ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Emcitate 350 microgram dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 350 micrograms tiratricol.

Excipient with known effect

Each tablet contains 19 mg of lactose (corresponding to 20 mg of lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

White, oblong tablet (size: 10 mm long, 5 mm wide) with score lines on both sides.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

4.2 Posology and method of administration

Treatment should be initiated and monitored by physicians who are experienced in the management of patients with rare genetic disorders such as MCT8 deficiency.

Posology

Dosing of Emcitate should be titrated on an individual patient basis based on the patient's thyroid hormone levels.

The dose should be increased stepwise approximately every two weeks during a titration period until a maintenance dose has been reached. It is generally recommended to titrate the dose until the serum T3 level is below the midpoint of the normal range for age. The dose may be further adjusted based on the patient's response to treatment on clinical features of MCT8 deficiency.

The need for further dose adjustments should be reassessed on a regular basis in accordance with clinical practice (see section 4.4).

TSH and (F)T4 levels may provide further information to guide individual dosing.

Adults, adolescents, children, and infants with a body weight of 10 kg or above

Dose titration and adjustment
The recommended starting dose for patients with a body weight of 10 kg or above is 350 micrograms daily.

A recommended dose titration regimen is shown in Table 1. The daily dose should be gradually increased by 350 micrograms every two weeks until a maintenance dose has been reached. It is generally recommended to titrate the dose until the serum T3 level is below the midpoint of the normal range for age. Smaller dose escalation steps (half tablets) may be used when a patient is approaching target serum T3 levels, as appropriate. The dose may be further adjusted based on the patient's response to treatment on clinical features of MCT8 deficiency. The total daily dose should be administered in 1 to 3 doses, spread throughout the day (e.g. morning, midday, evening).

Table 1. Recommended dose titration regimen in patients with a body weight of 10 kg or above

Titration	**Total daily dose (micrograms)**	**Number of tablets/day**
Starting dose	350	1
Week 2	700	2
Week 4	1 050	3
Week 6	1 400	4
Week 8	1 750	5
Week 10	2 100	6
Dose titration should continue in increments of 350 micrograms until a maintenance dose has been reached. It is not recommended to exceed a daily dose of 80 micrograms/kg in patients with a body weight between 10 and 40 kg; 60 micrograms/kg in patients with a body weight between 40 and 60 kg; and 50 micrograms/kg in patients with a body weight above 60 kg.		

Children and infants with a body weight below 10 kg

Dose titration and adjustment
The recommended starting dose for patients with a body weight below 10 kg is 175 micrograms (a half tablet) daily.

A recommended dose titration regimen is shown in Table 2. The daily dose should be gradually increased by 175 micrograms every two weeks until a maintenance dose has been reached. It is generally recommended to titrate the dose until the serum T3 level is below the midpoint of the normal range for age. The dose may be further adjusted based on the patient's response to treatment on clinical features of MCT8 deficiency. The total daily dose should be administered in 1 to 3 doses, spread throughout the day (e.g. morning, midday, evening).

Table 2. Recommended dose titration regimen in patients with a body weight below 10 kg

Titration	**Total daily dose (micrograms)**	**Number of tablets/day**
Starting dose	175	0.5
Week 2	350	1
Week 4	525	1.5
Week 6	700	2
Week 8	875	2.5
Week 10	1 050	3
Dose titration should continue in increments of 175 micrograms until a maintenance dose has been reached. It is not recommended to exceed a daily dose of 100 micrograms/kg in patients with a body weight below 10 kg.		

Maintenance dose

The dose of Emcitate is titrated on an individual basis until a maintenance dose has been reached. It is generally recommended to titrate the dose until the serum T3 level is below the midpoint of the normal range for age. The dose may be further adjusted based on the patient's response to treatment on clinical features of MCT8 deficiency. The need for further dose adjustments should be reassessed on a regular basis in accordance with clinical practice (see section 4.4).

