CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213793Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213793
PDUFA Goal Date	November 24, 2020
OSE RCM #	2019-1952
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston , Pharm.D.
Deputy Division Director (acting)	Doris Auth, Pharm.D.
Review Completion Date	November 19, 2020
Subject	Evaluation of Need for a REMS
Established Name	Setmelanotide
Trade Name	Imcivree
Name of Applicant	Rhythm Pharmaceuticals, Inc.
Therapeutic Class	A melanocortin-4 receptor (MC4R) agonist
Formulations	10 mg/ml injection solution in a multi-dose vial
Dosing Regimen	Give as a subcutaneous injection. Adult patients: 2 mg once daily for 2 weeks, then 3 mg once daily. Pediatric patients: 1 mg once daily for 2 weeks, then 2 mg once daily.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Imcivree (setmelanotide) is necessary to ensure the benefits outweigh its risks. Rhythm Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 213793 for Imcivree (setmelanotide) with the proposed indication for chronic weight management in adult and pediatric patients 6 years of age and older with pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency obesity confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS). The label also contains Limitations of Use: setmelanotide is not indicated for the treatment of patients with POMC, PCSK1, or LEPR deficiency obesity in cases where POMC, PCSK1, or LEPR variants are classified as benign or likely benign as it would not be expected to be effective in these populations. The risks associated with setmelanotide include disturbance in sexual arousal, depression and suicidal ideation, and skin pigmentation/darkening of pre-existing nevi. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Diabetes, Lipid disorders, and Obesity (DDLO) agree that a REMS is not needed to ensure the benefits of setmelanotide outweigh its risks. The risks associated with setmelanotide include disturbance in sexual arousal, depression and suicidal ideation, and increased skin pigmentation and darkening of pre-existing nevi. These risks will be communicated in the prescribing information, Section 5 Warnings and Precautions. The labeling will also include a stopping rule in Section 2.4 Monitoring, to stop therapy if patients do not experience clinically meaningful weight loss after 12 weeks of therapy. At the time of this review, none of these risks warrant a Boxed Warning.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Imcivree (setmelanotide) is necessary to ensure the benefits outweigh its risks. Rhythm Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 213793 for setmelanotide with the proposed indication for chronic weight management in adult and pediatric patients 6 years of age and older with pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency obesity confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).The proposed label also contained the following Limitations of Use: setmelanotide is not indicated for the treatment of patients with POMC, PCSK1, or LEPR deficiency obesity in cases where POMC, PCSK1, or LEPR variants are classified as benign or likely benign as it would not be expected to be effective in these populations. This application is under review in the Division of Diabetes, Lipid disorders, and Obesity (DDLO). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Setmelanotide, a new molecular entity (NME)[a], is a melanocortin 4 receptor (MC4R) agonist, proposed for the treatment of obesity (b) (4) associated with POMC, PCSK1, or LEPR deficiency based on genetic testing in adults and pediatric patients 6 years of age and older. Setmelanotide is an injectable given by the subcutaneous route. The recommended dose for adult patients is 2 mg once daily for 2 weeks, then 3 mg once daily. The recommended dose for pediatric patients is 1 mg once daily for 2 weeks, then 2 mg once daily. Setmelanotide is not currently approved in any jurisdiction.

Setmelanotide is a synthetic octapeptide and is being developed for the treatment of rare genetic disorders of obesity, particularly POMC/PCSK1 and LEPR deficiency obesity. The MC4R receptor in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4R receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 213793 relevant to this review:

- 04/04/2016: Orphan drug designation for treatment of POMC deficiency obesity granted.
- 05/01/2017: Breakthrough therapy designation for the treatment of obesity associated with genetic defects upstream of the MC4R receptor in the leptin-melanocortin pathway.
- 11/27/2017: Orphan drug designation for treatment of LEPR deficiency obesity granted.
- 03/27/2020: NDA 213793 application received, under priority review
- 07/15/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for setmelanotide.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

POMC and LEPR deficiency obesities[1] are ultra-rare genetic disorders. POMC and LEPR deficiency are caused by genetic defects that compromise the normal activity of the MC4R pathway.[2] The MC4R pathway is a hypothalamic pathway critical for regulation of appetite, energy expenditure, and body weight. In patients with the rare genetic disorders of obesity, MC4R pathway signaling is impaired due to genetic variants upstream of the MC4R, leading to insatiable hunger (hyperphagia) and early onset severe obesity, and ultimately potentially life-threatening co-morbidities.[b] These genetic disorders are

