ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMCIVREE 10 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient 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 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 from 12 to 17 years of age

For adults and children from 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 may be increased to 3 mg once daily (Table 1).

In patients from 12 to 17 years of age, 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 from 12 to 17 years of age

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 from 6 to < 12 years of age)

For paediatric patients from 6 to < 12 years of age, 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 may 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 from 2 to < 6 years of age)

For paediatric patients from 2 to < 6 years of age, the dose titration in Table 3 should be followed.

For paediatric patients from 2 to < 6 years of age, 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, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, dose titration should be continued.

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	1.5 mg once daily	0.15 ml once daily

Patient weight/treatment week	Daily dose	Volume to be injected
1 mg dose once daily is well tolerated)		
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 treatment. 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 treatment 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.

Bardet-Biedl syndrome

Adult population and children from 16 to 17 years of age

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

Table 4 Dose titration in adults and paediatric patients from 16 to 17 years of age

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, the dose should be reduced to 1 mg (0.1 ml) once daily. If the 1 mg once daily dose is tolerated, dose titration should be continued.

Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

Paediatric population (children from 6 to < 16 years of age)

For paediatric patients from 6 to < 16 years of age, 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, the dose should be reduced to 0.5 mg (0.05 ml) once daily. If the 0.5 mg once daily dose is tolerated, the dose should be increased to 1 mg once daily and dose titration should be continued.

Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

Paediatric population (children from 2 to < 6 years of age)

For paediatric patients from 2 to < 6 years of age, the dose titration in Table 6 should be followed.

For paediatric patients from 2 to < 6 years of age, 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, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, dose titration should be continued.

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 treatment. 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 treatment 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 from 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 from 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 from 12 to 17 years of age 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, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, dose titration should be continued.

Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

For paediatric patients from 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, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

Setmelanotide has not been studied in patients from 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 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

Patient weight/treatment week	Daily dose	Volume to be injected
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, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

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 from 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 from 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 from 16 to 17 years of age 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, the dose should be reduced to 0.25 mg (0.025 ml) once daily. If the 0.25 mg once daily dose is tolerated, dose titration should be continued.

Following the starting dose, if a subsequent dose is not tolerated, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

For paediatric patients from 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, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

Setmelanotide has not been studied in patients from 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, the dose should be reduced to the previous dose level. If the reduced dose is tolerated, dose titration should be continued.

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 of age)

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 65 years of age and above 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 package leaflet for complete administration instructions with illustrations.

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

Table 13 Administration syringe and needle gauge, 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 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 studies 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 studies, 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. Consideration should be given to discontinuing treatment if patients experience suicidal thoughts or behaviours.

Paediatric population

The prescribing physician should periodically assess response to setmelanotide treatment. 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 with known effect

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 (aged less than 3 years). Patients aged 2 years 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 non-clinical 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 non-clinical 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 newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from IMCIVREE treatment taking into account the benefit of breastfeeding for the child and the benefit of treatment 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 only minor influence on the ability to drive and use machines, due to somnolence.

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 obtained from clinical studies and post-marketing surveillance are listed below by MedDRA system organ class and frequency, following the frequency convention defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1 000 to < 1/100).

Table 14 Adverse reactions

System organ class	Frequency		
	Very common	**Common**	**Uncommon**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Melanocytic naevus	-	Dysplastic naevus
Blood and lymphatic system disorders	-	Eosinophilia	-
Metabolism and nutritional disorders	-	-	Appetite disorder, thirst
Psychiatric disorders	-	Depression, insomnia, disturbance in sexual arousal, libido increased	Sleep disorder, nightmares, libido decreased
Nervous system disorders	Headache	Dizziness	Somnolence, migraine, parosmia, dysguesia
Eye disorders	-	-	Scleral discolouration
Ear and labyrinth disorders	-	-	Vertigo
Vascular disorders	-	-	Hot flush
Respiratory, thoracic and mediastinal disorders	-	Cough	Yawning, rhinorrhoea
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
Skin and subcutaneous tissue disorders	Hyperpigmentation disorders[a]	Pruritus, rash, dry skin, skin lesion, alopecia	Erythema, skin striae, hyperhidrosis, lipodystrophy acquired, urticaria, skin exfoliation

System organ class	Frequency		
	Very common	**Common**	**Uncommon**
Musculoskeletal and connective tissue disorders	-	Back pain, myalgia, muscle spasms	Arthralgia, musculoskeletal pain, pain in extremity, blood creatine phosphokinase increased
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]
General disorders and administrative site conditions	Injection site reactions[a], fatigue	Asthenia, pain	Temperature intolerance, chills

[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 treatment. 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 treatment, 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 treatment (within the first month), was mild and did not lead to discontinuation of treatment. 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

The observed incidence of anti-drug antibodies (ADA) to setmelanotide is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful

comparisons of the incidence of ADA in setmelanotide pivotal studies with the incidence of ADA in other studies.

