



Rhythm Pharmaceuticals Announces Marketing Authorisation of ▼IMCIVREE® (setmelanotide) in Great Britain

September 21, 2021

– IMCIVREE is indicated for treatment of obesity and 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 six years of age and above –

– First-ever authorised treatment option in Great Britain (England, Scotland and Wales) for these rare genetic diseases of obesity –

– IMCIVREE selected as 'highly specialised technology' and scheduled for review by National Institute for Health and Care Excellence (NICE) in December 2021 –

BOSTON, Sept. 21, 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 Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) has granted marketing authorisation to IMCIVREE® (setmelanotide) 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.

"This is a significant step for individuals living with the severe obesity and insatiable hunger, known as hyperphagia, that characterise POMC, PCSK1 or LEPR deficiency," said Sadaf Farooqi, M.D., Ph.D., professor at the Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre. "Until today, there were no authorised therapies that address the impairments in the melanocortin-4 receptor (MC4R) pathway that drive these rare diseases. With IMCIVREE, eligible patients now may have access to a pharmacological therapy specifically intended to address the underlying cause of their disease."

IMCIVREE was selected for evaluation as a "Highly Specialised Technology" by the National Institute for Health and Care Excellence (NICE). NICE is scheduled to review the dossier for IMCIVREE in December 2021. Guidance for coverage of IMCIVREE under the United Kingdom's National Health Service (NHS) is anticipated in the second quarter of 2022.

"With this authorisation in Great Britain following authorisation in the European Union and approval in the United States, we are advancing our goal of delivering IMCIVREE to patients globally as the first and only treatment option to address the severe obesity and hyperphagia caused by POMC, PCSK1 or LEPR deficiencies," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "Our Phase 3 trials confirmed that treatment with IMCIVREE may deliver a clinically meaningful impact on obesity and hyperphagia, and we are executing on our country-by-country strategy to achieve market access."

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 MHRA authorisation 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, 8 of 10 patients with obesity due to POMC or PCSK1 deficiency achieved greater than 10 percent body weight loss after one year of treatment with IMCIVREE and 5 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, nausea, and headache. Warnings and precautions include skin monitoring, heart rate and blood pressure monitoring, prolonged penile erection, and depression.

IMCIVREE (setmelanotide) Indication^{vi}

In Great Britain, 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.

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.

Limitations of Use^{vi}

IMCIVREE should be prescribed and supervised by physicians with expertise in obesity with underlying genetic aetiology.

Important Safety Information ^{vi}

WARNINGS AND PRECAUTIONS

Skin Monitoring: Setmelanotide may lead to generalised 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 IMCIVREE. Consideration should be given to discontinuing IMCIVREE if patients experience suicidal thoughts or behaviours.

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.

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, 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

Report any SUSPECTED ADVERSE REACTIONS via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

See [MHRA SmPC](#) for IMCIVREE^{vi}.

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).

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 commercialisation 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 commercialisation 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.

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^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](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 [here](#).



Source: Rhythm Pharmaceuticals, Inc.