

RESEARCH MONOGRAPH . COMPOUND PROFILE

Setmelanotide

An FDA-approved (2020) selective MC4 receptor agonist (Imcivree) for genetic obesity disorders (POMC, LEPR, PCSK1 deficiency).

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COMPOUND CLASS	Selective MC4 receptor agonist

ABSTRACT

Setmelanotide (Imcivree; RM-493; CAS 920014-72-8; molecular weight 1117.34) is a selective MC4 receptor agonist developed by Rhythm Pharmaceuticals and approved by the FDA in 2020 for chronic weight management in adults and children aged 6 years and older with obesity due to proopiomelanocortin (POMC), leptin receptor (LEPR), or PCSK1 deficiency. The compound is also approved for Bardet-Biedl syndrome obesity (2022). Mechanism is selective MC4 agonism in the hypothalamus, restoring downstream signaling in the leptin-melanocortin pathway disrupted by upstream genetic defects. The drug produces clinically meaningful weight loss in the genetically defined responder populations but minimal effect in non-genetic obesity. Pharmacokinetics: subcutaneous administration daily; plasma half-life approximately 11 hours. Approved doses are 2 to 3 mg once daily.

1. Compound Identification

Setmelanotide is described as selective mc4 receptor agonist. An FDA-approved (2020) selective MC4 receptor agonist (Imcivree) for genetic obesity disorders (POMC, LEPR, PCSK1 deficiency).

1.1 Class summary

Selective MC4 receptor agonist

1.2 Subtitle

An FDA-approved (2020) selective MC4 receptor agonist (Imcivree) for genetic obesity disorders (POMC, LEPR, PCSK1 deficiency).

2. Abstract

Setmelanotide (Imcivree; RM-493; CAS 920014-72-8; molecular weight 1117.34) is a selective MC4 receptor agonist developed by Rhythm Pharmaceuticals and approved by the FDA in 2020 for chronic weight management in adults and children aged 6 years and older with obesity due to proopiomelanocortin (POMC), leptin receptor (LEPR), or PCSK1 deficiency. The compound is also approved for Bardet-Biedl syndrome obesity (2022). Mechanism is selective MC4 agonism in the hypothalamus, restoring downstream signaling in the leptin-melanocortin pathway disrupted by upstream genetic defects. The drug produces clinically meaningful weight loss in the genetically defined responder populations but minimal effect in non-genetic obesity. Pharmacokinetics: subcutaneous administration daily; plasma half-life approximately 11 hours. Approved doses are 2 to 3 mg once daily.

3. Mechanism of Action

Selective MC4 receptor agonist; restores melanocortin pathway signaling in genetic obesity disorders.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

2 to 3 mg SC once daily.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Clement K, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency. Lancet Diabetes Endocrinol 2020.

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