In patients with BBS or in patients with POMC, PCSK1, or LEPR deficiency, there is insufficient information to characterise the ADA response to setmelanotide and the effects of ADA on pharmacokinetics, pharmacodynamics, safety, or efficacy of setmelanotide.

In patients 2 to < 6 years old, antibodies to setmelanotide were detected in one subject who was confirmed positive with a low titre and with no subsequent positive ADA (see Study 4 in section 5.1). Due to the small number of subjects positive to ADA to setmelanotide and limited sample size, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety or efficacy of setmelanotide is unknown.

A low incidence of antibodies to alpha-MSH has been detected in clinical studies to date. These include pre-existing antibodies to alpha-MSH as well as development of antibodies to alpha-MSH while on treatment. Due to this low incidence, there is insufficient data to characterise the effects of anti-alpha-MSH antibodies on the pharmacokinetics, pharmacodynamics, safety or efficacy of setmelanotide. None of the patients with POMC deficiency were confirmed to have antibodies to alpha-MSH.

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 studies (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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 medicinal product and had at least 1 baseline assessment.

[1] From the Clopper-Pearson (exact) method

[2] Testing the null hypothesis: proportion =5 %

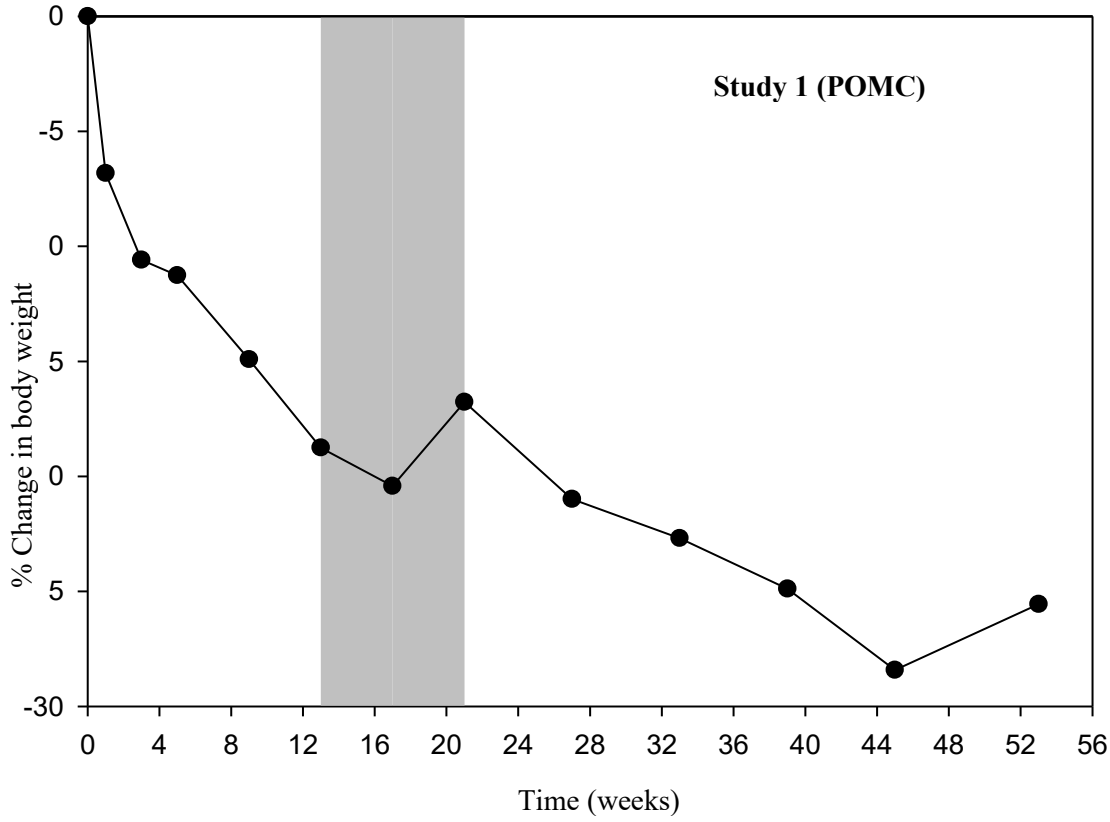
Table 16 Percent change from baseline in weight and hunger at 1 year in Study 1

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 medicinal product, 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 medicinal product and had at least 1 baseline assessment.