Missed or delayed dose

If a dose is missed and there are more than 4 hours to the next scheduled dose, it should be taken as soon as possible. If a dose is missed and the next dose is scheduled within 4 hours, the dose should be omitted and the next dose taken according to the regular schedule.

Laboratory tests (T3 measurements)

It is recommended to measure individual T3 levels using a liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Tiratricol cross-reacts with T3 when assessed by immunoassay, which may cause unreliable test results. Expert advice should be sought for test result interpretation when initiating, titrating and adjusting the dose of tiratricol using immunoassay method (see section 4.4).

Hypermetabolic signs and symptoms

If hypermetabolic signs and symptoms (such as hyperhidrosis, irritability, anxiety, insomnia, nightmares, hyperthermia, tachycardia, transient elevations in systolic blood pressure (SBP), or diarrhoea) either occur for the first time or worsen, and do not resolve within 2 weeks, the dose should be reduced according to the steps in the dose titration regimen until signs and symptoms resolve (see Table 1 or Table 2). Following the resolution of hypermetabolic signs and symptoms, dose titration may be resumed, as clinically appropriate (see section 4.4).

Special populations

Hepatic impairment
No specific studies have been performed in patients with hepatic impairment. In these patients, careful dose titration and regular monitoring of serum concentrations of T3 are recommended (see section 4.4).

Renal impairment
No specific studies have been performed in patients with renal impairment. In these patients, careful dose titration and regular monitoring of serum concentrations of T3 are recommended (see section 4.4).

Method of administration

For oral use or administration through gastroenteral feeding tube.

Oral use

Emcitate dispersible tablets are intended to be dispersed in water before being swallowed.

The dispersion should be prepared in a dedicated small glass, by dispersing the tablet(s) (maximum 4 tablets at each dosing occasion) in 30 mL of drinking water, by stirring with a teaspoon for 1 minute. No other liquids should be used. The dispersion should be cloudy white. The dispersion should then be withdrawn from the glass with a 40 mL oral syringe and given orally to the patient with the syringe without delay. It must be ensured that the plunger is slowly and gently pushed down to gently squirt the dispersion into the inside of the cheek of the patient.

An additional 10 mL of drinking water should be added to the glass and stirred with a teaspoon for around 5 seconds to ensure that any remaining product is dispersed. This dispersion should be withdrawn from the glass with the same syringe, and given to the patient without delay.

Through gastroenteral feeding tube

Emcitate can be administered through a gastroenteral feeding tube.

The preparation of the dispersion should be performed as described above for oral use.

It must be ensured that the gastroenteral feeding tube is free from obstruction before administration and the instructions for the selected gastroenteral feeding tube regarding flushing, administration, and rinsing procedures must be followed.

The contents of the syringe should be administered immediately into the gastroenteral feeding tube (30 mL + 10 mL for all age groups).

For additional information regarding administration through gastroenteral feeding tube, and stability of the dispersion, see section 6.6.

4.3 Contraindications

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

Hyperthyroidism for other reasons than MCT8 deficiency (e.g. Grave's Disease).

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Hypermetabolic signs and symptoms

At initiation of Emcitate treatment and/or during dose titration, new onset or worsening of hypermetabolic signs and symptoms, such as hyperhidrosis, irritability, anxiety, insomnia, nightmares, hyperthermia, tachycardia, transient elevations in systolic blood pressure (SBP), or diarrhoea, may occur (see section 4.8). These signs and symptoms are usually transient and resolve spontaneously within a few days. If hypermetabolic signs and symptoms do not resolve within 2 weeks, the dose should be reduced according to the steps in the dose titration regimen (see section 4.2). Following the resolution of hypermetabolic signs and symptoms, dose titration may be resumed, as clinically appropriate.

Cardiac disease

Caution should be used during dose titration in patients with cardiac disease, as they may be at increased risk of adverse reactions associated with a hypermetabolic state (see section 4.8).

