Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

IMCIVREE 10 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 10 mg of setmelanotide.

Each vial contains 10 mg setmelanotide in 1 ml of solution for injection.

Excipient(s) with known effect
1 ml of solution contains 10 mg benzyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 2 years of age and above.

4.2 Posology and method of administration

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

Posology

POMC, including PCSK1, deficiency and LEPR deficiency

Adult population and children more than 12 years of age

For adults and children 12 to 17 years of age, the starting dose is a 1 mg once daily subcutaneous injection for 2 weeks. After 2 weeks, if setmelanotide is well-tolerated (see section 4.4), the dose can be increased to a 2 mg once daily subcutaneous injection (Table 1). If dose escalation is not tolerated, patients may maintain administration of the 1 mg once daily dose.

If additional weight loss is desired in adult patients, the dose can be increased to a 2.5 mg once daily subcutaneous injection. If the 2.5 mg once daily dose is well-tolerated, the dose can be increased to 3 mg once daily (Table 1).

In patients aged 12 to 17 years, if weight remains above the 90th percentile with the 2 mg once daily subcutaneous injection and additional weight loss is desired, the dose may be increased to 2.5 mg with a maximum dose of 3 mg once daily (Table 1).

Table 1 Dose titration in adults and paediatric patients 12 years of age or more

Week	Daily dose	Volume to be injected
Weeks 1 - 2	1 mg once daily	0.1 ml once daily
Week 3 and onward	2 mg once daily	0.2 ml once daily
If clinical response is insufficient and 2 mg dose once daily is well tolerated	2.5 mg once daily	0.25 ml once daily
If clinical response is insufficient and 2.5 mg dose once daily is well tolerated	3 mg once daily	0.3 ml once daily

Paediatric population (children aged 6 to <12 years)

For patients aged 6 to <12 years, the starting dose is a 0.5 mg once daily subcutaneous injection for 2 weeks. If tolerated after 2 weeks, the dose can be increased to 1 mg once daily. If dose escalation is not tolerated, paediatric patients may maintain administration of the 0.5 mg once daily dose. If the 1 mg dose is tolerated after 2 weeks, the dose can be increased to 2 mg once daily. If weight remains above the 90th percentile with the 2 mg once daily subcutaneous injection and additional weight loss is desired, the dose may be increased to 2.5 mg once daily (Table 2).

Table 2 Dose titration for paediatric patients from 6 to <12 years of age

Week	Daily dose	Volume to be injected
Weeks 1 - 2	0.5 mg once daily	0.05 ml once daily
Weeks 3 - 4	1 mg once daily	0.1 ml once daily
Week 5 and onward	2 mg once daily	0.2 ml once daily
If clinical response is insufficient and 2 mg dose once daily is well tolerated	2.5 mg once daily	0.25 ml once daily

Paediatric population (children aged 2 to <6 years)

For patients aged 2 to <6 years, the dose titration in Table 3 should be followed.

For patients aged 2 to <6 years, the starting dose is a 0.5 mg once daily subcutaneous injection for 2 weeks. If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, continue dose titration.

Table 3 Dose titration for paediatric patients from 2 to <6 years of age

Patient weight/treatment week	Daily dose	Volume to be injected
<20 kg		
Week 1 and onward	0.5 mg once daily	0.05 ml once daily
20-<30 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if clinical response is insufficient and 0.5 mg dose is well tolerated)	1 mg once daily	0.1 ml once daily
30-<40 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily

Week 5 and onward (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily
≥40 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
Weeks 5-6 (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily
Weeks 7-8 (if clinical response is insufficient and 1.5 mg dose once daily is well tolerated)	2 mg once daily	0.2 ml once daily
Week 9 and onward (if clinical response is insufficient and 2 mg dose once daily is well tolerated)	2.5 mg once daily	0.25 ml once daily

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 (see section 4.4).

Weight loss and control of hunger associated with setmelanotide can be maintained as long as the therapy is continued uninterrupted. If treatment is discontinued, or if compliance to the dosing regimen is not maintained, symptoms of POMC and LEPR deficiency obesity will return.

Evaluate weight loss after 12-16 weeks of treatment. If a patient has not lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential, discontinue IMCIVREE as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Bardet-Biedl Syndrome

Adult population and children more than 16 years of age

For adults and children 16 to 17 years of age, the dose titration in Table 4 should be followed.

Table 4 Dose titration in adults and paediatric patients 16 years of age or more

Week	Daily dose	Volume to be injected
Weeks 1-2	2 mg once daily	0.2 ml once daily
Week 3 and onward (if 2 mg dose once daily is well tolerated)	3 mg once daily	0.3 ml once daily

If the 2 mg starting dose is not tolerated, reduce to 1 mg (0.1 ml) once daily. If the 1 mg once daily dose is tolerated, continue dose titration.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If reduced dose is tolerated, continue dose titration.

Paediatric population (children aged 6 to <16 years)

For patients aged 6 to <16 years, the dose titration in Table 5 should be followed.

Table 5 Dose titration for paediatric patients from 6 to <16 years of age

Week	Daily dose	Volume to be injected
Week 1	1 mg once daily	0.1 ml once daily
Week 2 (if 1 mg dose once daily is well tolerated)	2 mg once daily	0.2 ml once daily

Week 3 and onward (if 2 mg dose once daily is well tolerated)	3 mg once daily	0.3 ml once daily

If the 1 mg starting dose is not tolerated, reduce to 0.5 mg (0.05 ml) once daily. If the 0.5 mg once daily dose is tolerated, increase the dose to 1 mg once daily and continue dose titration.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

Paediatric population (children aged 2 to <6 years)

For patients aged 2 to <6 years, the dose titration in Table 6 should be followed.

For patients aged 2 to <6 years, the starting dose is a 0.5 mg once daily subcutaneous injection for 2 weeks. If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, continue dose titration.

Table 6 Dose titration for paediatric patients from 2 to <6 years of age

Patient weight/treatment week	Daily dose	Volume to be injected
<20 kg		
Week 1 and onward	0.5 mg once daily	0.05 ml once daily
20-<30 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if clinical response is insufficient and 0.5 mg dose is well tolerated)	1 mg once daily	0.1 ml once daily
30-<40 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
Week 5 and onward (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily
≥40 kg		
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
Weeks 5-6 (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily
Weeks 7-8 (if clinical response is insufficient and 1.5 mg dose once daily is well tolerated)	2 mg once daily	0.2 ml once daily
Week 9 and onward (if clinical response is insufficient and 2 mg dose once daily is well tolerated)	2.5 mg once daily	0.25 ml once daily

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 (see section 4.4).