[1] From the Clopper-Pearson (exact) method

[2] Testing the null hypothesis: proportion =5 %

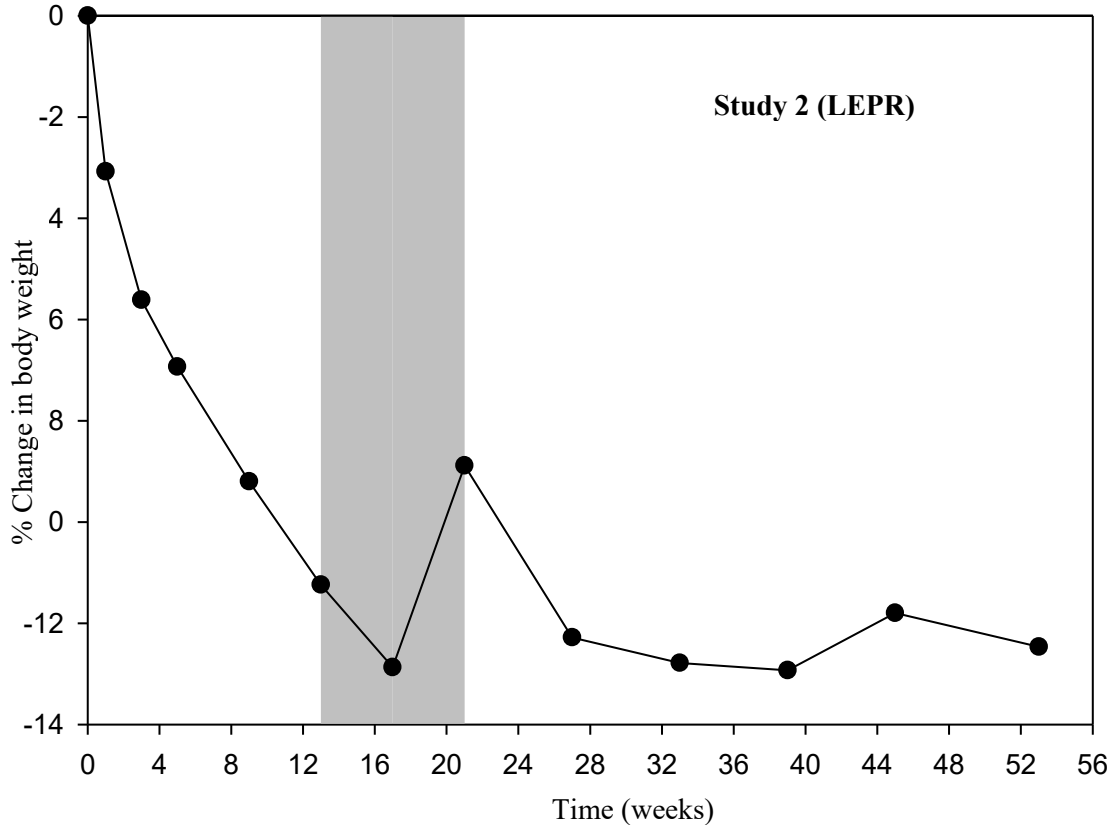
Table 18 Percent change from baseline in weight and hunger at 1 year in Study 2

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 medicinal product, 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 setmelanotide 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 setmelanotide 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 the effect of setmelanotide 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 from 2 to < 6 years of age 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 from 2 to < 6 years of age 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 from 2 to < 6 years of age 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])

		Patients with POMC or LEPR (n=7)	Patients with BBS (n=5)	Total (N=12)
Parameter	**Statistic**	**%**	**%**	**%**
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, 54 of the patients treated with setmelanotide were from 2 to 17 years of age 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.

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 $C_{max,ss}$, 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 7 087 observations, of which 6 847 samples had quantifiable setmelanotide concentrations. The PK data were predominantly from 271 adults and 87 adolescents (from 12 to < 18 years of age). There were also 41 children from 6 to < 12 years of age and 11 children from 2 to < 6 years of age. 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 75.2 L. 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 (from 2 to 17 years of age). 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 65 years of age and above 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. Setmelanotide 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, 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/m^2/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
Phenol
Benzyl alcohol
Disodium edetate
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After first opening

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 °C to 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.

Packs of:
- 1 multidose vial.
- 10 multidose vials.

Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1564/0001
EU/1/21/1564/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2021
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMCIVREE 10 mg/ml solution for injection
setmelanotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: mPEG-2000-DSPE, carmellose sodium, mannitol, phenol, benzyl alcohol, disodium edetate, water for injections, hydrochloric acid, sodium hydroxide.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 multidose vial (1 ml).
10 multidose vials (1 ml).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze. Keep the vial in the outer carton in order to protect from light.

Unopened vial
Store in a refrigerator.

After opening
Do not store above 30 °C.
Discard after 28 days.
Date of opening:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1564/0001
EU/1/21/1564/0002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IMCIVREE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IMCIVREE 10 mg/ml injection
setmelanotide
For SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial (1 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

IMCIVREE 10 mg/ml solution for injection
setmelanotide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMCIVREE is and what it is used for
2. What you need to know before you use IMCIVREE
3. How to use IMCIVREE
4. Possible side effects
5. How to store IMCIVREE
6. Contents of the pack and other information

1. What IMCIVREE is and what it is used for

IMCIVREE contains the active substance setmelanotide. It is used in adults and children of 2 years and above, to treat obesity caused by certain genetic conditions that affect how your brain controls feelings of hunger.

The genetic conditions this medicine is used to treat are:
- Bardet-Biedl syndrome (BBS)
- POMC (pro-opiomelanocortin) deficiency obesity
- PCSK1 (proprotein convertase subtilisin/kexin type 1) deficiency obesity
- LEPR (leptin receptor) deficiency obesity.