Interference with laboratory tests

Tiratricol cross-reacts with T3 if assessed by immunoassay, which may cause unreliable test results. It is recommended to use an LC/MS/MS method to measure T3 levels. Care should be taken if an immunoassay method is used. Specific guidelines should be followed for interpreting T3 test results when determining or adjusting the dose of tiratricol (see section 4.2).

Diabetes

Caution should be used in patients with diabetes (see section 4.5).

Hepatic impairment

The safety and efficacy of Emcitate in patients with hepatic impairment have not been studied. Special care is required in these patients (see section 4.2).

Renal impairment

The safety and efficacy of Emcitate in patients with renal impairment have not been studied. Special care is required in these patients (see section 4.2).

Misuse for weight reduction

Tiratricol should not be taken for weight reduction. It may cause serious or life-threatening undesirable effects, particularly in combination with orlistat (see section 4.5 under "Orlistat").

Lactose

Emcitate tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of tiratricol

No clinical interaction studies have been performed evaluating the effect of other medicinal products on tiratricol. The potential interactions described below are based on the *in vitro* characterisation of tiratricol and on known pharmacokinetic or pharmacodynamic interactions of thyromimetic agents with other medicinal products and not specifically studied with tiratricol.

Concomitant use with precaution

Medicinal products that may affect the absorption of tiratricol
Antacids, charcoal, calcium, cationic resins (e.g. cholestyramine), iron, sucralphate, and other gastrointestinal agents may interfere with the gastrointestinal absorption of tiratricol. These treatments should be taken before or after tiratricol (more than 2 hours before or after if possible). In the case of cholestyramine, tiratricol should be taken 1 hour before or 4 hours after the resin dose. Adjustment of the tiratricol dose may be required to obtain the desired effect.

Proton pump inhibitors (PPIs)
Co-administration with PPIs may cause a decrease in the absorption of the thyroid hormones, due to the increase of the intragastric pH caused by PPIs such as omeprazole, esomeprazole, pantoprazole, rabeprazole and lansoprazole. Serum concentrations of T3 should be monitored and dose adjustment of tiratricol considered when initiating, changing or discontinuing PPI treatment.

Sevelamer
Sevelamer may decrease the concentration of thyroid hormones and result in reduced efficacy of tiratricol. Sevelamer should be taken more than 2 hours before or after administration of tiratricol.

Medicinal products with enzyme-inducing effect including anti-epileptics
Medicinal products that can induce the enzyme system in the liver, such as barbiturates, phenytoin carbamazepine, rifabutin, rifampicin or products containing St. John's wort (*Hypericum perforatum*) may increase the hepatic clearance of tiratricol. Serum concentrations of T3 should be monitored and dose adjustment of tiratricol considered when initiating, changing or discontinuing an antiepileptic treatment regimen or other enzyme inducing agents.

Antimalarial medicinal products

Concomitant use of tiratricol and antimalarial medicinal products (chloroquine, proguanil) may cause clinical hypothyroidism. Monitoring of serum concentrations of T3 and dose adjustment of tiratricol may be necessary during and after treatment with antimalarial medicinal products.

Medicinal products that may affect the plasma binding of tiratricol/T3
Anabolic steroids and glucocorticoids are known to decrease serum Thyroxine-Binding Globulin (TBG) concentration and may result in lower T3 and tiratricol serum concentration.

Salicylates, anti-coagulants, anti-inflammatory and anti-convulsant medicinal products may cause protein binding site displacement of T3, and potentially tiratricol, from (TBG) and thereby altering serum levels of thyroid hormones, i.e. lower total concentrations but free concentrations remain the same.

Non-contraceptive oestrogens
Non-contraceptive oestrogen and oestrogen containing products (including hormone replacement therapy) may increase the requirement of tiratricol treatment dose.

Orlistat
Orlistat may decrease tiratricol absorption which may result in hypothyroidism (changes in thyroid function should be monitored).