Weight loss and control of hunger associated with setmelanotide can be maintained as long as the therapy is continued uninterrupted. If treatment is discontinued, or if compliance to the dosing regimen is not maintained, symptoms of obesity and/or hunger in BBS will return.

Missed dose

If a dose is missed, the once daily regimen should be resumed at the dose prescribed with the next scheduled dose.

Special populations

Renal impairment

POMC, including PCSK1, deficiency and LEPR deficiency

For adults and children 2 to 17 years of age with mild or moderate renal impairment (see section 5.2), no dose adjustments are necessary.

For adults and children 12 to 17 years of age with severe renal impairment (see section 5.2), the dose titration in Table 7 should be followed.

Table 7 Dose titration in adults and paediatric patients 12 years of age or more with severe renal impairment

Week	Daily dose	Volume to be injected
Weeks 1 - 2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
If clinical response is insufficient and 1 mg dose once daily is well tolerated	2 mg once daily	0.2 ml once daily
If clinical response is insufficient and 2 mg dose once daily is well tolerated	2.5 mg once daily	0.25 ml once daily
If clinical response is insufficient and 2.5 mg dose once daily is well tolerated	3 mg once daily	0.3 ml once daily

If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, continue dose titration.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

For patients aged 6 to <12 years of age with severe renal impairment, the dose titration in Table 8 should be followed.

Table 8 Dose titration for paediatric patients from 6 to <12 years of age with severe renal impairment

Week	Daily dose	Volume to be injected
Weeks 1 - 2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if 0.5 mg once daily is well tolerated)	1 mg once daily	0.1 ml once daily
If clinical response is insufficient and 1 mg dose once daily is well tolerated	2 mg once daily	0.2 ml once daily

If the 0.25 mg starting dose is not tolerated, treatment should be discontinued.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

Setmelanotide has not been studied in patients aged 2 to <6 years of age with severe renal impairment. Dose titration should be guided by tolerability (Table 9) and patients should be monitored closely.

Table 9 Dose titration for paediatric patients from 2 to <6 years of age with severe renal impairment

Patient weight/treatment week	Daily dose	Volume to be injected
<20 kg		
Week 1 and onward	0.25 mg once daily	0.025 ml once daily
20-<30 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Week 3 and onward (if clinical response is	0.5 mg once daily	0.05 ml once daily
insufficient and 0.25 mg dose is well tolerated)		
30-<40 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
≥40 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Weeks 5-6 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
Weeks 7 and onward (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily

If the 0.25 mg starting dose is not tolerated, treatment should be discontinued.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

Setmelanotide has not been studied in patients with end-stage renal disease. Setmelanotide should not be administered to patients with end-stage renal disease (see section 5.2).

Bardet-Biedl Syndrome

For adults and children 2 to 17 years of age with mild or moderate renal impairment (see section 5.2), no dose adjustments are necessary.

For adults and children 16 to 17 years of age with severe renal impairment (see section 5.2), the dose titration in Table 10 should be followed.

Table 10 Dose titration in adults and paediatric patients 16 years of age or more with severe renal impairment

Week	Daily dose	Volume to be injected
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
If clinical response is insufficient and 1 mg dose once daily is well tolerated	2 mg once daily	0.2 ml once daily
If clinical response is insufficient and 2 mg dose once daily is well tolerated	2.5 mg once daily	0.25 ml once daily
If clinical response is insufficient and 2.5 mg dose once daily is well tolerated	3 mg once daily	0.3 ml once daily

If the 0.5 mg starting dose is not tolerated, reduce to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, continue dose titration.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

For patients aged 6 to <16 years of age with severe renal impairment, the dose titration in Table 11 should be followed

Table 11 Dose titration for paediatric patients from 6 to <16 years of age with severe renal impairment

Week	Daily dose	Volume to be injected
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if 0.5 mg once daily is well tolerated)	1 mg once daily	0.1 ml once daily
If clinical response is insufficient and 1 mg dose once daily is well tolerated	2 mg once daily	0.2 ml once daily

If the 0.25 mg starting dose is not tolerated, treatment should be discontinued.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

Setmelanotide has not been studied in patients aged 2 to <6 years of age with severe renal impairment. Dose titration should be guided by tolerability (Table 12) and patients should be monitored closely.

Table 12 Dose titration for paediatric patients from 2 to <6 years of age with severe renal impairment

Patient weight/treatment week	Daily dose	Volume to be injected
<20 kg		
Week 1 and onward	0.25 mg once daily	0.025 ml once daily
20-<30 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Week 3 and onward (if clinical response is insufficient and 0.25 mg dose is well tolerated)	0.5 mg once daily	0.05 ml once daily
30-<40 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
≥40 kg		
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if clinical response is insufficient and 0.25 mg dose once daily is well tolerated)	0.5 mg once daily	0.05 ml once daily
Weeks 5-6 (if clinical response is insufficient and 0.5 mg dose once daily is well tolerated)	1 mg once daily	0.1 ml once daily
Weeks 7 and onward (if clinical response is insufficient and 1 mg dose once daily is well tolerated)	1.5 mg once daily	0.15 ml once daily

If the 0.25 mg starting dose is not tolerated, treatment should be discontinued.

Following the starting dose, if a subsequent dose is not tolerated, reduce to the previous dose level. If the reduced dose is tolerated, continue dose titration.

Setmelanotide has not been studied in patients with end-stage renal disease. Setmelanotide should not be administered to patients with end-stage renal disease (see section 5.2).

Hepatic impairment

Setmelanotide has not been studied in patients with hepatic impairment. Setmelanotide should not be administered to patients with hepatic impairment.

Paediatric population (<2 years)

The safety and efficacy of setmelanotide in children less than 2 years of age has not yet been established. No data are available.

Elderly

Although no apparent age-related differences have been observed, data obtained from elderly patients is not sufficient to determine whether they respond differently from younger patients. There is no evidence indicating any special precautions are required for treating an elderly population (see section 5.2).

Method of administration

For subcutaneous use.

Setmelanotide should be injected once daily, at the beginning of the day (to maximise hunger reduction during awake period), without regard to the timing of meals.