People with these conditions lack certain natural substances involved in controlling appetite or these substances do not work properly. This increases hunger levels and leads to obesity. The medicine helps to restore control of appetite and reduces symptoms of the condition.

2. What you need to know before you use IMCIVREE

Do not use IMCIVREE
- if you are allergic to setmelanotide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using this medicine.

Before you start and during treatment with this medicine your doctor should examine your skin for any markings or dark areas. Whilst you are using this medicine you may get more marks or dark patches on your skin. A check before you start treatment will help you identify any new marks that appear once you have used this medicine.

It is very common (may affect more than 1 in 10 people) for male patients to get spontaneous erections

of the penis when using this medicine. If an erection lasts more than 4 hours, please see a doctor urgently. Prolonged erections (priapism) can reduce your ability to get erections in the future if not treated.

Children
Do not give this medicine to children under the age of 2 years since there is no information on use in children below this age.

Other medicines and IMCIVREE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

It is not recommended to use this medicine when pregnant or while trying to get pregnant, as it has not been studied in pregnant women. Weight loss during pregnancy can harm the baby.

Talk to your doctor before taking this medicine if you are breast-feeding. Your doctor will discuss with you the benefits and risks of taking this medicine during this time.

Driving and using machines
This medicine has no or only a minor effect on your ability to drive or use machines, due to drowsiness.

IMCIVREE contains benzyl alcohol
This medicine contains 10 mg benzyl alcohol in each 1 ml which is equivalent to 1 mg for each mg of your dose.

Benzyl alcohol has been linked with the risk of severe side effects in young children (less than 3 years old). There is an increased possibility that benzyl alcohol could build-up in their body (called "metabolic acidosis") leading to "gasping syndrome". Children aged 2 years old should be monitored by their doctor for signs of this build-up (including rapid heartbeat, rapid breathing, or confusion).

Benzyl alcohol may cause allergic reactions.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

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

3. How to use IMCIVREE

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

This medicine is given as an injection under the skin, once a day, at the start of the day. The medicine is for long-term use.

Your doctor will advise you on the right dose to inject.

Pro-opiomelanocortin deficiency obesity, proprotein convertase subtilisin/kexin type 1 deficiency

obesity and leptin receptor deficiency obesity.

In **adults and children from 12 to 17 years of age**, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**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 dose is not enough and side effects are acceptable	2.5 mg once daily	0.25 ml once daily
If dose is not enough and side effects are acceptable	3 mg once daily	0.3 ml once daily

In **children from 6 to less than 12 years of age**, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**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 dose is not enough and side effects are acceptable	2.5 mg once daily	0.25 ml once daily

In **children from 2 to less than 6 years of age**, recommended doses are as follows:

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 dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	1 mg once daily	0.1 ml once daily
Week 5 and onward (if dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	1 mg once daily	0.1 ml once daily
Weeks 5-6 (if dose is not enough and side effects are acceptable)	1.5 mg once daily	0.15 ml once daily
Weeks 7-8 (if dose is not enough and side effects are acceptable)	2 mg once daily	0.2 ml once daily
Week 9 and onward (if dose is not enough and side effects are acceptable)	2.5 mg once daily	0.25 ml once daily

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

In patients with mild or moderate kidney disease, no changes to the dosing regimen are needed.

For **adults and children from 12 to 17 years of age** with severe renal impairment, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**Volume to be injected**
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if side effects are acceptable)	1 mg once daily	0.1 ml once daily
If dose is not enough and side effects are acceptable	2 mg once daily	0.2 ml once daily
If dose is not enough and side effects are acceptable	2.5 mg once daily	0.25 ml once daily

If dose is not enough and side effects are acceptable	3 mg once daily	0.3 ml once daily

If side effects of the 0.5 mg starting dose are not acceptable, it will be reduced to 0.25 mg (0.025 ml). If side effects of the 0.25 mg once daily dose are acceptable, the dose will continue to be increased.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 3 mg dose are not acceptable, it will be reduced to 2.5 mg, and you will continue on this dose.

In **children from 6 to less than 12 years of age** with severe renal impairment, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**Volume to be injected**
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if side effects are acceptable)	1 mg once daily	0.1 ml once daily
If dose is not enough and side effects are acceptable	2 mg once daily	0.2 ml once daily

If side effects of the 0.25 mg starting dose are not acceptable, treatment should be discontinued.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 2 mg dose are not acceptable, it will be reduced to 1 mg, and you will continue on this dose.

In **children from 2 to less than 6 years of age** with severe renal impairment, recommended doses are as follows:

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 dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Weeks 5-6 (if dose is not enough and side effects are acceptable)	1 mg once daily	0.1 ml once daily
Weeks 7 and onward (if dose is not enough and side effects are acceptable)	1.5 mg once daily	0.15 ml once daily

If side effects of the 0.25 mg starting dose are not acceptable, treatment should be discontinued.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

Bardet-Biedl syndrome

In **adults and children from 16 to 17 years of age**, recommended doses are as follows:

Treatment week	Daily dose in mg	Volume to be injected
Weeks 1-2	2 mg once daily	0.2 ml once daily
Week 3 and onward (if side effects are acceptable)	3 mg once daily	0.3 ml once daily

If side effects of the 2 mg starting dose are not acceptable, it will be reduced to 1 mg (0.1 ml). If side effects of the 1 mg once daily dose are acceptable, the dose will continue to be increased.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 3 mg dose are not acceptable, it will be reduced to 2 mg, and you will continue on this dose.