Effect of tiratricol on the pharmacokinetics of other medicinal products

Concomitant use with precaution

Based on *in vitro* data there is an indication that tiratricol may induce CYP3A4 at a gut level and therefore medicinal products with narrow therapeutic indices that are dependent on CYP3A4, including but not limited to: alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, atorvastatin, lovastatin, and simvastatin should be used with caution. Similar precautions should be applied to other agents that are known to depend on CYP3A4 for metabolism. Medicinal products that are substrates of P-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP) efflux transporters with narrow therapeutic indices should also be used with caution.

Pharmacodynamic interactions

Concomitant use not recommended

Other medicinal products used to treat thyroid conditions
Taking tiratricol in combination with other thyromimetic medicinal products or other medicinal products used to treat thyroid conditions (e.g. levothyroxine, propylthiouracil, and carbimazole) may increase the risk of symptoms of hyperthyroidism or hypothyroidism.

Psychostimulants
Administration of psychostimulants (e.g. caffeine, norepinephrine–dopamine reuptake inhibitors (NDRIs), and amphetamines) in combination with high doses of tiratricol may lead to increased heart rate and blood pressure. Concomitant use of psychostimulants and tiratricol is not recommended.

Concomitant use with precaution

Anti-diabetic agents
Tiratricol may reduce blood glucose levels. The dose of anti-diabetic agents may need to be adjusted if administered concomitantly with tiratricol. Periodic monitoring of blood glucose is necessary (see section 4.4).

Oral anticoagulants
The effect of anti-coagulant therapy may be increased during treatment with tiratricol. This may increase the risk of haemorrhage. The dose of anti-coagulant therapy may have to be adjusted if administered concomitantly with tiratricol.

4.6 Fertility, pregnancy and lactation

MCT8 deficiency is an X-linked disease that almost exclusively affects males.

Pregnancy

Tiratricol crosses the placenta. There are no or limited amount of data from the use of tiratricol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Emcitate is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment.

Breast-feeding

It is unknown whether tiratricol/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Emcitate therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

A study in rats showed no impact on fertility and mating ability (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions associated with the use of tiratricol treatment were hyperhidrosis (7%), diarrhoea (6%), irritability (2%), anxiety (2%), and nightmares (2%). These reactions usually occurred at the start of treatment and/or when the dose was increased, and generally resolved within a few days.

Tabulated list of of adverse reactions

The safety assessment of tiratricol is based on data from clinical trials. Adverse reactions are listed by MedDRA system organ class and frequency convention as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Table 3. Adverse reactions

System organ class	Adverse reaction	Frequency category
Psychiatric disorders	Irritability	Common
	Anxiety	Common
	Nightmares	Common
	Insomnia	Not known

Cardiac disorders	Tachycardia	Not known
Gastrointestinal disorders	Diarrhoea	Common
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
General disorders and administration site conditions	Hyperthermia	Not known

Description of selected adverse reactions

Hypermetabolic signs and symptoms
In clinical trials in patients with MCT8 deficiency, the onset of the observed adverse reactions hyperhidrosis, irritability, anxiety, and nightmares coincided with treatment initiation or dose modification. In all cases, these reactions were mild and resolved spontaneously.

At initiation of tiratricol treatment and/or during dose titration, new onset or worsening of hypermetabolic signs and symptoms, such as hyperhidrosis, irritability, anxiety, insomnia, nightmares, hyperthermia, tachycardia, transient elevations in systolic blood pressure (SBP), or diarrhoea, may occur (see section 4.4).

Paediatric population

Safety data were evaluated in 63 patients between 0 and 17 years of age, in Triac Trial I and Triac Trial II combined. Thirty (30) patients were below 2 years of age at start of treatment, 25 patients were between 2 and 11 years of age and 8 patients were between 12 and 17 years of age. There is no indication from clinical trial data that the safety profile in any subset of the paediatric population is different from the safety profile in adult patients.

