Rhythm Pharmaceuticals Announces Pre-Marketing Early Access Authorization for Setmelanotide for Use in Patients with Hypothalamic Obesity in France

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-- Reimbursed early access program allows for patients with hypothalamic obesity in France to receive setmelanotide treatment --
-- Early access designation for hypothalamic obesity comes in addition to Bardet-Biedl syndrome --

BOSTON, Aug. 07, 2023 (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 French National Agency for Medicines and Health Products Safety (ANSM) and French National Authority for Health (HAS) have granted pre-marketing early access authorization AP1 (Autorisation d'Accès Précoce), for IMCIVREE ® (setmelanotide), an MC4R agonist, for patients with lesional hypothalamic obesity.

AP1 allows for early access to innovative therapies in France prior to European regulatory approval when a positive benefit/risk ratio is recognized and when no other therapeutic alternatives are available. The AP1 for setmelanotide was granted following review of efficacy and safety data from Rhythm's Phase 2 trial by the ANSM and HAS. Products included in the AP1 programs are fully covered by France's National Health System and Rhythm can expect to be reimbursed for any patients receiving treatments through this program.

Setmelanotide has been available through a similar program for patients in France with Bardet-Biedl syndrome (BBS) since July 2022.

"We are delighted to announce that the French regulatory authorities granted this unique AP1 status to setmelanotide, as this is a recognition of the seriousness of the unmet medical need and what we believe to be a significant first step towards our goal of expanding access to setmelanotide to include patients with hypothalamic obesity globally," said Yann Mazabraud, Executive Vice President and Head of International at Rhythm. "We look forward to continuing to work with French experts to deliver setmelanotide to patients in France."

Hypothalamic obesity is a rare, acquired form of extreme obesity that occurs following damage to the hypothalamic region of the brain, which includes the MC4R pathway and is responsible for controlling physiological functions such as hunger and weight regulation. It most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma or other rare brain tumors. Patients experience rapid weight gain, a reduction in energy expenditure and increase in hunger in the first six to 12 months following tumor resection, and ultimately develop severe obesity. Rhythm estimates there are approximately 500-2,000 patients living with hypothalamic obesity in France, with approximately 50 to 200 new cases each year. In the United States, the Company estimates the prevalence in hypothalamic obesity to be approximately 5,000-10,000 patients with an annual incidence of approximately 500 new patients.

As previously announced, Rhythm's Phase 3 trial in hypothalamic obesity is ongoing following strong Phase 2 trial data that showed meaningful weight loss was sustained and progressed in patients with hypothalamic obesity treated with setmelanotide. The Company enrolled 18 patients with hypothalamic obesity in its Phase 2 trial. Sixteen of 18 patients (89%) achieved the primary endpoint of 5 percent or greater reduction in body mass index (BMI) after 16 weeks of treatment. Overall, there was a 14.5 mean percent reduction in BMI (N=18) at Week 16 from baseline.

"There are currently no effective or approved therapeutic options for patients with hypothalamic obesity, and it is important to understand that efforts to control weight and appetite with traditional lifestyle changes are not sufficient," said Professor Christine Poitou, Professor of Nutrition, Pitié-Salpêtrière University Hospital, Paris. "This AP1 addresses a significant unmet need for patients with severe obesity and hyperphagia, two hallmark symptoms of hypothalamic obesity, for the first time."

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) diseases. Rhythm's lead asset, IMCIVREE (setmelanotide) is approved by the U.S. Food and Drug Administration (FDA) and authorized by the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) for use in accordance with product labeling. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare MC4R pathway diseases, as well as a preclinical suite of investigational candidates for the treatment of congenital hyperinsulinism. Rhythm's headquarters

is in Boston, MA.

Setmelanotide Indication
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.

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 proopiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

In Canada, setmelanotide is indicated for the treatment of obesity due to Bardet-Biedl syndrome (BBS) or genetically-confirmed biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency due to variants interpreted as pathogenic, likely pathogenic, or of uncertain significance in adults and children 6 years of age and above.

Limitations of Use
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.

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

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.

Pediatric 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-fetal 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 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 for patients with hypothalamic obesity, our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of IMCIVREE in France, the United States and other international regions, including expectations surrounding coverage and availability of IMCIVREE in France and related revenues. 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, risks relating to our liquidity and expenses, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks relating to product liability lawsuits, inability to maintain our collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, the impact of the COVID-19 pandemic and general economic conditions on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the three months ended March 31, 2023 and our other filings with the 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.

Corporate Contact:
David Connolly
Executive Director, Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

Media Contact:
Adam Daley
Berry & Company Public Relations
212-253-8881
adaley@berrypr.com

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