SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 coloured 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 loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 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**

*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 more than 12 years of age*

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily dose</th>
<th>Volume to be injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1 - 2</td>
<td>1 mg once daily</td>
<td>0.1 ml once daily</td>
</tr>
<tr>
<td>Week 3 and onward</td>
<td>2 mg once daily</td>
<td>0.2 ml once daily</td>
</tr>
<tr>
<td>If clinical response is insufficient and 2 mg dose once daily is well tolerated</td>
<td>2.5 mg once daily</td>
<td>0.25 ml once daily</td>
</tr>
<tr>
<td>If clinical response is insufficient and 2.5 mg dose once daily is well tolerated</td>
<td>3 mg once daily</td>
<td>0.3 ml once daily</td>
</tr>
</tbody>
</table>

*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*

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily dose</th>
<th>Volume to be injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients from 6 to &lt;12 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1 - 2</td>
<td>0.5 mg once daily</td>
<td>0.05 ml once daily</td>
</tr>
<tr>
<td>Weeks 3 - 5</td>
<td>1 mg once daily</td>
<td>0.1 ml once daily</td>
</tr>
</tbody>
</table>
Week 6 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

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.

**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**

For patients with mild renal impairment (see section 5.2), 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 the 1 mg dose is tolerated after 2 weeks, the dose can be increased to 2 mg once daily.

For patients aged 6 to <12 years with mild renal impairment, the maximum dose is 2 mg once daily.

For patients more than 12 years of age, if additional weight loss is desired, the dose may be increased to 2.5 mg once daily. If the 2.5 mg once daily dose is well-tolerated, the dose can be increased to 3 mg once daily (Table 3).

Setmelanotide should not be administered to any patients with moderate or severe renal impairment.

**Table 3 Dose titration for patients with mild renal impairment**

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily dose</th>
<th>Volume to be injected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients with mild renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1 - 2</td>
<td>0.5 mg once daily</td>
<td>0.05 ml once daily</td>
</tr>
<tr>
<td>Weeks 3 - 5</td>
<td>1 mg once daily</td>
<td>0.1 ml once daily</td>
</tr>
<tr>
<td>Week 6 and onward</td>
<td>2 mg once daily</td>
<td>0.2 ml once daily</td>
</tr>
<tr>
<td><strong>Patients more than 12 years of age with mild renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If clinical response is insufficient and 2 mg dose once daily is well tolerated</td>
<td>2.5 mg once daily</td>
<td>0.25 ml once daily</td>
</tr>
<tr>
<td>If clinical response is insufficient and 2.5 mg dose once daily is well tolerated</td>
<td>3 mg once daily</td>
<td>0.3 ml once daily</td>
</tr>
</tbody>
</table>
Hepatic impairment

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

Paediatric population (<6 years)

The safety and efficacy of setmelanotide in children less than 6 years of age has not yet been established. No data are available.

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.

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.

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.

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.

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 (51%), injection site reaction (39%), nausea (33%), and headache (26%).

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 4 Adverse reactions

<table>
<thead>
<tr>
<th>MedDRA System organ class</th>
<th>Frequency</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hyperpigmentation disorders</td>
<td>Pruritis, rash, dry skin, erythema, hyperhidrosis</td>
<td>Dermal cyst, dermatitis, nail disorder alopecia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Injection site reactions</td>
<td>Fatigue, asthenia, pain, chills</td>
<td>Chest pain, temperature intolerance, feeling cold, feeling hot</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Vomiting, diarrhoea, abdominal pain, dry mouth, dyspepsia, constipation, flatulence, abdominal discomfort</td>
<td>Gingival discoloration, abdominal distention, salivary hypersecretion</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td>Somnolence, hyperaesthesia, migraine, parosmia, taste disorders</td>
<td></td>
</tr>
<tr>
<td>MedDRA System organ class</td>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Spontaneous penile erection, erection increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female sexual arousal disorder, genital discomfort, genital disorder female, genital hyperaesthesia, ejaculation disorder, libido decreased, libido increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, depressed mood, disturbance in sexual arousal, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)</td>
<td>Melanocytic naevus, Dysplastic naevus, Eye Nevis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain, myalgia, muscle spasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia, musculoskeletal chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Yawning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Scleral discolouration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Ocular icterus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Description of selected adverse reactions**

**Injection site reactions**
Injection site reactions occurred in 39% of patients treated with setmelanotide. The most common injection site reactions were injection site erythema (24%), injection site pruritus (17%), injection site induration (11%), and injection site pain (10%). 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, reaction, swelling, haemorrhage, hypersensitivity, haematoma, nodule, discoloration, erosion, inflammation, irritation, warmth, atrophy, dryness, hypertrophy, rash, scab, scar, and urticaria.

**Hyperpigmentation**
Skin darkening was observed in 51% 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 macule, skin hyperpigmentation, skin discoloration, lentigo, acanthosis nigricans, hair colour changes, nail discoloration, pigmentation disorder, skin hypopigmentation, acanthosis, ephelides, melanocytic hyperplasia, melanoderma, nail pigmentation, pigmentation lip, solar lentigo, oral mucosal discoloration, and tongue discoloration.

**Gastrointestinal disturbance**

Nausea and vomiting were reported in 33% and 12.4% of patients, respectively, treated with setmelanotide. Nausea 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**

Penile erection, erection increased, and ejaculation disorder were reported in 19%, 7%, and <1% of patients treated with setmelanotide, respectively; none of these patients reported prolonged erections (greater 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 23% of adult and paediatric patients 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 (23%), 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.