In **children from 6 to less than 16 years of age**, recommended doses are as follows:

Treatment week	Daily dose in mg	Volume to be injected
Week 1	1 mg once daily	0.1 ml once daily
Week 2 (if side effects are acceptable)	2 mg once daily	0.2 ml once daily
Week 3 and onward (if side effects are acceptable)	3 mg once daily	0.3 ml once daily

If side effects of the 1 mg starting dose are not acceptable, it will be reduced to 0.5 mg (0.05 ml). If side effects of the 0.5 mg dose are acceptable, the dose will continue to be increased.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level.

If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 3 mg dose are not acceptable, it will be reduced to 2 mg, and you will continue on this dose.

In **children from 2 to less than 6 years of age**, recommended doses are as follows:

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 dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	1 mg once daily	0.1 ml once daily
Week 5 and onward (if dose is not enough and side effects are acceptable)	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 dose is not enough and side effects	1 mg once daily	0.1 ml once daily

are acceptable)		
Weeks 5-6 (if dose is not enough and side effects are acceptable)	1.5 mg once daily	0.15 ml once daily
Weeks 7-8 (if dose is not enough and side effects are acceptable)	2 mg once daily	0.2 ml once daily
Week 9 and onward (if dose is not enough and side effects are acceptable)	2.5 mg once daily	0.25 ml once daily

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

In patients with mild or moderate kidney disease, no changes to the dosing regimen are needed.

For **adults and children from 16 to 17 years of age** with severe renal impairment, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**Volume to be injected**
Weeks 1-2	0.5 mg once daily	0.05 ml once daily
Week 3 and onward (if side effects are acceptable)	1 mg once daily	0.1 ml once daily
If dose is not enough and side effects are acceptable	2 mg once daily	0.2 ml once daily
If dose is not enough and side effects are acceptable	2.5 mg once daily	0.25 ml once daily
If dose is not enough and side effects are acceptable	3 mg once daily	0.3 ml once daily

If side effects of the 0.5 mg starting dose are not acceptable, it will be reduced to 0.25 mg (0.025 ml). If side effects of the 0.25 mg once daily dose are acceptable, the dose will continue to be increased.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 3 mg dose are not acceptable, it will be reduced to 2.5 mg, and you will continue on this dose.

In **children from 6 to less than 16 years of age** with severe renal impairment, recommended doses are as follows:

Treatment week	**Daily dose in mg**	**Volume to be injected**
Weeks 1-2	0.25 mg once daily	0.025 ml once daily
Weeks 3-4 (if side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if side effects are acceptable)	1 mg once daily	0.1 ml once daily
If dose is not enough and side effects are acceptable	2 mg once daily	0.2 ml once daily

If side effects of the 0.25 mg starting dose are not acceptable, treatment should be discontinued.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level.

If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

If side effects of the 2 mg dose are not acceptable, it will be reduced to 1 mg, and you will continue on this dose.

In **children from 2 to less than 6 years of age** with severe renal impairment, recommended doses are as follows:

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 dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Week 5 and onward (if dose is not enough and side effects are acceptable)	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 dose is not enough and side effects are acceptable)	0.5 mg once daily	0.05 ml once daily
Weeks 5-6 (if dose is not enough and side effects are acceptable)	1 mg once daily	0.1 ml once daily
Weeks 7 and onward (if dose is not enough and side effects are acceptable)	1.5 mg once daily	0.15 ml once daily

If side effects of the 0.25 mg starting dose are not acceptable, treatment should be discontinued.

Following the starting dose, if side effects of a subsequent dose are not acceptable, the dose will be reduced to the previous dose level. If the side effects of the reduced dose are acceptable, the dose will continue to be increased.

Your doctor should regularly check how well this medicine is working; the doctor may adjust the dose if necessary. In growing children and adolescents, the impact on weight loss and their growth and development should be monitored.

This medicine is intended for long-term use. Discontinuation or irregular use may lead to a return or worsening of your symptoms. Make sure to closely follow the dosing schedule as instructed by your doctor or pharmacist.

How to inject IMCIVREE

This medicine is injected into the fatty layer under the skin, in the stomach. Your doctor, pharmacist or nurse will show you how to do this. Once you are comfortable injecting yourself or your child, you will be able to do this at home.

This medicine should be injected at the start of your day to maximise hunger reduction when awake. This medicine can be taken without regard to the timing of meals.

Before injecting this medicine, please read the following instructions carefully.

Step 1. Prepare for the injection
- Get the items you will need and place on a clean, flat surface.