Setmelanotide should be injected subcutaneously in the abdomen, alternating the abdominal area each day.

Prior to initiation of treatment, patients should be trained by their healthcare professional on proper injection technique, to reduce the risk of administration errors such as needle sticks and incomplete dosing. Refer to the patient leaflet for complete administration instructions with illustrations.

Setmelanotide should be administered using the syringe volumes and needle sizes shown in Table 13.

Table 13 Administration syringe and needle size, by setmelanotide dose

Setmelanotide dose	Syringe	Needle gauge and length
For doses of: 0.25 mg (0.025 ml or 2.5 units) once daily	0.3 ml syringe with 0.5 (half) unit increments	29 to 31 gauge 6 to13 mm needle
For doses of: 0.5 mg to 3 mg (0.05 ml to 0.3 ml) once daily	1 ml syringe with 0.01 ml dosing increments	28 to 29 gauge 6 to 13 mm needle

See section 6.6 for instructions on handling IMCIVREE.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Skin monitoring

Setmelanotide may lead to generalised increased skin pigmentation and darkening of pre-existing nevi because of its pharmacologic effect (see sections 4.8 and 5.1). 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 (see section 4.8). 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 (see section 4.8).

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

Benzyl alcohol
This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions.

There is an increased risk due to accumulation of benzyl alcohol in young children (less than 3 years old). Patients aged 2 years old should be monitored for any sign of metabolic acidosis (tachycardia, rapid breathing, confusion) while under treatment.

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 (see also section 4.2).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free."

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In vitro studies showed that setmelanotide has low potential for pharmacokinetic interactions related to cytochrome P450 (CYP) transporters and plasma protein binding.

4.6 Fertility, pregnancy, and lactation

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 (see section 5.3).

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 foetal 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.

Patients who are pregnant should be advised of the potential risk from the excipient benzyl alcohol (see section 4.4).

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 (see section 5.3).

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.

Patients who are breastfeeding should be advised of the potential risk from the excipient benzyl alcohol (see section 4.4).

Fertility

No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

IMCIVREE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are hyperpigmentation disorders (67%), injection site reactions (46%), nausea (36%), and headache (20%).

Tabulated list of adverse reactions

Adverse reactions observed in clinical trials are listed below by system organ class and frequency, following the MedDRA frequency convention defined as: very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1000 to <1/100).

Table 14 Adverse reactions

MedDRA System organ class	Frequency		
	Very common	**Common**	**Uncommon**
Skin and subcutaneous tissue disorders	Hyperpigmentation disorders[a]	Pruritus, rash, dry skin, skin lesion, alopecia	Erythema, skin striae, hyperhidrosis, lipodystrophy acquired, urticaria, skin exfoliation
General disorders and administrative site conditions	Injection site reactions[a], fatigue	Asthenia, pain	Temperature intolerance, chills
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, abdominal pain, dry mouth, dyspepsia, constipation, abdominal discomfort, gastrooesophageal reflux disease	Gingival discolouration, abdominal distension, salivary hypersecretion, flatulence
Hepatobiliary disorders			Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased
Nervous system disorders	Headache	Dizziness	Somnolence, migraine, parosmia, dysguesia,
Reproductive system and breast disorders	Spontaneous penile erection [b], erection increased[b]	Vulvovaginal discomfort[c]	Female sexual arousal disorder[c], genital discomfort, genital disorder female[c], genital hyperaesthesia, dysmenorrhoea[c]
Psychiatric disorders		Depression, insomnia, disturbance in sexual arousal, libido increased	Sleep disorder, nightmare, libido decreased
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)	Melanocytic naevus		Dysplastic naevus

MedDRA System organ class	Frequency		
	Very common	Common	Uncommon
Blood and lymphatic system disorders		Eosinophilia	
Musculoskeletal and connective tissue disorders		Back pain, myalgia, muscle spasms	Arthralgia, musculoskeletal pain, pain in extremity, blood creatine phosphokinase increased
Respiratory, thoracic and mediastinal disorders		Cough	Yawning, rhinorrhoea
Eye disorders			Scleral discolouration
Vascular disorders			Hot flush
Ear and labyrinth disorders			Vertigo
Metabolism and nutritional disorders			Appetite disorder, thirst

[a] Grouped term (see "Description of selected adverse reactions" for full list of terms included).
[b] Male-only denominator.
[c] Female-only denominator.

Description of selected adverse reactions

Injection site reactions
Injection site reactions occurred in 46% of patients treated with setmelanotide. The most common injection site reactions were injection site erythema (28%), injection site pruritus (21%), injection site induration (16%), and injection site pain (16%). These reactions were typically mild, of short duration, and did not progress or lead to discontinuation of therapy. Injection site reactions include injection site-associated events of erythema, pruritus, oedema, pain, induration, bruising, swelling, haemorrhage, hypersensitivity, haematoma, nodule, discolouration, irritation, warmth, hypertrophy and urticaria.

Hyperpigmentation disorders
Skin darkening was observed in 67% of patients treated with setmelanotide. This generally occurred within 2 to 3 weeks of starting therapy, continued for the duration of treatment, and resolved upon discontinuation of treatment. This darkening of skin is mechanism based, resulting from stimulation of the MC1 receptor. Hyperpigmentation disorders include skin hyperpigmentation, skin discolouration, ephelides, hair colour changes, lentigo, macule, nail discolouration, melanoderma, pigmentation disorder, solar lentigo, acanthosis, nigricans, café au lait spots, nail pigmentation, pigmentation lip, tongue pigmentation, gingival hyperpigmentation and oral pigmentation.

Gastrointestinal disturbance
Nausea and vomiting were reported in 36% and 16% of patients, respectively, treated with setmelanotide. Nausea and vomiting generally occurred at initiation of therapy (within the first month), was mild and did not lead to discontinuation of therapy. These effects were transient and did not impact compliance with the recommended daily injections.

Penile erections
Spontaneous penile erection and erection increased were reported in 16% and 14% of male patients treated with setmelanotide, respectively; none of these patients reported prolonged erections (longer than 4 hours) requiring urgent medical evaluation (see section 4.4). This effect may be due to melanocortin 4 (MC4) receptor neural stimulation.