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

Signs and symptoms of a hypermetabolic state may appear in cases of overdose. Decreasing the dose of Emcitate or temporarily discontinuing treatment alleviates these symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: thyroid hormones, ATC code: H03AA04

Mechanism of action

Tiratricol (3,3',5-triiodothyroacetic acid) is a naturally circulating metabolite of active thyroid hormone (T3) with a high degree of structural similarity and follows the same downward degradation pathway (deiodination and conjugation) and elimination via bile and urine. Tiratricol is biologically active, binds with high affinity to the thyroid hormone receptors TRα and TRβ and exerts similar biological effects to T3, although with different tissue specificity. Tiratricol has been demonstrated to be able to enter MCT8 dependent cells without a functioning MCT8 transporter unlike T3 and T4. Tiratricol can thereby replace T3 in MCT8 dependent tissues and restore normal thyroid hormone activity across tissues.

Clinical efficacy and safety

The effect of tiratricol in treatment of patients with MCT8 deficiency was evaluated in a single arm, open label, multicentre study (Triac Trial I) conducted in 46 patients treated for up to 12 months with an individually titrated dose of tiratricol based on serum T3 levels (target range 1.4 to 2.5 nmol/L). The median age of patients enrolled was 7.1 years, with a range from 10 months to 66.8 years. Forty (40) patients were treated for at least 12 months. The median daily maintenance dose administered was 700 micrograms (38.9 micrograms/kg body weight) with a range from 350 micrograms to 2 100 micrograms. Tiratricol treatment reduced the mean serum T3 concentration from 4.97 nmol/L at baseline to 1.82 nmol/L at month 12 (target range 1.4 to 2.5 nmol/L). All 45 patients with post-baseline T3 values presented a decrease from baseline to month 12 or last available assessment. At month 12, or last available assessment, 25 out of 45 patients (56%) attained serum T3 levels within the target range, 13 out of 45 patients (29%) had T3 levels below the target range, and 7 out of 45 patients (16%) had serum T3 levels above the target range. The results for the primary endpoint are presented in Table 4 and Figure 1.

Table 4. Mean change in serum T3 from baseline to month 12 in Triac Trial I (intention-to-treat (ITT) population)

Variable	N	Baseline mean (SD)	Month 12 mean (SD)	Difference mean [95% CI]	p-value
Serum T3 (nmol/L)	45	4.97 (1.55)	1.82 (0.69)	-3.15 [-3.62; -2.68]	< 0.0001

Figure 1. Serum T3 concentrations at baseline and month 12 in Triac Trial I (ITT population)