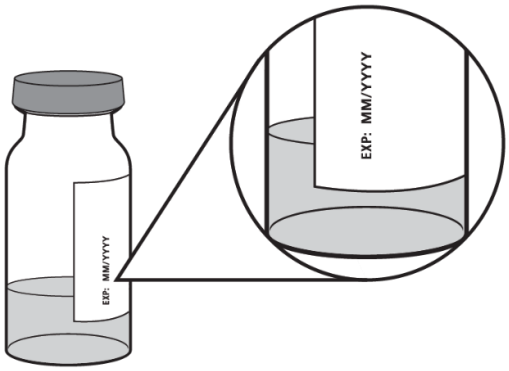
You will need the following items that are supplied separately:



- Wash your hands with soap and warm water.
- Open the 2 alcohol wipes and the gauze pad.

Step 2 Examine the vial

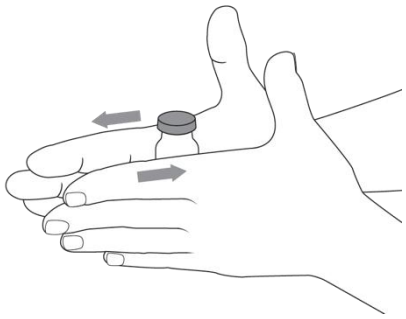
- Check the expiry date on the vial label, this is shown after 'EXP': MM/YYYY.



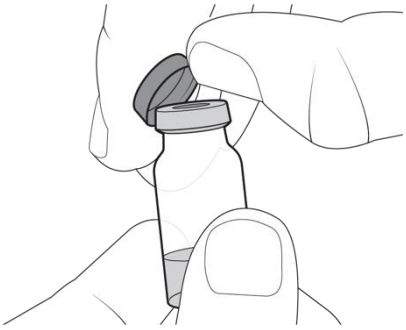
- The liquid should look clear to slightly yellow.
- Do not use if:
  - the expiry date has passed
  - the liquid is cloudy
  - there are particles floating in the vial
  - the plastic cap on a new vial is broken or missing
  - the vial has been stored at temperatures greater than 30 °C.

Step 3. Prepare the vial

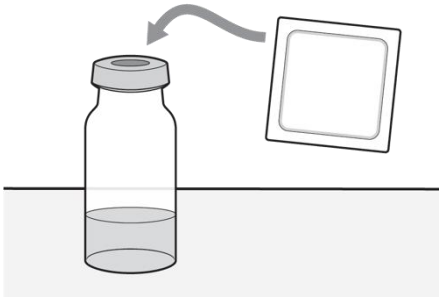
- Before use, let the vial reach room temperature. This can be done by removing the vial from the refrigerator 15 minutes before injection or by rolling the vial gently between the palms of your hands for 60 seconds.
  - Do not use warm water, a microwave or other appliance to heat the vial
  - Do not shake the vial



- If using a new vial, remove the plastic cap and throw it away in your household waste.

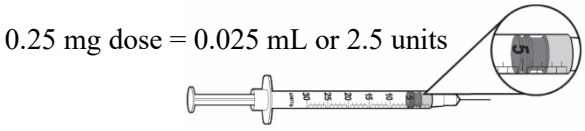


- Clean the top of the grey vial stopper with an alcohol wipe. Throw away the used alcohol wipe in your household waste.
  - Do not remove the vial stopper

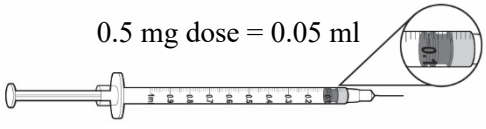


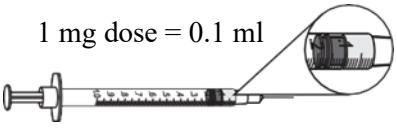
Step 4. Prepare the syringe

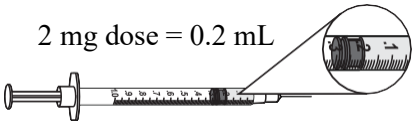
- For doses of 0.25 mg (0.025 ml or 2.5 units), use a 0.3 ml syringe with 0.5 (half) unit increments and a 29 to 31 gauge needle with a 6 to 13 mm needle length, suitable for injection under the skin.

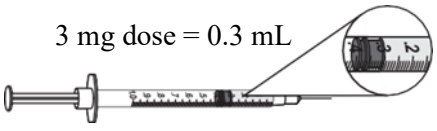


- For doses of 0.5 mg to 3 mg (0.05 ml to 0.3 ml), use a 1 ml syringe with 0.01 ml dosing increments and a 28 to 29 gauge needle with a 6 to 13 mm needle length, suitable for injection under the skin.