Immunogenicity

Due to the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with setmelanotide. There was no observation of

a rapid decline in setmelanotide concentrations that would suggest the presence of anti-drug antibodies. In clinical trials (RM-493-012 and RM-493-015), the rate of adult and paediatric patients with POMC- or LEPR-deficiency who screened positive for antibody to setmelanotide was 68% (19 out of 28), and 32 % screened negative. The 68% of patients who screened positive for antibodies to setmelanotide were inconclusive for antibodies to setmelanotide in the confirmatory assay.

Approximately 13% of adult and paediatric patients aged 6 to <18 years with LEPR-deficiency (3 patients) confirmed positive for antibodies to alpha-MSH that were classified as low-titre and non-persistent. Of these 3 patients (13%), 2 tested positive post-IMCIVREE treatment and 1 was positive pre-treatment. None of the patients with POMC-deficiency were confirmed to have antibodies to alpha-MSH.

One paediatric patient with BBS aged ≥12 years confirmed positive to setmelanotide anti-drug antibodies with a very low titre.

Paediatric population

A total of 221 paediatric patients (n=12 aged 2 to <6 years; n=72 aged 6 to <12 years, n=137 aged 12 to <18 years) have been exposed to setmelanotide, including 21 paediatric patients with POMC or LEPR deficiency obesity who participated in the pivotal clinical trials (n=7 aged 2 to <6 years; n=6 aged 6 to <12 years, n=8 aged 12 to <18 years) and 33 paediatric patients with BBS (n=5 aged 2 to <6 years; n=8 aged 6 to <12 years, n=20 aged 12 to <18 years). The frequency, type and severity of adverse reactions were similar in the adult and paediatric populations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

The symptoms of setmelanotide overdose may include nausea and penile erection. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. In cases of overdose, blood pressure and heart rate should be monitored regularly over 48 hours or as long as clinically relevant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-obesity preparations, excl. diet products, centrally acting anti-obesity products, ATC code: A08AA12

Mechanism of action

Setmelanotide is a selective MC4 receptor agonist. MC4 receptors 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 is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

Pharmacodynamic effects

Skin pigmentation

Setmelanotide is a selective MC4 receptor agonist with less activity at the melanocortin 1 (MC1) receptor. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light (see sections 4.4 and 4.8).

Clinical efficacy and safety

POMC, including PCSK1, deficiency and LEPR deficiency

The safety and efficacy of setmelanotide for the treatment of POMC and LEPR deficiency obesity were established in 2 identically designed, 1-year open-label pivotal studies, each with a double-blind, placebo-controlled withdrawal period:

- Study 1 (RM-493-012) enrolled patients aged 6 years and above with genetically confirmed POMC (including PCSK1) deficiency obesity.
- Study 2 (RM-493-015) enrolled patients aged 6 years and above with genetically confirmed LEPR deficiency obesity.

In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m^2. Weight in children was ≥95th percentile using growth chart assessment.

Dose titration occurred over a 2- to 12-week period, followed by a 10-week open-label treatment period. Patients who achieved at least a 5 kg weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the open-label treatment period continued into a double-blind, placebo-controlled, withdrawal period lasting 8 weeks (4-week placebo treatment and 4-week setmelanotide treatment). Following the withdrawal sequence, patients re-initiated active treatment with setmelanotide at the therapeutic dose for up to 32 weeks. Twenty-one patients (10 in Study 1 and 11 in Study 2) have been treated for at least 1 year and are included in the efficacy analyses.

Additional supportive data were gathered in an investigator-led study and an ongoing extension study.

Study 1 (RM-493-012)

In Study 1, 80% of patients with POMC deficiency obesity met the primary endpoint, achieving a ≥10% weight loss after 1 year of treatment with setmelanotide and 50% of patients with POMC deficiency obesity achieved a predefined clinically meaningful ≥25% improvement in hunger score from baseline at 1 year (Table 15).

Statistically significant and clinically meaningful mean percent decreases from baseline for body weight of 25.6% were reported for Study 1. Changes in hunger were assessed using a patient and caregiver questionnaire completed daily for 'most hunger over the last 24 hours' at 1 year for patients ≥12 years of age. Statistically significant and clinically meaningful mean percent decreases from baseline for hunger as a weekly average in the last 24 hours of 27.1% were reported for Study 1 (Table 16).

When treatment with setmelanotide was withdrawn in patients who had lost weight during the 10-week open-label period, these patients gained weight (Figure 1) and the mean hunger scores increased over the 4 weeks of placebo treatment.

Table 15 Proportion of patients achieving at least 10% weight loss and the proportion of patients achieving at least 25% improvement in daily hunger from baseline at 1 year in Study 1

Parameter		Statistic
Patients achieving at least 10% weight loss at 1 year (N=10)	n (%)	8 (80.0%)
	90% CI[1]	(49.31%, 96.32%)
	P-value[2]	<0.0001
Patients achieving at least 25% hunger improvement from baseline at 1 year (N=8)	n (%)	4 (50.0)
	90% CI[1]	(19.29, 80.71)
	P-value[1]	0.0004

Note: The analysis set includes patients who received at least 1 dose of study drug and had at least 1 baseline assessment.

