Imcivree Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx and GenRx standard prior authorization program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
8/1/2023	7/1/2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Imcivree® (setmelanotide) Subcutaneous injection	Chronic weight management in adult and pediatric patients 6 years of age or older with monogenic or syndromic obesity due to: • Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (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) • Bardet-Biedl syndrome (BBS) Limitations of Use: 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, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Monogenic Obesity Disorders	There is a strong genetic component to human obesity. Most genes that influence an individual's predisposition to gain weight are not yet known. However, a glimpse into the long-term regulation of body weight has come from studying extreme human obesity caused by single gene defects. These monogenic (single-gene) obesity disorders have confirmed that the hypothalamic leptin-melanocortin system is critical for energy balance in humans because disruption of these pathways causes the most severe obesity phenotypes. Approximately 20 different genes and at least 3 different mechanisms implicated in monogenic causes of obesity have been identified, however, they account for less than 5% of all severe obesity. Monogenic forms of obesity can be divided into three broad categories; the category further discussed in this program is that which is caused by mutations in genes that have a physiologic role in the hypothalamic Leptin-Melanocortin system of energy balance. Obesity due to leptin receptor mutations, proopiomelanocortin mutations, and proprotein convertase mutations will be addressed further here.(2,3)

	Congenital leptin (LEP) and leptin receptor (LEPR) deficiency are rare, autosomal recessive disorders associated with severe obesity from a very young age (before 2 years). The clinical phenotypes associated with congenital leptin and leptin receptor deficiencies are similar. Patients are born of normal birth weight but exhibit rapid weight gain in the first few months of life resulting in severe obesity. Affected subjects are characterized by intense hyperphagia with food seeking behavior and aggression when food is denied.(4) Leptin suppresses food intake in part by acting on hypothalamic neurons expressing pro-opiomelanocortin (POMC). People who are homozygous or compound heterozygous for loss of function mutations in the POMC gene are hyperphagic and develop early-onset obesity due to loss of melanocortin signaling at the MC4R in the hypothalamus. In the pituitary, POMC is the precursor for adrenocorticotropin (ACTH). As such, POMC deficiency presents in neonatal life with findings of secondary adrenal insufficiency: hypoglycemia, cholestatic jaundice, or other features of adrenal crisis requiring long-term corticosteroid replacement therapy.(2,4,5,6) Such children have pale skin, and white Caucasians have red hair, due to the lack of melanocortin function at melanocortin 1 receptors in the skin.(2,4,6) The prevalence of POMC is believed to be fewer than 10 patients worldwide.(2,3,5) Prohormone convertase-1 (PCSK1, also known as PC1/3) is an enzyme that acts upon a range of substrates including proinsulin, proglucagon, and POMC. Compound heterozygous or homozygous mutations in PCSK1 cause neonatal small bowel enteropathy, glucocorticoid deficiency (secondary to ACTH deficiency), hypogonadotropic hypogonadism and postprandial hypoglycemia due to impaired processing of proinsulin to insulin as well as severe, early onset obesity.(4) The prevalence of PCSK1 deficiency is believed to be fewer than 20 patients worldwide.(3) Rhythm Pharmaceuticals has started a registry for patients with certain rare genetic disorders of obesity, and their "Uncovering Rare Obesity Program" offers free genetic testing in the United States for patients of all ages.
Syndromic Obesity Disorders	Syndromic obesity corresponds to severe obesity associated with additional phenotypes (e.g., mental retardation, dysmorphic features, and organ-specific developmental abnormalities). Prader-Willi (PWS) and Bardet-Biedl (BBS) syndromes are the two syndromes most frequently linked with obesity, though many other syndromes are now associated with obesity.(3) BBS is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties, and hypogonadism.(2,3,4,8) Diagnosis is based on clinical findings; four primary features OR three primary and two secondary features are required to make a clinical diagnosis.(8,9) Molecular genetic testing is also available and currently 16 genes are known to be associated with Bardet–Biedl syndrome (BBS); this accounts for approximately 80% of those clinically diagnosed with BBS.(8)
Efficacy	Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure.(1,5) In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.(1,6) The safety and efficacy of setmelanotide for chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03287960) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency. The studies enrolled patients with bi-allelic, homozygous, or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not

	eligible for treatment. In both studies, adult patients had a body mass index (BMI) of greater than or equal to 30 kg/m^2.(1,7) Weight in pediatric patients was greater than or equal to 95th percentile using growth chart assessments.(1) In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a greater than or equal to 10% weight loss after 1 year of treatment. In Study 2, 46% of patients with obesity due to LEPR deficiency achieved a greater than or equal to 10% weight loss after 1 year of treatment.(1,7) The safety and efficacy of setmelanotide for chronic weight management in adult and pediatric patients aged 6 years and older with obesity and a clinical diagnosis of Bardet-Biedl syndrome (BBS) were assessed in a 66-week clinical study, which included a 14-week randomized, doubleblind, placebo-controlled period and a 52-week open-label period (Study 3 [NCT03746522]). The study enrolled patients aged 6 years and above with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of greater than or equal to 30 kg/m^2 and pediatric patients had weight greater than or equal to 97th percentile using growth chart assessments.(1,9) Clinical diagnosis of BBS in study participants required four primary features OR three primary and two secondary features.(9) In Study 3, 38.7% of patients with obesity due to BBS met the primary endpoint, achieving a greater than or equal to 10% weight loss after 1 year of treatment.(1)

