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: the risk that the EC or other regulatory agencies, may not approve Palynziq for the treatment of patients aged 16 and older with phenylketonuria (PKU), who have uncontrolled blood Phe concentrations greater than 600 micromol/L on existing management; 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 Annual Report on Form 10-K for the year ended December 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.

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[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: February 2019

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