1 From the Clopper-Pearson (exact) method

2 Testing the null hypothesis: proportion =5%

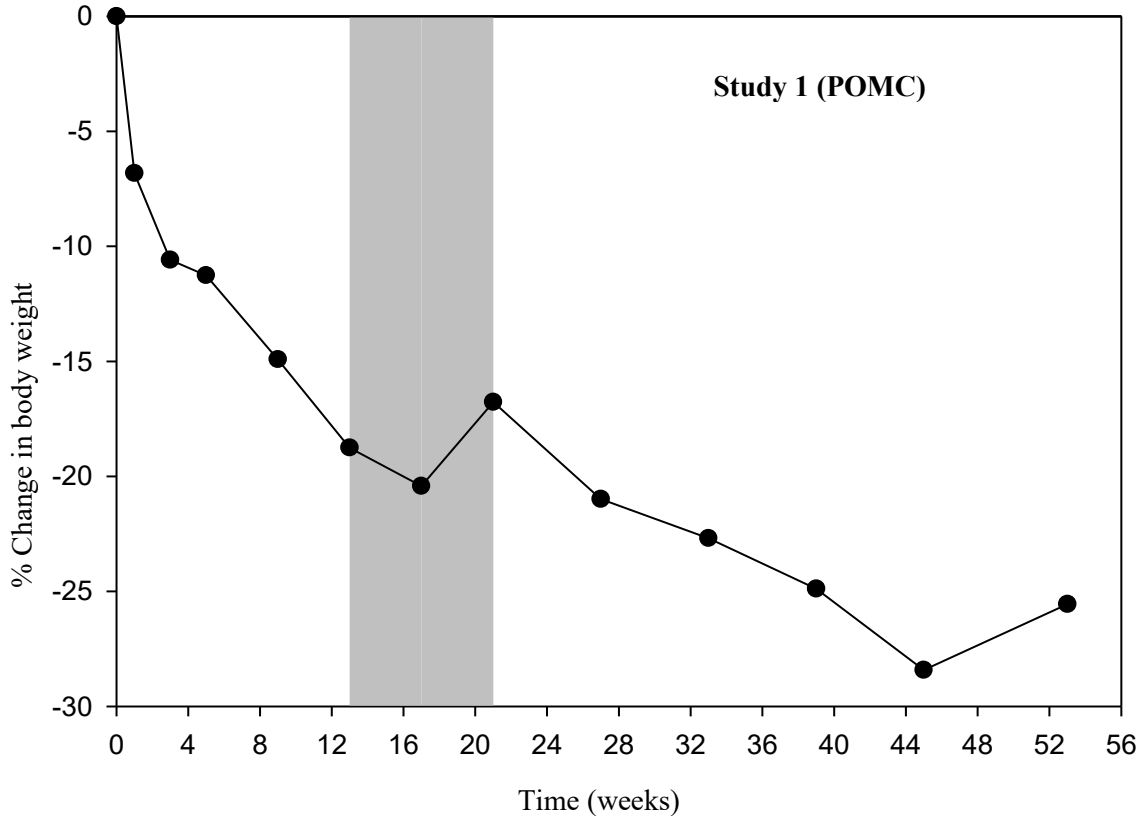
Table 16 Percent change from baseline in weight and hunger at 1 year in Study 1

Parameter	Statistic	Body weight (kg) (N=9)	Hunger score[1] (N=7)
Baseline	Mean (SD)	115.0 (37.77)	8.1 (0.78)
	Median	114.7	8.0
	Min, Max	55.9, 186.7	7, 9
1 year	Mean (SD)	83.1 (21.43)	5.8 (2.02)
	Median	82.7	6.0
	Min, Max	54.5, 121.8	3, 8
Percent change from baseline to 1 year (%)	Mean (SD)	-25.6 (9.88)	-27.06 (28.11)
	Median	-27.3	-14.29
	Min, Max	-35.6, -2.4	-72.2, -1.4
	LS Mean	-25.39	-27.77
	90% CI	(-28.80, -21.98)	(-40.58, -14.96)
	P-value	<0.0001	0.0005

Note: This analysis includes patients who received at least one dose of study drug, had at least one baseline assessment, and demonstrated ≥5 kg weight loss (or 5% of body weight if weight was <100 kg at baseline) over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal period.

[1] Hunger ranges from 0 to 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary and was averaged to calculate a weekly score for analysis.

Figure 1 Percent body weight change from baseline by visit (Study 1 [N=9])



Study 2 (RM-493-015)

In Study 2, 46% of patients with LEPR deficiency obesity met the primary endpoint, achieving a ≥10% weight loss after 1 year of treatment with setmelanotide and 73% of patients with LEPR deficiency obesity achieved a predefined clinically meaningful ≥25% improvement in hunger score from baseline at 1 year (Table 17).

Statistically significant and clinically meaningful mean percent decreases from baseline for body weight of 12.5% were reported for Study 2. Changes in hunger were assessed using a patient and caregiver questionnaire completed daily for 'most hunger over the last 24 hours' at 1 year for patients ≥12 years of age. Statistically significant and clinically meaningful mean percent decreases from baseline for hunger as a weekly average in the last 24 hours of 43.7% were reported for Study 2 (Table 18).

When treatment with setmelanotide was withdrawn in patients who had lost weight during the 10-week open-label period, these patients gained weight (Figure 2) and the mean hunger scores increased over the 4 weeks of placebo treatment.

Table 17 Proportion of patients achieving at least 10% weight loss and the proportion of patients achieving at least 25% improvement in daily hunger from baseline at 1 year in Study 2

Parameter		Statistic
Patients achieving at least 10% weight loss at 1 year (N=11)	n (%)	5 (45.5%)
	90% CI[1]	(19.96%, 72.88%)
	P-value[2]	0.0002
Patients achieving at least 25% hunger improvement from baseline at 1 year (N=11)	n (%)	8 (72.7)
	90% CI[1]	(43.56, 92.12)
	P-value[1]	<0.0001

Note: The analysis set includes patients who received at least 1 dose of study drug and had at least 1 baseline assessment.

1 From the Clopper-Pearson (exact) method

2 Testing the null hypothesis: proportion =5%

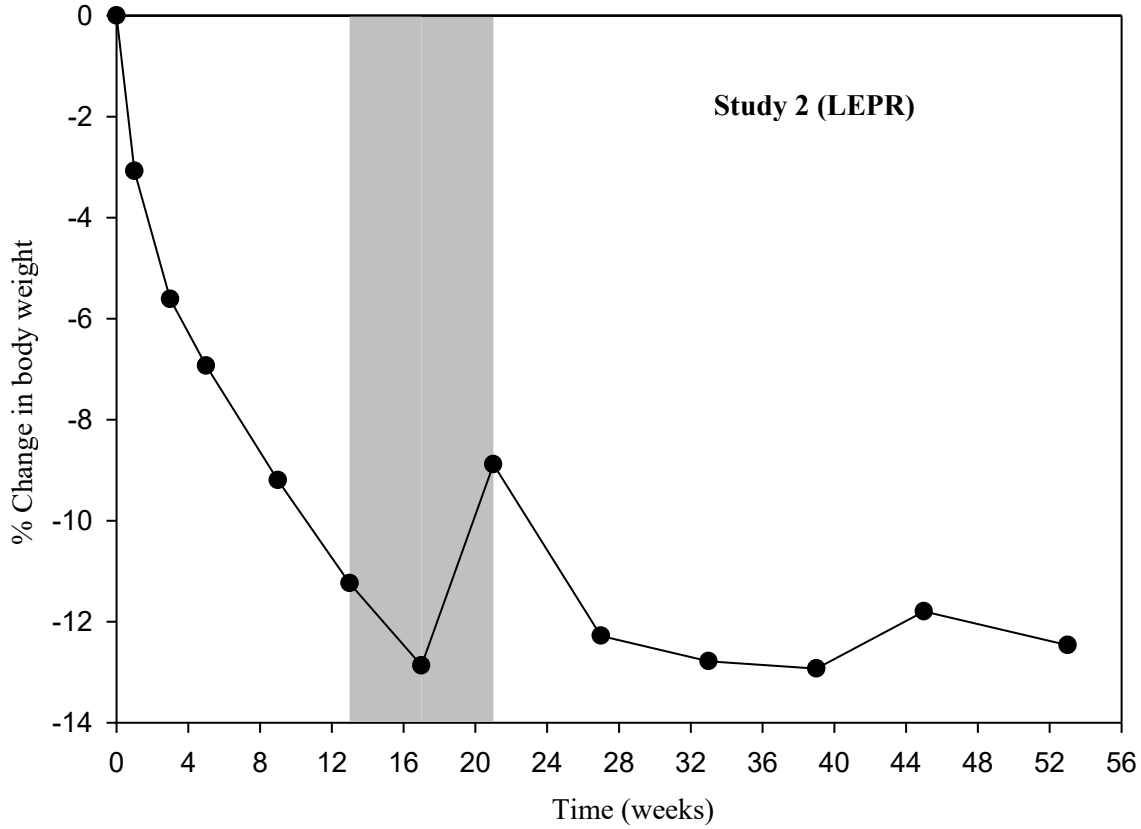
Table 18 Percent change from baseline in weight and hunger at 1 year in Study 2

