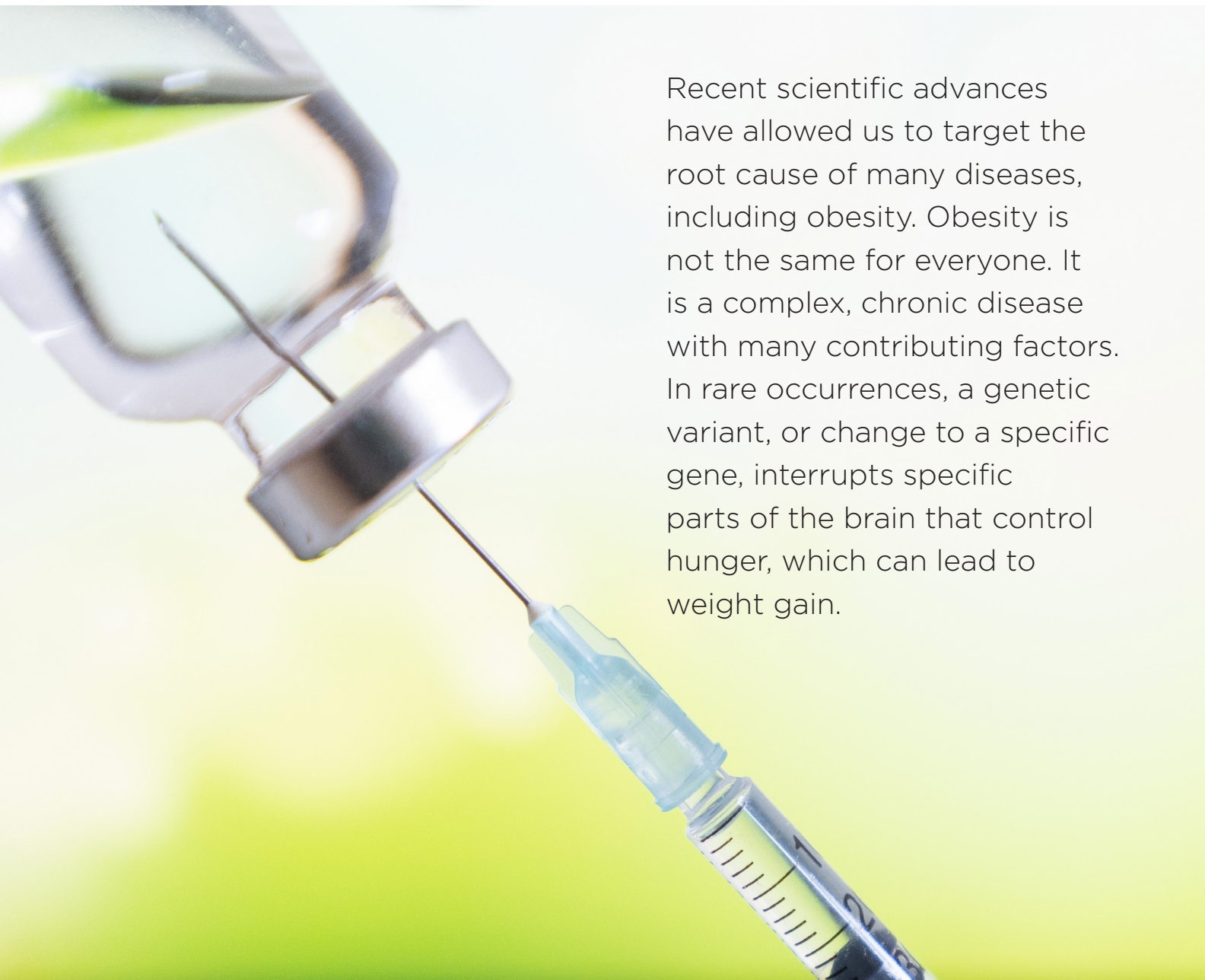
IMCIVREE™ (setmelanotide) –

The First FDA-Approved Therapy for Specific Rare Genetic Diseases of Obesity

by Jennifer Miller, MD



Recent scientific advances have allowed us to target the root cause of many diseases, including obesity. Obesity is not the same for everyone. It is a complex, chronic disease with many contributing factors. In rare occurrences, a genetic variant, or change to a specific gene, interrupts specific parts of the brain that control hunger, which can lead to weight gain.

What is IMCIVREE™ (setmelanotide)?

The U.S. Food & Drug Administration (FDA) recently approved IMCIVREE™ (setmelanotide), which is a daily injection given under the skin. It was approved for chronic weight management in adult and pediatric patients six years of age and older with obesity due to these genetic conditions:

- **Proopiomelanocortin (POMC)** –The neuron system that causes weight-loss. If you are deficient in POMC, it can affect your inability to lose weight.
- **Proprotein convertase subtilisin/kexin type 1 (PCSK1)** – Disrupts the regulation of glucose homeostasis and food intake. Maintaining glucose homeostasis would mean that your body is using glyocen and insulin to balance each other out so that your body remains steady and healthy. If they are unable to do this, your body is not in homeostasis.
- **Leptin receptor (LEPR) deficiency** – Causes constant hunger and quick weight gain leading to obesity.

These conditions occur when both copies of the relevant gene (*one inherited from the mother and one from the father*) have a specific change, or variant.