REFERENCES

Number	Reference
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2	Ranadive SA, Vaisse C. Lessons from Extreme Human Obesity: Monogenic Disorders. Endocrinol Metab Clin North Am. 2008 Sep;37(3):733-753.
3	Huvenne H, Dubern B, Clement K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obes Facts. 2016 Jun;9(3):158-173.
4	Farooqi IS, O'Rahilly S. The Genetics of Obesity in Humans. [Updated 2017 Dec 23]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279064/.
5	Low MJ. New Hormone Treatment for Obesity Caused by POMC-Deficiency. Nat Rev Endocrinol. 2016 Sep;12:627-628.
6	Kuhnen P, Clement K, Wiegand S, et al. Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. N Engl J Med. 2016;375:240-246.
7	Clement K, van den Akker E, Argente J, 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, Multicenter, Phase 3 Trials. Lancet Diabetes Endocrinol. 2020 Dec;8(12):960-970.
8	Forsythe E, Beales PL. Bardet-Biedl Syndrome. Eur J Hum Genet. 2013 Jan;21(1):8-13.
9	Haws RM, Gordon G, Han JC, et al. The Efficacy and Safety of Setmelanotide in Individuals with Bardet-Biedl Syndrome or Alstrom Syndrome: Phase 3 Trial Design. Contemp Clin Trials Commun. 2021 Jun;22:100780.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Imcivree	setmelanotide acetate subcutaneous soln	10 MG/ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Imcivree	Setmelanotide Acetate Subcutaneous Soln	10 MG/ML	10	Vials	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Imcivree	setmelanotide acetate subcutaneous soln	10 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Imcivree	Setmelanotide Acetate Subcutaneous Soln	10 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient's benefit plan covers the requested agent **AND** 2. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of monogenic obesity due to pro-opiomelanocortin (POMC) deficiency, proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency, or leptin receptor (LEPR) deficiency **AND** 2. Genetic testing with an FDA-approved test has confirmed variants in POMC, PCSK1, or LEPR genes (medical records required) **AND** 3. The patient's genetic status is bi-allelic, homozygous, or compound heterozygous (NOT double heterozygous) **AND**

Module	Clinical Criteria for Approval
	4. The patient's genetic variant is interpreted as pathogenic, likely pathogenic, OR of uncertain significance (VUS) **AND** 5. The patient's genetic variant is NOT classified as benign or likely benign **OR** B. BOTH of the following: 1. The patient has a diagnosis of syndromic obesity due to Bardet-Biedl syndrome (BBS) **AND** 2. The patient's diagnosis has been clinically confirmed by four primary features OR three primary and two secondary features (medical records required) (i.e., primary features [rod-cone dystrophy, polydactyly, obesity, genital anomalies, renal anomalies, learning difficulties]; secondary features [speech delay, developmental delay, diabetes mellitus, dental anomalies, congenital heart disease, bracydactyly/syndactyly, ataxia/poor coordination, anosmia/hyposmia]) **AND** 3. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 4. ONE of the following: A. For adult patients, the body mass index (BMI) is greater than or equal to 30 kg/m^2 **OR** B. For pediatric patients, weight is greater than or equal to 95th percentile (for POMC, PCSK1, or LEPR) or 97th percentile (for BBS) using growth chart assessments **AND** 5. ONE of the following: A. The patient is newly starting therapy **OR** B. ONE of the following: 1. For patients with obesity due to POMC, PCSK1, or LEPR deficiency, ONE of the following: A. The patient is currently being treated and has received less than 16 weeks (4 months) of therapy **OR** B. The patient has received at least 16 weeks of therapy, and has achieved a weight loss of ONE of the following: 1. Weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** 2. For patients with continued growth potential, weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **OR** 2. For patients with obesity due to BBS, ONE of the following: A. The patient is currently being treated and has received less than one year of therapy **OR** B. The patient has received at least one year of therapy, and has achieved a weight loss of ONE of the following: 1. Weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** 2. For patients aged less than 18 years, weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 4 months for POMC, PCSK1, or LEPR deficiency; 12 months for BBS NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient's benefit plan covers the requested agent **AND** 3. ONE of the following: A. For adult patients, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** B. ONE of the following: 1. For patients with POMC, PCSK1, or LEPR deficiency AND continued growth potential, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **OR** 2. For patients with BBS AND are aged less than 18 years, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) is greater than the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial - 4 months for POMC, PCSK1, or LEPR deficiency; 12 months for BBS Renewal - 12 months