Parameter	Statistic	Body weight (kg) (N=7)	Hunger score[1] (N=7)
Baseline	Mean (SD)	131.7 (32.6)	7.0 (0.77)
	Median	120.5	7.0
	Min, Max	89.4, 170.4	6, 8
1 year	Mean (SD)	115.0 (29.6)	4.1 (2.09)
	Median	104.1	3.0
	Min, Max	81.7, 149.9	2, 8
Percent change from baseline to 1 year (%)	Mean (SD)	-12.5 (8.9)	-43.7 (23.69)
	Median	-15.3	-52.7
	Min, Max	-23.3, 0.1	-67, 0
	LS Mean	-12.47	-41.93
	90% CI	(-16.10, -8.83)	(-54.76, -29.09)
	P-value	<0.0001	<0.0001

Note: This analysis includes patients who received at least one dose of study drug, had at least one baseline assessment, and demonstrated ≥5 kg weight loss (or 5% of body weight if weight was <100 kg at baseline) over the 12-week open-label treatment period and proceeded into the double-blind, placebo-controlled withdrawal period.

[1] Hunger ranges from 0 to 10 on a Likert-type scale; 0 = not hungry at all and 10 = hungriest possible. Hunger score was captured in a daily diary and was averaged to calculate a weekly score for analysis.

Figure 2 Percent Body Weight Change from Baseline by Visit (Study 2 [N=7])



Bardet-Biedl Syndrome

Study 3 (RM-493-023)

The safety and efficacy of IMCIVREE for the treatment of patients aged 6 years and older with obesity due to BBS were assessed in a 1-year clinical study with a 14-week placebo-controlled period (Study 3 [RM-493-023]). The study enrolled patients aged 6 years and above with obesity and BBS. Adult patients had a BMI of ≥30 kg/m^2. Paediatric patients had a BMI ≥97th percentile for age and sex using growth chart assessments.

Eligible patients entered a 14-week, randomized, double-blind, placebo-controlled treatment period (Period 1) followed by a 38-week open-label treatment period (Period 2) in which all patients received setmelanotide. To maintain the blind through Period 2, dose titration to a fixed dose of 3 mg was done during the first 2 weeks of both Period 1 and Period 2. Thirty-two patients have been treated for at least 1 year and are included in the efficacy analyses.

In Study 3, 35.7% of patients with BBS aged ≥12 years and 46.7% of patients with BBS aged ≥18 years met the primary endpoint, achieving a ≥10% weight loss after 1 year of treatment with setmelanotide (Table 19). The effect of IMCIVREE on body weight in patients assessed by the investigator as cognitively impaired was similar to patients who were not cognitively impaired.

In Study 3, ~52 weeks of treatment with setmelanotide resulted in clinically meaningful reductions in BMI Z-scores occurring in 100% of the BBS patients aged <12 years, with consistent results observed in patients ≥12 and <18 years of age. In patients aged <18 years, the mean reduction from baseline in BMI Z-score was 0.75 and the mean reduction from baseline in percent of the 95th percentile for BMI for age and sex was 17.3%.

Patients 12 years and older who were able to self-report their hunger, recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was

scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible"). Statistically significant and clinically meaningful mean percent decreases from baseline at 1 year for most/worst hunger of 30.5% were reported for Study 3 (Table 20).

Table 19 Body weight (kg) – proportion of all patients, patients with BBS aged ≥12 years and patients with BBS aged ≥18 years achieving at least 10% weight loss from baseline at 1 year (Study 3 [Full Analysis Set])

Parameter	Statistic[1]	Patients ≥12 years	Patients ≥18 years
Patients achieving at least 10% weight loss at year 1	N	28	15
	%	35.7	46.7
	95% CI[1]	(18.6, 55.9)	(21.3, 73.4)
	P-value	0.0002	0.0003

1 Estimated %, 95% confidence interval and p-value are based on Rubin's Rule. P-value is one-sided and compared with alpha=0.025.

Table 20 Daily hunger scores – change from baseline at 1 year in all patients and patients with BBS aged ≥12 years (Study 3 [Full Analysis Set])

Timepoint	Statistic	Patients ≥12 years
Baseline	N	14
	Mean (SD)	6.99 (1.893)
	Median	7.29
	Min, Max	4.0, 10.0
Week 52	N	14
	Mean (SD)	4.87 (2.499)
	Median	4.43
	Min, Max	2.0, 10.0
Change at week 52	N	14
	Mean (SD)	-2.12 (2.051)
	Median	-1.69
	Min, Max	-6.7, 0.0
	95% CI [1]	-3.31, -0.94
	p-value [1]	0.0010
% Change at week 52	N	14
	Mean (SD)	-30.45 (26.485)
	Median	-25.00
	Min, Max	-77.0, 0.0
	95% CI [1]	-45.74, -15.16
	p-value [1]	0.0004

Abbreviations: CI=confidence interval; Max=maximum; Min=minimum; SD=Standard Deviation.