We all have pathways that are responsible for carrying messages between the brain and the body. One of these pathways signals to the body when to eat and when to stop eating, and helps regulate metabolism. Changes in the POMC, PCSK1, and LEPR genes can "block" this pathway, stopping these messages from getting through. Symptoms of POMC, PCSK1, or LEPR deficiency, include severe obesity early in life and intense hunger. IMCIVREE™ is the first-ever FDA-approved therapy for obesity due to these conditions.

The Usage of IMCIVREE™

IMCIVREE™ should not be used in people with obesity due to suspected POMC, PCSK1, or LEPR deficiency not confirmed by genetic testing (benign or likely benign result), or other types of obesity not related to POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic conditions and general obesity. It is not known if IMCIVREE™ is safe and effective in children under six years of age.

Why Would I Need IMCIVREE™ (setmelanotide)?

People living with obesity due to POMC, PCSK1 or LEPR deficiency struggle with:

- Extreme, insatiable hunger all the time
- Focusing on anything else except for hunger

Insatiable hunger, or hyperphagia, is not the same as regular hunger. It is a deep hunger that feels like the body is always in need of food. Children, from early infancy up to the age of 10, may gain far more weight than would be expected for their age. This is called early-onset obesity. IMCIVREE™ helps activate the areas in the brain that control appetite, feeling full, and metabolism to help lose weight and keep it off.

Research into these diseases is ongoing and is helping us gain a better understanding of disease-causing genetic variants. The use of genetic testing to identify and properly diagnose patients with certain genetic variants can help physicians, patients and families to better understand the underlying cause of certain severe cases of obesity.

> "The use of genetic testing to identify and properly diagnose patients with certain genetic variants can help physicians, patients and families to better understand the underlying cause of certain severe cases of obesity."

Genetic Testing

Before IMCIVREE™ can be used, a genetic test must show that the changes, or variants, are considered pathogenic, likely pathogenic or uncertain. Genetic testing results don't always provide a "yes" or "no" answer. In some cases, testing may provide clues rather than a clear diagnosis. A positive result means the genetic test revealed a change in your genes that is likely to explain your/your child's obesity. These are known as pathogenic (disease-causing) or likely pathogenic variants.

Sometimes, tests return a result of "Variant of Unknown Significance" or "VUS." This means that there is a variant in your genes, but scientists do not have enough information to know with certainty that the variant is disease-causing. Always speak with your doctor or a genetic counselor to understand your specific results.

IMCIVREE™ Clinical Study Results

IMCIVREE™ was evaluated in two clinical studies of people six years and older: one study for people with obesity due to POMC or PCSK1 deficiency, and one for people with obesity due to LEPR deficiency.

In the study of people with obesity due to POMC or PCSK1 deficiency, IMCIVREE™ reduced weight and hunger. Eight out of ten people lost at least 10% of their body weight at one year. After one year, eight participants also experienced a decrease in hunger.

In the study of people with obesity due to LEPR deficiency, IMCIVREE™ reduced their weight and hunger, too. Five out of eleven people lost at least 10% of their body weight at one year.

In both studies, treatment was stopped for a period of time to see how IMCIVREE™ was impacting weight and hunger. Over this withdrawal period, weight increased. When the withdrawal period ended and treatment was re-started, weight-loss continued. Hunger generally increased but decreased once again when treatment was re-started.

Side Effects of IMCIVREE™

As with many medicines, side effects are possible. IMCIVREE™ may cause serious side effects, including:

- Problems with male and female sexual function
- Depression and suicidal thoughts or actions
- Increased skin pigmentation
- Darkening of skin lesions (moles or nevi) that a patient already has
- Benzyl alcohol toxicity

Benzyl alcohol is a preservative in IMCIVREE™ that can cause serious side effects, including death, in premature and low-birth weight infants who have received medicines that contain benzyl alcohol.

Common side effects of IMCIVREE™:

- Injection site reactions
- Darkening of the skin
- Nausea
- Headache
- Diarrhea
- Abdominal pain
- Back pain
- Fatigue
- Vomiting
- Depression
- Upper respiratory tract infections
- Erections that happen without any sexual activity in males

Conclusion

I know that many patients and families who live with rare genetic diseases of obesity face an often-burdensome stigma associated with severe obesity at any age. There have been too many individuals who end up in tears during an initial visit with me because they had been struggling to find anyone who will listen or understand how difficult it can be to continue without a diagnosis or an effective treatment plan for themselves or their loved ones. Some have told me stories about locking cabinets and refrigerators and significantly limiting social activities to try to control disruptive food-seeking behavior. Even then, some patients pulled cabinet doors off their hinges, foraged for food in trash and left home to find food.

The science of obesity continues to evolve, and we must recognize that it is a complex disease that can sometimes be driven by genetics. Understanding the underlying causes of obesity can help healthcare providers identify, diagnose, and ultimately manage individuals with rare genetic diseases of obesity – a patient community with high unmet needs.

About the Author:
Jennifer Miller, MD, is a professor in the division of pediatric endocrinology at the University of Florida. She specializes in the care and treatment of individuals with genetic causes of early-onset excessive weight gain. Dr. Miller served as a principal investigator for clinical trials evaluating setmelanotide and is a consultant to Rhythm Pharmaceuticals, the manufacturer of IMCIVREE™.