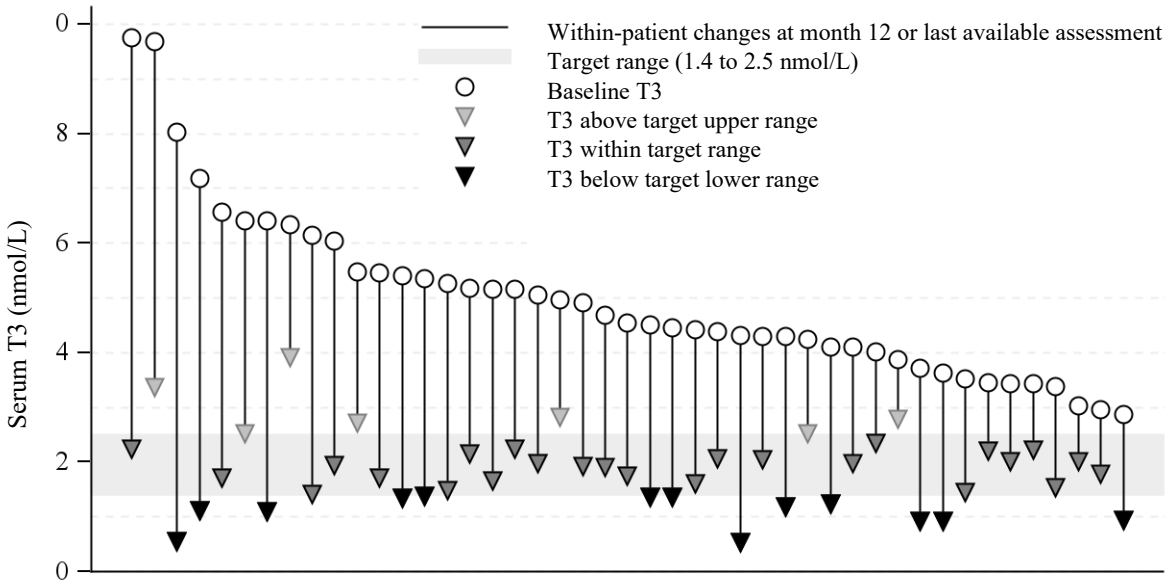

Table 5. Other thyroid hormones – analysis of mean change from baseline to month 12 in Triac Trial I (ITT population)

Variable	N	Baseline mean (SD)	Month 12 mean (SD)	Difference mean [95% CI]	p-value
TSH (mU/L)	45	2.91 (1.68)	1.02 (1.14)	-1.89 [-2.39; -1.39]	<0.0001
Free T4 (pmol/L)	45	9.68 (2.96)	3.39 (1.60)	-6.28 [-7.15; -5.41]	<0.0001
Total T4 (nmol/L)	45	55.96 (12.95)	24.38 (9.44)	-31.58 [-35.15; -28.01]	<0.0001
rT3 (nmol/L)	45	0.12 (0.10)	0.04 (0.04)	-0.08 [-0.10; -0.05]	<0.0001

In Triac Trial I, the mean body weight for age MCT8 Z score (comparing tiratricol treated MCT8 patients with untreated MCT8 patients) was increased from 0.46 at baseline to 0.96 at month 12 (mean change 0.51; 95% CI: 0.25, 0.76), while the mean body weight for age Z scores (comparing tiratricol treated MCT8 patients with a normal population) increased modestly from -2.85 at baseline to -2.63 at month 12 (mean change 0.22; 95% CI: -0.01, 0.45). Results were similar in patients with or without gastroenteral feeding tube at baseline. In total, 40 out of 45 patients (89%) increased in body weight; 28 out of 45 (62%) had an increase in body weight for age Z score, and 28 out of 36 (78%) had an increase in body weight for age MCT8 Z score.

In patients below 2.5 years of age, based on few individuals, mean body weight for age MCT8 Z score increased from -0.10 at baseline to 0.41 at month 12 (n=3), while the mean body weight for age Z scores increased modestly from -1.65 at baseline to -1.61 at month 12 (n=4).

Mean resting heart rate was reduced from 112.4 bpm at baseline to 103.5 bpm at month 12 (mean change -8.9 bpm; 95% CI: -15.6, -2.3), while the mean heart rate for age Z scores (comparing tiratricol treated MCT8 deficiency patients with a normal population) decreased from 1.72 at baseline to 1.38 at month 12 (mean change -0.33; 95% CI: -0.77, 0.10). In patients with tachycardia at baseline, mean resting heart rate was reduced from 131.4 bpm at baseline to 109.6 bpm at month 12 (mean change -21.9 bpm; 95% CI: -30.0, -13.8), while the mean heart rate for age Z scores decreased from 2.80 at baseline to 1.75 at month 12 (mean change -1.05; 95% CI: -1.55, -0.54). In total, 23 out of 34 patients (67%) had a decrease in resting heart rate. In patients with tachycardia at baseline, 15 out of 16 (94%) had a decrease in resting heart rate.

Mean systolic blood pressure was reduced from 107.1 mmHg at baseline to 103.0 mmHg at month 12 (mean change -4.1 mmHg; 95% CI: -8.1, 0.1). In hypertensive patients, mean systolic blood pressure was reduced from 110.9 mmHg at baseline to 102.5 mmHg at month 12 (mean change -8.4 mmHg; 95% CI: -11.7, -5.0). The percentage of patients with hypertension was reduced from 40% at baseline to 17% at month 12 (p=0.02). In total, 24 out of 35 patients (69%) had a decrease in systolic blood pressure. In patients with hypertension at baseline, 12 out of 12 (100%) had a decrease in systolic blood pressure.

