



Rhythm Pharmaceuticals Announces IMCIVREE® (setmelanotide) Granted Marketing Authorization by European Commission for Treatment of Obesity and Control of Hunger in Bardet-Biedl Syndrome

September 6, 2022

-- Setmelanotide now FDA-approved and EC-authorized for Bardet-Biedl syndrome (BBS) --

-- EC authorization for BBS makes Rhythm eligible to receive second \$37.5M tranche under Revenue Interest Agreement with HealthCare Royalty --

-- Health Canada grants Priority Review status for new drug submission for setmelanotide for treatment of obesity and control of hunger in BBS and biallelic POMC, PCSK1 or LEPR deficiencies --

BOSTON, Sept. 06, 2022 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases, today announced that the European Commission (EC) has expanded the marketing authorization for IMCIVREE® (setmelanotide) to include the treatment of obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adult and pediatric patients 6 years of age and older.

"Patients and families have long endured a significant need for a therapy to address the burdens of hyperphagia and severe obesity often associated with BBS," said Philip Beales, M.D., University College London, UCL Great Ormond Street Institute of Child Health. "Having new treatment options available can help address the physical and emotional aspects of this devastating disease, offering patients and their families relief and improved quality of life."

BBS is a rare genetic disease that affects approximately 2,500 people in the European Union (EU) and United Kingdom (UK). People living with BBS may experience insatiable hunger, also known as hyperphagia, and severe obesity beginning early in life. Approximately 1,500 patients have been diagnosed with BBS and are now being cared for at academic settings in the EU and UK.

Under the terms of the Revenue Interest Financing Agreement with HealthCare Royalty Partners announced on June 16, 2022, Rhythm is now eligible to receive an additional investment of \$37.5 million following EC marketing authorization for setmelanotide for BBS. Rhythm had received an initial investment amount of \$37.5 million from HealthCare Royalty as a result of the approval of setmelanotide by the U.S. Food and Drug Administration (FDA), and the Company remains eligible for an additional investment amount of \$25 million, which would be payable upon the achievement of certain agreed sales milestones in 2023.

Priority Review Status Granted for New Drug Submission for Setmelanotide in Canada

Rhythm also announced today that Health Canada has granted Priority Review for Rhythm's New Drug Submission for setmelanotide, indicated in adult and pediatric patients 6 years of age and older with impairments in the MC4R pathway due to genetic diseases, for the treatment of obesity and control of hunger in BBS or biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency.

Priority Review shortens Health Canada's submission review performance target to 180 days, in comparison to 300 days for non-priority review. Priority Review may be granted for drug submissions in Canada for a serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada or a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

"These two important regulatory milestones underscore the global unmet need to treat the hyperphagia and severe obesity associated with these rare MC4R pathway diseases," said David Meeker, M.D., Chairman, President and Chief Executive Officer of Rhythm. "We are working closely with Health Technology Assessment bodies and payers throughout the EU on a country-by-country basis to achieve market access and reimbursement in order to make IMCIVREE available to eligible patients as rapidly as possible. Taken together with the recent FDA approval for BBS in June, we are making significant advances in our mission of delivering the first precision medicine for MC4R pathway diseases to patients across the world."

About Rhythm Pharmaceuticals

Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living

with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. Rhythm's precision medicine, setmelanotide, is approved by the U.S. Food and Drug Administration (FDA) for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). The European Commission (EC) has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity and is leveraging the Rhythm Engine and the largest known obesity DNA database -- now with approximately 45,000 sequencing samples -- to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. Rhythm's headquarters is in Boston, MA.

Setmelanotide Indication

In the European Union, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) or genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

In the United States, setmelanotide is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) or BBS.

Limitations of Use

In the United States and Europe, Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1 or LEPR deficiency with *POMC*, *PCSK1* or *LEPR* variants classified as benign or likely benign
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity.

WARNINGS AND PRECAUTIONS

Skin Monitoring: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing naevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and during treatment with setmelanotide.

Heart rate and blood pressure monitoring: Heart rate and blood pressure should be monitored as part of standard clinical practice at each medical visit (at least every 6 months) for patients treated with setmelanotide.

Prolonged penile erection: Spontaneous penile erections have been reported in clinical trials with setmelanotide. Patients who have a penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment of priapism.

Depression: In clinical trials, depression has been reported in patients treated with setmelanotide. Patients with depression should be monitored at each medical visit during treatment with setmelanotide. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.

Paediatric Population: The prescribing physician should periodically assess response to setmelanotide therapy. In growing children, the impact of weight loss on growth and maturation should be evaluated. The prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Excipients: This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Patients who are pregnant or breastfeeding should be advised of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. This medicinal product should be used with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free."

ADVERSE REACTIONS

The most frequent adverse reactions are hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache

(26%).

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of setmelanotide in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects. As a precautionary measure, setmelanotide should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in fetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide treatment as there was no proof of teratogenicity in the nonclinical data. If a patient who is taking setmelanotide and still losing weight gets pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring for the recommended weight gain during pregnancy. The treating physician should carefully monitor weight during pregnancy in a patient taking setmelanotide.

Breast-feeding

It is unknown whether setmelanotide is excreted in human milk. A nonclinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from setmelanotide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility

No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337. See [Summary of Product Characteristics' APPENDIX V](#) for a list of European national reporting systems to communicate adverse reactions.

Please see the full Prescribing Information for additional Important Safety Information.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, the potential benefits of setmelanotide for patients with BBS, and our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of setmelanotide in Europe, Canada, the United States and other international regions. Statements using word such as “expect”, “anticipate”, “believe”, “may”, “will” and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and the other important factors discussed under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2022 and our other filings with the U.S. Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

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