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

rare, with the estimated number of affected individuals in the United States (US) of 100-500 for POMC deficiency and 500-2,000 for LEPR deficiency[c].[3]

POMC deficiency obesity is a disorder caused by variants in the POMC or PCSK1 genes that can lead to severe obesity beginning early in life and insatiable hunger, in addition to endocrine abnormalities. The features of POMC deficiency may include hyperphagia (68%), early-onset severe obesity (90%), ACTH deficiency and hypocortisolism (68%), light or pale skin color (66%), hypoglycemia (52%), and red hair (29%).

LEPR deficiency obesity is a disorder caused by variants in the LEPR gene that can lead to severe obesity beginning early in life and insatiable hunger, in addition to endocrine abnormalities. The features of LEPR deficiency may include hyperphagia (91%), early-onset severe obesity (97%), hyperinsulinemia (49%), hypogonadotropic hypogonadism (34%), and delayed puberty (35%).

3.2 Description of Current Treatment Options

A calorie-controlled diet along with behavior modification, and an increase in physical activity are cornerstones for all obesity treatments. Other options, such as the use of weight loss medications and surgical approaches can be considered if weight loss levels at a still unacceptable range or if medical problems are not controlled. Medical weight management may be offered to individuals affected by obesity who have failed to achieve weight-loss through diet and exercise alone.

There is no approved medication for the obesity associated with POMC or LEPR deficiency obesity at the current time. Although some of the related non-obesity endocrine manifestations can be managed by hormone replacement therapy (ACTH, l-thyroxine, sex hormone replacement, etc.), no options exist to treat the insatiable hunger. Drugs approved for general obesity have not resulted in weight reduction in these obesity disorders caused by genetic defects, as these drugs do not address the underlying MC4R pathway signaling defects that lead to obesity and unrelenting hunger.

Surgical approaches, such as gastric or intestinal banding/bypass operations are considered contraindicated because patients with POMC and LEPR deficiency obesity continue to experience extreme hunger after surgery. Continued excessive food consumption often leads to anatomical complications.

Lifestyle modification (diet and exercise) is the only intervention for patients with POMC and LEPR deficiency obesity in the absence of drug therapy and contraindication of surgical intervention. However, lifestyle modification is rarely successful over the short-term and almost never effective in the long-term due to the intense drive to eat caused by the absence of satiety signals.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4 Benefit Assessment

The efficacy of setmelanotide was evaluated in two identically designed, 1-year open label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT 02896192) enrolled patients aged 6 years and older with genetically confirmed or suspected POMC or PCSK1 deficiency obesity. Study 2 (NCT 03287960) enrolled patients aged 6 and older with genetically confirmed or suspected LEPR deficiency obesity. In both studies, the local genetic testing results were centrally confirmed using Sanger sequencing. The studies enrolled patients with biallelic, homozygous, or compound heterozygous pathogenic, likely pathogenic variants for either the POMC or PCSK1 genes (Study 1), or the LEPR gene (Study 2). In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m^2. The weight in pediatric patients was ≥95th percentile using growth chart assessment.

In both studies, a 10-week open label treatment period followed a 2 to 12 week titration period. Patients who achieved at least a 5 kg weight loss at the end of the open-label treatment period continued into a double-blind withdrawal period lasting 8 weeks, including 4 weeks of setmelanotide followed by 4 weeks of placebo (investigators and patients were blinded to this sequence). Following the withdrawal sequence, patients re-initiated active treatment with setmelanotide for up to 32 weeks. Ten patients in Study 1 and eleven patients in Study 2 were treated for at least one year.[4]

The primary outcome measure was effect on body weight. In Study 1, 80% of patients with POMC deficiency obesity met the primary endpoint, achieving a ≥10% weight loss after one year of treatment with setmelanotide. In Study 2, 46% of patients with LEPR deficiency obesity achieved a ≥10% weight loss after one year of treatment with setmelanotide, with P-value <0.0001 in both studies. When treatment with setmelanotide was withdrawn in patients who had lost weight during 10-week open label period, these patients gained an average of 5.5 kg in Study 1 and 5 kg in Study 2 over four weeks. Re-initiation of treatment resulted in resumed weight loss in both studies.[d]