In Triac Trial I, all patients (45 out of 45; 100%) improved in at least one of the variables: body weight, resting heart rate, or systolic blood pressure and 31 out of 45 (69%) improved in at least two of these three variables. In total, 39 out of 45 patients (87%) improved in at least one of the variables: body weight for age MCT8 Z score, resting heart rate Z score, or systolic blood pressure Z score and 21 out of 45 (47%) improved in at least two of these three variables.

The mean number of premature atrial contractions measured by 24-hour ECG decreased from 899.7 PACs/24-hours at baseline to 313.9 PACs/24-hours at month 12 (mean change -586; 95% CI: -955, -217).

Creatinine kinase concentrations increased from 108 U/L at baseline to 160.7 U/L at month 12 (mean change 52.7; 95% CI: 27.3,78.1; p=0.0001).

5.2 Pharmacokinetic properties

Absorption

The absorption of tiratricol following oral dosing is rapid with a median t_{max} of 0.5 hours following doses between 175 and 1 050 micrograms in fasted healthy volunteers.

Distribution

The *in vitro* plasma protein binding of tiratricol is high, with protein binding of > 99% in human plasma. The bioavailability of tiratricol (F) was 67 ± 6% suggesting tiratricol is well absorbed from the gastrointestinal (GI) tract.

Biotransformation

Tiratricol is a naturally circulating metabolite of active T3 with a high degree of structural similarity and follows the same metabolic pathway. The major human metabolic pathway of tiratricol is by stepwise deiodination, sulfation and glucuronidation mainly in the liver, similar to T3.

Elimination

Following C_{max}, serum concentrations declined in a generally biphasic manner and remained quantifiable until between 3 and 48 hours post dose. The geometric mean $t_{½}$ was between 13.3 – 14.0 hours for the 350 microgram and 1 050 microgram doses, respectively. Tiratricol is eliminated through bile and urine.

Linearity

C_{max} following treatment with the 175 microgram, 350 microgram, and 1 050 microgram doses (about 2 to 13.5 micrograms / kg bodyweight) increased proportionally with dose, whereas the area under the curve (AUC) increased in a slightly greater than proportional manner with increasing dose.

Pharmacokinetic/pharmacodynamic relationship(s)

In the clinical trial studying the effect of tiratricol in patients with MCT8 deficiency, the dose was individually titrated based on T3 levels.

5.3 Preclinical safety data

No conventional studies of carcinogenic potential have been conducted with tiratricol. Tiratricol was devoid of mutagenic activity when tested in the Ames Salmonella assay and showed no increase in chromosomal aberrations when tested *in vitro* and *in vivo*.

Embryofetal development studies showed embryolethality in rabbits and embryolethality and structural myocardial damage in rats. On a mg/body surface area (BSA) dose comparison, the no-observed-adverse-effect-levels (NOAELs) in the rat and rabbit studies were slightly lower and slightly higher, respectively, than the highest clinical dose in adult patients.

No effects on mating ability or fertility were observed in a study in male and female rats administered high and otherwise toxic doses of tiratricol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogen phosphate
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

After dispersion:

The 30 mL dispersion can be stored below 25 °C for up to 4 hours in the glass, and then be resuspended by stirring for 1 minute with a teaspoon prior to administration.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.

For storage conditions after dispersion of the medicinal product, see section 6.3.

6.5 Nature and contents of container

PVC/Aluminium blister.

Pack size of 60 dispersible tablets.

6.6 Special precautions for disposal and other handling

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

The product can be administered through a gastroenteral feeding tube.
The product has been tested using a percutaneous endoscopic gastrostomy (PEG) silicone tube (lumen 12 French, maximum length 34 cm), and nasogastric (NG) polyurethane tubes (lumen 6 French and 8 French, maximum length 56 cm). This product has not been tested with other types of tubes or tube materials. A 3 mL flush volume (water) is recommended.