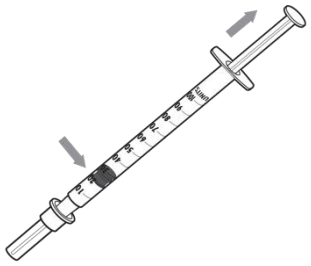




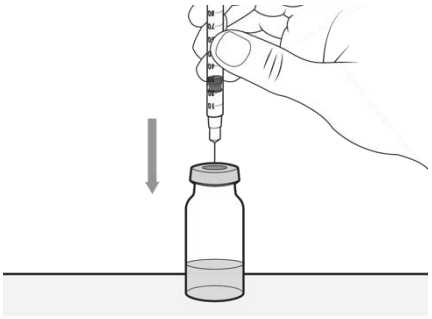




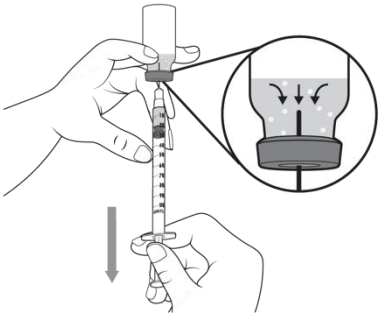
- Keep the protective needle cap on and pull back the plunger to fill the syringe with air equal to the amount of the medicine to be used.



- Remove the needle cap from the syringe. Pull the cap straight off and away from your body.
- Place the vial upright on a flat surface. Hold the syringe and place it directly over the vial. Insert the needle straight down into the centre of the grey vial stopper.

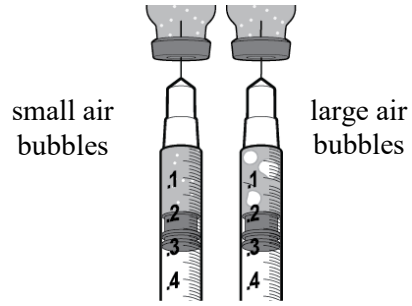


- Push the plunger down to inject the air from the syringe into the vial.
- Without removing the needle, gently turn the vial upside down.
  - Make sure the tip of the needle is fully in the medicine liquid and not in the air above the liquid



- Slowly pull back the plunger to fill the syringe with the amount medicine needed for your dose. When measuring your dose, be sure to read the units starting from the end closest to the black rubber stopper.

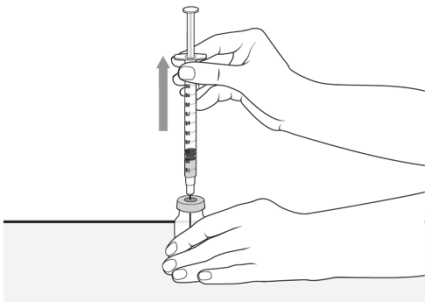
- Keep the needle in the vial and check for any large air bubbles in the syringe.



- If you see air bubbles these will need to be removed from the syringe. To remove:
  - Gently tap the side of the syringe with your finger to move the air bubble to the top of the syringe
  - Empty the syringe back into the vial
  - Follow the above steps to fill your syringe again. Pull the plunger more slowly this time and make sure the tip of the needle is always fully in the liquid in the vial to reduce the chance of air bubbles

- Once there are no large air bubbles in the syringe, place the vial upright on a hard surface.

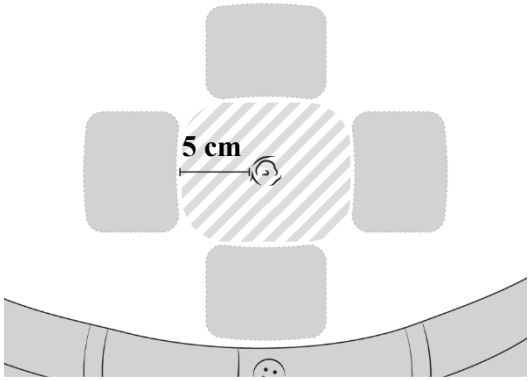
- Hold the vial with one hand and the barrel of the syringe between the fingertips of your other hand. Pull the needle straight up and out of the vial.



- Place the syringe on the hard surface, make sure the needle does not touch the surface. Do not recap the needle.

Step 5. Prepare the injection site

- Choose the area on your stomach for the injection.
  - Change your injection site each day
  - Make sure the injection site is at least 5 cm away from the belly button
  - Do not inject an area that is red, swollen, or irritated



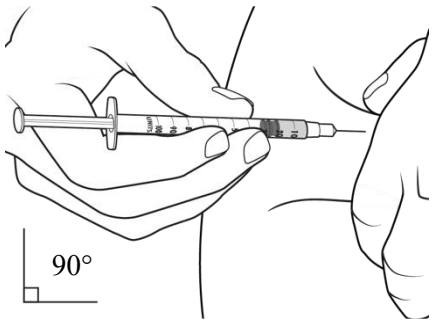
- Clean your chosen injection site with your second alcohol wipe using a circular motion.

- Allow the skin to dry for about 10 seconds.
- Do not touch, fan, or blow on the cleaned area.