The secondary outcome measure was effect on hunger. Changes in patient-reported hunger were assessed by the Daily Hunger Questionnaire for patients aged ≥12 years, with a hunger score ranging from 0 (not hungry at all) to 10 (hungriest possible). In Study 1, 50% of patients achieved a predefined clinically meaningful ≥25% improvement from baseline at one year. In Study 2, 73% of patients achieved a ≥25% improvement from baseline at one year. When treatment with setmelanotide was withdrawn in patients who had lost weight during the 10-week open label period, some of these patients had increased in hunger score in both studies, although the degree of increase was highly variable among different patients. Re-initiation of treatment resulted in a reversal of this increase in hunger score in the subset of patients in both studies.

5 Risk Assessment & Safe-Use Conditions

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The safety of setmelanotide was evaluated in 27 patients with Study 1 POMC/PCSK1 deficiency (14 patients) or Study 2 LEPR deficiency (13 patients) who received at least one dose of setmelanotide in clinical studies of 52 weeks duration. One death was reported in the LEPR deficiency study. The patient died as a result of injuries sustained as a passenger in an automobile accident.[5]

The risks discussed below reflect exposure to setmelanotide and are currently included in the draft labeling in Warnings and Precautions.[4]

5.1 Disturbance in Sexual Arousal

(b) (4)

5.2 Depression and Suicidal Ideation

(b) (4)

5.3 Skin Pigmentation and Darkening of Pre-Existing Nevi

(b) (4)

6 Expected Postmarket Use

Setmelanotide is intended for once daily patient self-administration, or caregiver administration at home. It will be provided in a 1 ml multi-dose single patient use vial. In addition, it is intended to be dispensed from specialty pharmacies only. Patient prescribing information (PPI) and Instruction for use (IFU) are also provided to patients and caregivers.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for setmelanotide beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of setmelanotide on the basis of the efficacy and safety information currently available. The MC4R pathway is a hypothalamic pathway, which is critical for regulation of appetite, energy expenditure, and body weight. The genetic defects affecting the MC4R pathway include, but are not limited to, POMC deficiency obesity due to mutations in the POMC gene, PCSK1 deficiency obesity due to mutations in PCSK1 gene, and LEPR deficiency obesity due to mutations in the LEPR gene. These MC4R pathway mutations cause rare genetic disorders of obesity that start early in childhood, progress over time, and can become life-threatening in severity. There is no approved medication for obesity and insatiable hunger associated with these rare genetic disorders of obesity at the current time. Drugs approved for general obesity have not resulted in weight reduction in these obesity disorders caused by genetic defects, as these drugs do not address the underlying MC4R pathway signaling defects that lead to obesity and unrelenting hunger. Setmelanotide is a synthetic, cyclic octapeptide that functions as a MC4R agonist.

This reviewer recommends that, if setmelanotide is approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks associated with setmelanotide include disturbances in sexual arousal, depression/suicidal ideation, and skin pigmentation/darkening of pre-existing nevi. None of these risks warrant a Boxed Warning at this time, and will be communicated in Section 5 Warnings and Precautions in the labeling. The labeling also includes a stopping rule in Section 2.4 Monitoring, to stop therapy if patients do not experience clinically meaningful weight loss after 12 weeks of therapy.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for setmelanotide to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Klish WJ, Skelton JA. Defiition, epidemiology, and etiology of obesity in children and adolescents uptodate.com, accessed 10/01/2020

[2] Perreault L. Genetic contribution and pathophysiology of obesity, uptodate.com, accessed 09/29/2020

[3] Early-onset, severe obesity, and insatiable hunger (hyperphagia): common symptoms www.uncommonobesity.com/clinical-presentation, accessed 07/17/2020

[4] Draft Prescribing Information for setmelanotide, accessed 10/06/2020

[5] John Sharretts, MD, Director of Division of Diabetes, Lipid disorders, and Obesity, draft Division Director Summary Review for Regulatory Action for setmelanotide NDA 213793 reviewed 11/13/2020

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