[1] 95% CI and p-value are based on Rubin's Rule; p-value is one-sided.

Note: Baseline is the last assessment prior to initiation of setmelanotide in both studies.

Note: The Daily Hunger Questionnaire is not administered to patients <12 years or to patients with cognitive impairment as assessed by the Investigator.

Supportive of IMCIVREE's effect on weight loss, there were general numeric improvements in cardiometabolic parameters, such as blood pressure, lipids, glycaemic parameters, and waist circumference.

Paediatric population

Study 4 (RM-493-033)

The safety and efficacy of setmelanotide for the treatment of patients aged 2 to <6 years with obesity due to POMC or LEPR deficiency or BBS were assessed in a 1-year open-label, non-controlled study (Study 4 [RM-493-033]). The study enrolled patients aged 2 to <6 years with a

BMI ≥97th percentile for age and sex using growth chart assessments and a body weight of at least 15 kg at baseline.

Eligible patients entered the study and received setmelanotide. Twelve patients were enrolled in the study and are included in the efficacy analyses. Given the study design and small sample size, efficacy findings require careful consideration.

In Study 4, 85.7% of patients with POMC or LEPR deficiency obesity and 80.0% of the patients with BBS met the primary endpoint, achieving a ≥0.2 BMI Z-score reduction after 1 year of treatment with setmelanotide (Table 21). The mean percent change from baseline to Week 52 in BMI was -25.597% for patients with POMC or LEPR deficiency obesity and -9.719% for patients with BBS (Table 22).

Table 21 BMI Z-score – proportion of all patients, patients with POMC or LEPR deficiency obesity, patients with BBS aged 2 to < 6 years achieving at least 0.2 reduction in BMI Z-score from baseline at 1 year (Study 4 [safety population])

Parameter	Statistic[1]	Patients with POMC or LEPR (n=7)	Patients with BBS (n=5)	Total (N=12)
Patients achieving at least 0.2 reduction in BMI Z-score at year 1	N	6	4	10
	%	85.7	80.0	83.3
	95% CI[1]	(54.1, 100)	(28.4, 99.5)	(58.7, 99.8)

1 Two-sided 95% CI was calculated using the Clopper-Pearson Method.

Table 22 Percent change in BMI from baseline at 1 year (Study 4 [safety population])

Parameter	Statistic	Patients with POMC or LEPR (n=7) %	Patients with BBS (n=5) %	Total (N=12) %
Baseline	N	7	5	12
	Mean (SD)	34.347 (7.0673)	23.716 (3.5184)	29.918 (7.8559)
	Median	32.196	22.986	28.670
	Min, Max	25.99, 42.54	19.31, 29.04	19.31, 42.54
Actual change from baseline to 1 year	N	6	5	11
	Mean (SD)	-8.250 (3.2392)	-2.363 (2.1579)	-5.574 (4.0697)
	Median	-9.237	-2.191	-4.940
	Min, Max	-11.16, -2.65	-4.94, 0.58	-11.16, 0.58
Percent change from baseline to 1 year (%)	N	6	5	11
	Mean (SD)	-25.597 (11.4911)	-9.719 (8.8383)	-18.380 (12.8851)
	95% CI[1]	(-37.66, -13.54)	(-20.69, 1.26)	(-27.04, -9.72)
	Median	-23.237	-8.978	-21.624
	Min, Max	-39.28, -8.24	-21.62, 2.54	-39.28, 2.54

[1] Two-sided 95% CI is calculated with Student's t-distribution.

In Study 4, ~52 weeks of treatment with setmelanotide resulted in a clinically meaningful reduction in BMI Z-score of -5.185 for patients with POMC or LEPR deficiency obesity and -1.331 for patients with BBS. The mean reduction from baseline in percent of the 95th percentile for BMI for age and sex was -47.595% for patients with POMC or LEPR deficiency obesity and -14.462% for patients with BBS.

In clinical studies, 44 of the patients treated with setmelanotide were aged 2 to 17 years at baseline (21 patients with POMC, PCSK1 or LEPR deficiency and 33 patients with BBS). Overall, efficacy and

safety in these younger patients showed similar trends as seen in older patients studied, with seemingly meaningful decreases in BMI demonstrated. In patients who had not yet completed their growth, a trend towards appropriate progression in pubertal development and increases in height were observed during the study period.

5.2 Pharmacokinetic properties

The mean steady state setmelanotide $C_{max,ss}$, AUC_{tau}, and trough concentration for a 3 mg dose administered subcutaneously to otherwise healthy volunteers with obesity (N=6) once daily for 12 weeks were 37.9 ng/ml, 495 h*ng/ml, and 6.77 ng/ml, respectively. Steady-state plasma concentrations of setmelanotide were achieved within 2 days with daily dosing of 1-3 mg setmelanotide. The accumulation of setmelanotide in the systemic circulation during once-daily dosing over 12 weeks was approximately 30%. Setmelanotide AUC and C_{max} increased proportionally following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

A population PK model comprised of 410 subjects pooled from 11 studies was conducted. These subjects contributed 7087 observations, of which 6847 samples had quantifiable setmelanotide concentrations. The PK data were predominantly from 271 adults and 87 adolescents (aged 12 to <18 years). There were also 41 children aged 6 to <12 years and 11 children aged 2 to <6 years. The population consisted of 166 males and 244 females with ages ranging from 2 to 78 years (mean = 29.7 years) and weights ranging from 17.8 to 246 kg(mean = 113 kg). The pooled population included 329 subjects with POMC, PCSK1, or LEPR deficiency, BBS, or other rare genetic diseases of obesity (80.2%) and 81 subjects without POMC, PCSK1, or LEPR deficiency, BBS, or other rare genetic diseases of obesity (19.8%); all subjects without POMC, PCSK1 or LEPR deficiency, BBS, or other rare genetic diseases of obesity were adults.

Absorption

After subcutaneous injection of setmelanotide, steady-state plasma concentrations of setmelanotide increased slowly, reaching maximum concentrations at a median t_{max} of 8.0 hours after dosing. The absolute bioavailability following subcutaneous administration of setmelanotide has not been investigated in humans. Estimate of the inter-individual variability (CV%) from the final population PK model was 39.9% (CL/F).

The PK of setmelanotide in patients with BBS was similar to that obtained in the population of patients with POMC, PCSK1, and LEPR deficiency, suggesting the disease state alone does not impact the PK of setmelanotide.