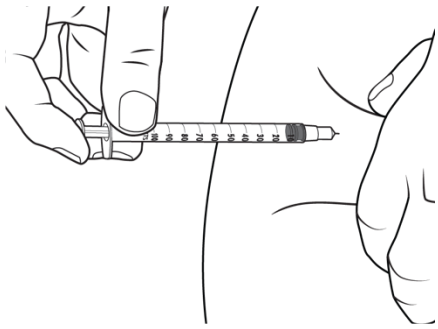
Step 6. Injecting IMCIVREE
- Place the syringe between your thumb and index finger of the hand you write with.
- With your other hand, gently pinch about 5 cm of skin between your thumb and index finger. Make sure you hold the skin fold until the injection is complete.



- Hold the middle of the syringe at a 90º angle to your skin and push the needle straight into the injection site, making sure the needle goes in all the way.
- Do not hold or push on the plunger while inserting the needle



- Holding the barrel of the syringe between your thumb and middle finger, use your index finger to slowly push the plunger to inject the medicine.



- Count to 5 after injecting this medicine to make sure all the medicine has left the syringe.
- Let go of the pinched skin and pull the out the needle.
- Use a gauze pad to gently apply pressure to the injection site, then throw gauze pad into your household waste.
- Place your used syringe in the sharps bin. Do not throw away in your household waste.
- If you still have medicine left in your vial, place the vial back in the carton and store either in your refrigerator or in a safe place at a temperature of less than 30 °C until it is time for your next dose.

If you use more IMCIVREE than you should
If you or your child use more of this medicine than you should, contact your doctor.

If you forget to use IMCIVREE
If you forget to inject the medicine, skip the dose and inject your next dose at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using IMCIVREE
If you stop using this medicine your hunger may return and your weight loss may stop.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- Skin neoplasm
- Headache
- Feeling sick (nausea)
- Being sick (vomiting)
- Dark areas or patches on your skin
- Spontaneous penile erections
- Increased penile erections
- Pain, bruising or inflammation (redness and/or swelling) at the site of injection
- Feeling tired

Common (may affect up to 1 in 10 people)
- An excess of eosinophils, a type of white blood cell
- Feeling depressed
- Trouble sleeping
- Disturbance in sexual arousal
- Increased sexual desire
- Feeling dizzy
- Cough
- Diarrhoea
- Stomach pain or discomfort
- Dry mouth
- Indigestion
- Feeling constipated
- Heartburn
- Dry, red or itchy skin
- Rash
- Lesions on your skin
- Hair loss
- Back pain
- Muscle pain or cramps
- Female genital discomfort
- Feeling weak
- Pain

Uncommon (may affect up to 1 in 100 people)
- Flat, coloured mole on your skin
- Appetite disorders
- Feeling thirsty
- Sleep disorder
- Nightmares

- Decreased sexual desire
- Drowsiness
- Migraine headache
- Loss or change in sense of smell
- Taste disorders
- Discolouration of the white part of the eyes
- Vertigo
- Hot flush
- Yawning
- Runny nose
- Discoloured gums
- Stomach bloating
- Increase in saliva
- Flatulence
- Blood tests showing increased liver enzyme levels
- Redness of the skin
- Lines or streaks on your skin
- Increased sweating
- Abnormal distribution of fat tissue
- Itchy rash
- Flaky skin
- Joint aches
- Pain in the muscles or bones
- Pain in arms or legs
- Blood tests showing increased muscle enzyme levels
- Female inability to achieve or maintain sexual arousal
- Genital discomfort or sensitivity
- Female genital disorder
- Period pains
- Sensitivity to hot or cold (feeling hot or cold)
- Chills

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store IMCIVREE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after 'EXP'. The expiry date refers to the last day of that month.

This medicine should be stored in a refrigerator at 2 °C to 8 °C until the expiry date on the carton and vial. Alternatively, this medicine may be kept at room temperature, no warmer than 30 °C, for up to 30 days or until the expiry date, whichever is sooner. Store all vials (even those you have opened) in the original carton to protect them from light. After you first use a vial, discard after 28 days.

Do not freeze this medicine.

If this medicine is exposed to temperatures above 30 °C do not use and discard according to local guidelines. Do not use this medicine if you notice floating particles or cloudiness.

Always use a new syringe for each injection.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMCIVREE contains

- The active substance is setmelanotide. Each multidose vial contains 10 mg setmelanotide in 1 ml of solution.

The other ingredients are:

- benzyl alcohol (see section 2 'IMCIVREE contains benzyl alcohol')
- N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl- glycero-3-phosphoethanolamine sodium salt (mPEG-2000-DSPE)
- Carmellose sodium (see section 2 'IMCIVREE contains sodium')
- Mannitol
- Phenol
- Disodium edetate (see section 2 'IMCIVREE contains sodium')
- Water for injections
- Hydrochloric acid (for pH-adjustment)
- Sodium hydroxide (for pH-adjustment)

What IMCIVREE looks like and contents of the pack

IMCIVREE is a clear colourless to slightly coloured solution.
This medicine comes in clear glass vials with a stopper and cap, containing 1 ml of solution for injection.

IMCIVREE is available in packs containing 1 or 10 multidose vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.