**Paediatric population**

A total of 74 paediatric patients (n=11 aged 6 to <12 years, n=63 aged 12 to <18 years) have been exposed to setmelanotide, including 14 paediatric patients with POMC or LEPR deficiency obesity who participated in the pivotal clinical trials (n=6 aged 6 to <12 years, n=8 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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: not yet assigned, 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

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/m². 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 5).

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 6).

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 5 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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving at least 10% weight loss at 1 year (N=10)</td>
<td>8 (80.0%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>90% CI</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients achieving at least 25% hunger improvement from baseline at 1 year (N=8)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>90% CI</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

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

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

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 7).

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 8).

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 7 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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>n (%)</th>
<th>90% CI1</th>
<th>P-value2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving at least 10% weight loss at 1 year (N=11)</td>
<td></td>
<td>5 (45.5%)</td>
<td>(19.96%, 72.88%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Patients achieving at least 25% hunger improvement from baseline at 1 year (N=11)</td>
<td></td>
<td>8 (72.7)</td>
<td>(43.56, 92.12)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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 8 Percent change from baseline in weight and hunger at 1 year in Study 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Body weight (kg) (N=7)</th>
<th>Hunger score1 (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>131.7 (32.6)</td>
<td>7.0 (0.77)</td>
</tr>
<tr>
<td>Median</td>
<td>120.5</td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>89.4, 170.4</td>
<td>6, 8</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>Mean (SD)</td>
<td>115.0 (29.6)</td>
<td>4.1 (2.09)</td>
</tr>
<tr>
<td>Median</td>
<td>104.1</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>81.7, 149.9</td>
<td>2, 8</td>
<td></td>
</tr>
<tr>
<td>Percent change from baseline to 1 year (%)</td>
<td>Mean (SD)</td>
<td>-12.5 (8.9)</td>
<td>-43.7 (23.69)</td>
</tr>
<tr>
<td>Median</td>
<td>-15.3</td>
<td></td>
<td>-52.7</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-23.3, 0.1</td>
<td>-67, 0</td>
<td></td>
</tr>
<tr>
<td>LS Mean</td>
<td>-12.47</td>
<td>-41.93</td>
<td></td>
</tr>
<tr>
<td>90% CI</td>
<td>(-16.10, -8.83)</td>
<td>(-54.76, -29.09)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

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.
**Parameter** | **Statistic** | **Body weight (kg)** (N=7) | **Hunger score**<sup>†</sup> (N=7)
--- | --- | --- | ---
Body weight (kg) | Hungry score<sup>1</sup> | (N=7) | (N=7)

<sup>1</sup>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])**

**Paediatric population**

In clinical studies, 14 of the patients treated with setmelanotide were aged 6 to 17 years at baseline. Overall, efficacy and safety in these younger patients were similar to older patients studied. Significant decreases in BMI were demonstrated. In patients who had not yet completed their growth, appropriate progression in pubertal development and increases in height were observed during the study period.

The European Medicines Agency has deferred the obligation to submit the results of studies with setmelanotide in one or more subsets of the paediatric population in treatment of appetite and general nutrition disorders (see section 4.2 for information on paediatric use).
5.2 Pharmacokinetic properties

The mean steady state setmelanotide $C_{\text{max,ss}}$, $\text{AUC}_{\text{tau}}$, and trough concentration for a 3 mg dose administered subcutaneously to healthy obese volunteers (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 $C_{\text{max}}$ increased proportionally following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

A population PK model comprised of 120 subjects in 8 studies in healthy obese patients or patients with rare genetic disorders of obesity was conducted. The study population consisted of 51 males and 69 females with ages ranging from 10 to 65 years and weights ranging from 55.9 to 209 kg. There were 4 children ages 10 to <12 years and 19 adolescents ages 12 to <17 years in the dataset. Studies enrolled 29 healthy, obese subjects and 91 patients with rare genetic disorders of obesity.

Absorption

After subcutaneous injection of setmelanotide, steady-state plasma concentrations of setmelanotide increased slowly, reaching maximum concentrations at a median $t_{\text{max}}$ 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 population PK model was 28.7% (CL/F) and intraindividual variability was 27.6%.

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 48.7L. 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 ($t_{\frac{1}{2}}$) 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 4.86 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 $C_{\text{max}}$ increased approximately linearly with dose following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg).

**Special populations**

**Paediatric population**

Setmelanotide has been evaluated in paediatric patients (aged 6 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 6 years and older.

**Elderly population**

Setmelanotide has not been evaluated in elderly patients.

**Renal impairment**

The majority of patients in the clinical studies had normal renal function. Population PK analysis suggests decreased clearance in patients with renal impairment. Patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m$^2$) should follow a modified dose regimen (see section 4.2, Table 3). IMCIVREE is not recommended for use in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m$^2$) or severe renal impairment (eGFR <30 mL/min/1.73 m$^2$).

**Hepatic impairment**

Setmelanotide is stable in human, rat, and monkey hepatocytes; therefore, a study in hepatically impaired patients was not conducted. IMCIVREE should 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, 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/m²/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

N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt (mPEG-2000-DSPE)
Carmellose sodium
Mannitol
6.2 Incompatibilities

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

6.3 Shelf life

2 years

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.

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 stopper and aluminium cap.

Pack size: 1 multidose vial.
6.6 Special precautions for disposal

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 MARKETING AUTHORITYHOLDER

Rhythm Pharmaceuticals Limited
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Dublin 2
D02 T380
Ireland

8 MARKETING AUTHORITY NUMBER(S)

PLGB 54365/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

15/09/2021

10 DATE OF REVISION OF THE TEXT

15/09/2021