Distribution

The mean apparent volume of distribution of setmelanotide after subcutaneous administration of setmelanotide 3 mg once daily was estimated from the population PK model to be 75.2L. Setmelanotide binding to human plasma protein is 79.1%.

In vitro experiments indicate that setmelanotide is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

In vitro data indicate that setmelanotide is very unlikely a P-gp or BCRP substrate.

Biotransformation

Setmelanotide did not appear to be metabolised by rat, monkey, or human hepatic microsomes or hepatocytes, or kidney microsomes.

Elimination

The effective elimination half-life (t½) of setmelanotide was approximately 11 hours. The total apparent steady state clearance of setmelanotide following subcutaneous administration of 3 mg once daily was estimated from the population PK model to be 7.15 L/h.

Approximately 39% of the administered setmelanotide dose was excreted unchanged in urine during the 24-hour dosing interval following subcutaneous administration of 3 mg once daily.

Linearity/non-linearity

Setmelanotide AUC and C_{max} increased approximately linearly with dose following multiple-dose subcutaneous administration in the range of 0.5 mg to 5 mg.

Special populations

Paediatric population

Setmelanotide has been evaluated in paediatric patients (aged 2 to 17 years). Simulations from the population PK analyses suggest slightly higher exposure in younger patients (who also have lower body weight) and provide support for the dosing regimen in patients 2 years and older.

Elderly population

Available data in a small sample of elderly patients suggest no marked changes in setmelanotide exposure with increased age. However, these data are too limited to draw definite conclusions.

Renal impairment

Pharmacokinetic analysis showed a 12%, 26%, and 49% lower clearance (CL/F) of setmelanotide in patients with mild, moderate, and severe renal impairment, respectively, as compared to patients with normal renal function.

POMC, including PCSK1, deficiency and LEPR deficiency

No dose adjustments for patients with mild (estimated glomerular filtration rate [eGFR] of 60-89 ml/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 ml/min/1.73 m^2) are needed. Dose adjustments are recommended for patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) (see section 4.2). Setmelanotide should not be administered to patients with end-stage renal disease (eGFR <15 ml/min/1.73 m^2) (see section 4.2).

Bardet-Biedl Syndrome

No dose adjustments for patients with mild (estimated glomerular filtration rate [eGFR] of 60-89 ml/min/1.73 m^2) or moderate renal impairment (eGFR of 30-59 ml/min/1.73 m^2) are needed. Dose adjustments are recommended for patients with severe renal impairment (eGFR 15-29 ml/min/1.73 m^2) (see section 4.2). Setmelanotide should not be administered to patients with end-stage renal disease (eGFR <15 ml/min/1.73 m^2) (see section 4.2).

Hepatic impairment

Setmelanotide is stable in human, rat, and monkey hepatocytes; therefore, a study in patients with hepatic impairment was not conducted. Setmelanotideshould not be used in patients with hepatic impairment.

Body weight

Setmelanotide CL/F varied with body weight according to a fixed allometric relationship.

Gender

No clinically significant differences in the pharmacokinetics of setmelanotide were observed based on sex.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity, fertility, teratogenicity, or postnatal development.

A developmental reproduction study in rabbits revealed increases in embryo-foetal resorption and post-implantation loss in pregnant rabbits treated with setmelanotide. These effects were attributed to extreme reductions in maternal food consumption related to the primary pharmacodynamic activity of setmelanotide. Similar reductions in food consumption and related embryo-foetal loss were not observed in a developmental reproduction study in rats. No teratogenic effects were observed in either species.

Dose-related setmelanotide concentrations were observed in milk 2 hours after subcutaneous injection in the pre-weaning phase of a pre- and postnatal development study in rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups at any dose.

In contrast to primates, variable cardiovascular effects, such as increased heart rate and blood pressure, were observed in rats and minipigs. The reason underlying those species differences remains unclear. In rat, the dose-dependent effects of setmelanotide on heart rate and blood pressure were linked to an increase in sympathetic tone and they were found to progressively diminish upon repeated daily dosing.

Minimal cytoplasmic vacuolation related to the excipient mPEG-DSPE was observed in the choroid plexus after chronic administration in adult rats and monkeys. Choroid plexus vacuolation was not observed in juvenile rats treated with setmelanotide/mPEG-DSPE from post-natal Days 7 to 55 at 9.5-times the human dose of mPEG-DSPE from 3 mg of setmelanotide on a mg/m^2/day basis.

The available carcinogenicity data in Tg.rasH2 mice indicate that setmelanotide/mPEG-DSPE does not pose a carcinogenic risk to patients, with a safety margin of 17 for setmelanotide based on AUC and a dose margin of 16 for mPEG-DSPE on a mg/m2/day basis, at the clinical dose of 3 mg/day. Due to the lack of pro-carcinogenic concern from the available non-clinical and clinical data on setmelanotide, a 2-year carcinogenicity study in rats has not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

mPEG-2000-DSPE
Mannitol
Benzyl alcohol
Carmellose sodium
Phenol
Disodium edetate
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After first use
28 days or until the expiry date (whichever is earlier).
Do not store above 30°C.

Chemical and physical in use stability has been demonstrated for 28 days at 2-30 °C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2°C to 30°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original carton in order to protect from light.

Unopened vials may be kept at room temperature, not to exceed 30°C, for up to 30 days.
or until the expiry date, whichever is sooner.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2R clear glass type I multidose vial with bromobutyl grey stopper and aluminium cap.

Pack size: 1 multidose vial.

6.6 Special precautions for disposal and other handling

IMCIVREE should be removed from the refrigerator approximately 15 minutes prior to administration. Alternatively, patients may warm the product prior to administration by rolling the vial gently between the palms of their hands for 60 seconds.

IMCIVREE should be inspected prior to each injection, and the solution should not be used if it is cloudy or contains particles.

If IMCIVREE is exposed to temperatures >30°C, it should be discarded and not used.

Always use a new syringe for each injection to prevent contamination.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Rhythm Pharmaceuticals Netherlands B.V.
Radarweg 29, 1043NX Amsterdam, Netherlands

8. LICENSE HOLDER

Medison Pharma Ltd.
Hashiloah 10, Petach-Tikva

9. REGISTRATION NUMBER

Imcivree 10 mg/ml solution for injection 171-28-37060-99

Revised in 11/2025

IMCIVREE-SPC-IL-1125-V1