Rhythm Pharmaceuticals Announces European Commission Authorization of IMCIVREE® (setmelanotide)▼ for the Treatment of Obesity and Control of Hunger Associated with POMC, PCSK1 and LEPR Deficiency

July 23, 2021

First-ever authorized treatment option in the European Union for these rare genetic diseases of obesity

BOSTON, July 23, 2021 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company committed to transforming the care of people living with rare genetic diseases of obesity, today announced that the European Commission (EC) has granted marketing authorization to IMCIVREE (setmelanotide) in the European Union (EU) for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

“Rhythm’s Phase 3 trials confirmed that treatment with IMCIVREE may deliver clinically meaningful impacts on obesity and severe hunger or hyperphagia. Many patients enrolled in these studies experienced weight loss of a magnitude that is unprecedented in the natural history of rare genetic diseases of obesity,” said Martin Wabitsch, M.D., professor of medicine and head of the Division of Pediatric Endocrinology and Diabetes at Ulm University Medical Center in Germany. “With this authorization, we are reminded of the importance of genetic testing, so that we can identify and properly diagnose patients with POMC, PCSK1 or LEPR deficiency obesity and offer eligible patients IMCIVREE, a pharmacological therapy designed to address the underlying cause of their disease.”

“With this authorization now in the EU, IMCIVREE becomes the first and only treatment option available to patients in EU countries and other territories including Northern Ireland to address the underlying cause of obesities driven by certain genetic defects in the melanocortin-4 (MC4) receptor pathway,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “This marks an important milestone for people in the EU member states living with POMC, PCSK1 or LEPR deficiency obesities, who now may have access to a therapy that has been shown to reduce hunger and body weight. We look forward to working closely with health authorities throughout the EU, as we commence the country-by-country reimbursement process and work to make IMCIVREE available to eligible patients as rapidly as possible.”

Obesity due to POMC, PCSK1 or LEPR deficiency is an ultra-rare disease caused by variants in *POMC, PCSK1* or *LEPR* genes that impair the MC4R pathway, which is a pathway in the hypothalamus that is responsible for regulating hunger, energy expenditure and consequently body weight.[i,ii] People living with obesity due to POMC, PCSK1 or LEPR deficiency struggle with extreme, insatiable hunger beginning at a young age, resulting in early-onset, severe obesity.[iii,iv] As an MC4R agonist, IMCIVREE is designed to restore impaired MC4R pathway activity arising due to genetic deficits upstream of the MC4 receptor.

The EC authorization of IMCIVREE is based on results from the largest studies conducted to date in obesity due to POMC, PCSK1 or LEPR deficiency.[v] In two Phase 3 clinical trials, 80 percent of ten patients with obesity due to POMC or PCSK1 deficiency achieved greater than ten percent body weight loss and 45.5 percent of 11 patients with obesity due to LEPR deficiency achieved greater than 10 percent body weight loss after one year of treatment with IMCIVREE. Additionally, in both studies, significant decreases in body mass index (BMI) were demonstrated across patients who were 6 to 17 years old at baseline (n=14).

In clinical trials, IMCIVREE was generally well-tolerated. The most common adverse events were injection site reaction, skin hyperpigmentation and nausea. Warnings and precautions include disturbance in sexual arousal, depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi.

IMCIVREE (setmelanotide) Indication[vi]
In the EU, IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with 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. IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

In the United States, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. The condition must be confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VOUS).

Limitations of Use[vi]
IMCIVREE should be prescribed and supervised by physicians with expertise in obesity with underlying genetic etiology. IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Important Safety Information[vi]

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with IMCIVREE. Instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: 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 IMCIVREE. Consideration should be given to discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

Skin Pigmentation and Darkening of Pre-Existing Nevi: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing nevi 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.

Pediatric Population: IMCIVREE is not approved for use in neonates or infants. The safety and efficacy of setmelanotide in children less than 6 years of age has not yet been established. No data are available.

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.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

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, IMCIVREE 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 IMCIVREE 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 the national reporting system listed in http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc.

See Full Product Information for IMCIVREE[vi].

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. The Company's precision medicine, IMCIVREE (setmelanotide), was approved in November 2020 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 obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing and by the European Commission (EC) in July 2021 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. IMCIVREE is the first-ever FDA-approved and EC-authorized therapy for these rare genetic diseases of obesity. Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity. The Company is leveraging the Rhythm Engine and the largest known obesity DNA database - now with approximately 37,500 sequencing samples - to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. The company is based in Boston, MA.

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, our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of setmelanotide. 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, the impact of our management transition, 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 quarterly period ended March 31, 2021 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
Head of Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

Investor Contact:
Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannah.deresiewicz@sternir.com

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

US-SET-2100029 07/2021

---

[i] Huvenne H, Duberne B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158-173.

[ii] Ellacott KL, Cone RD. The role of the central melanocortin system in the regulation of food intake and energy homeostasis: lessons from mouse models. *Philos Trans R Soc Land B Biol Sci*. 2006;361(1471):1265-1274.

[iii] Ayers KL, Glicksberg BS, Garfield AS, et al. Melanocortin 4 receptor pathway dysfunction in obesity: patient stratification aimed at MC4R agonist treatment. *J Clin Endocrinol Metab*. 2018;103(7):2601-2612.

[iv] Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC variants in humans. *Nat Genet*. 1998;19(2):155-157.

[v] Clément, K., et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *The Lancet Diabetes & Endocrinology*. Online first (2020). https://doi.org/10.1016/S2213-8587(20)30364-8

[vi] For the full product information, please see the Summary of Product Characteristics that can be found on www.ema.europa.eu.

Source: Rhythm Pharmaceuticals, Inc.