7. MARKETING AUTHORISATION HOLDER

Rare Thyroid Therapeutics International AB
Klara Norra Kyrkogata 26
111 22 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1897/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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

Cenexi
17 Rue De Pontoise
95520 Osny
France

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 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Emcitate 350 microgram dispersible tablets
tiratricol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains 350 micrograms of tiratricol.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersible tablet

60 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral 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

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.

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

Rare Thyroid Therapeutics International AB
Klara Norra Kyrkogata 26
111 22 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1897/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Emcitate

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 BLISTERS

PVC/ALU Blister

1. NAME OF THE MEDICINAL PRODUCT

Emcitate 350 microgram dispersible tablets
tiratricol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Rare Thyroid Therapeutics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Emcitate 350 microgram dispersible tablets
tiratricol

Read all of this leaflet carefully before you start taking 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 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Emcitate is and what it is used for

Emcitate contains the active substance tiratricol and belongs to a group of medicines called thyroid hormones.

Emcitate is used for the treatment of thyrotoxicosis in patients with MCT8 deficiency (Allan-Herndon-Dudley Syndrome).

Thyrotoxicosis in MCT8 deficiency happens because a protein in the body, called MCT8, is not working as it should. Because of this, thyroid hormones cannot move in and out of cells in the body, which can cause problems in the body and brain. The active substance in Emcitate, tiratricol, is very similar to a natural thyroid hormone in the body called T3. Unlike natural T3, tiratricol does not need MCT8 to move in and out of cells and this helps to get the different types of thyroid hormones in the body to the right levels.

2. What you need to know before you take Emcitate

Do not take Emcitate
- If you are allergic to tiratricol or any of the other ingredients of this medicine (listed in section 6).
- If you have a condition called hyperthyroidism (an overactive thyroid gland) that is not caused by MCT8 deficiency.
- If you are pregnant (see section 2, Pregnancy and breast-feeding).

Do not take Emcitate if this applies to you. If you are not sure, talk to your doctor or nurse before taking Emcitate.

Warnings and precautions
Talk to your doctor or nurse before taking Emcitate if:
- You have diabetes
- You have problems with your heart
- You have problems with your liver or kidneys

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before taking Emcitate.

Emcitate can cause some side effects called hypermetabolic symptoms (see section 4, Possible side effects). If you experience any of these symptoms and they persist, your doctor may adjust your dose of Emcitate. However, do not change the dose without talking to your doctor first.

Emcitate must not be taken for weight-loss. It can cause serious or life-threatening side effects, especially when taken together with orlistat for weight-loss.

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

Do not take Emcitate, and tell your doctor or nurse, if you are taking any of the following medicines:
- Medicines for thyroid conditions that work like thyroid hormones, such as levothyroxine, proplythiouracil and carbimazole. Taking them with Emcitate could make your thyroid hormone levels too high or too low.
- Psychostimulants (substances that increase brain activity), such as methylphenidate, amphetamines and caffeine. Taking them with Emcitate can raise your heart rate and blood pressure.

If any of the above apply to you (or you are not sure), do not take Emcitate and tell your doctor or nurse.

Some medicines should be taken well before or after you take Emcitate because they may lower how much Emcitate is absorbed in the body. Talk to your doctor or pharmacist before you take Emcitate if you are taking any of the following medicines:
- Antacids
- Charcoal tablets
- Calcium or iron medicines
- Sucralphate, a medicine for stomach problems
- Sevelamer carbonate, a medicine for kidney problems.

These should be taken at least 2 hours before or after you take Emcitate.

- Cholestyramine, a medicine to lower cholesterol

Take Emcitate at least 1 hour before or 4 hours after.

If you are not sure if the above applies to you, talk to your doctor or pharmacist before taking Emcitate.

Also tell your doctor or pharmacist if you are taking:
- Medicines for diabetes – Emcitate may lower blood glucose levels. This means that your doctor may decide to adjust the dose of diabetes medicines.
- Blood-thinning medicines – Emcitate may increase the effect of blood-thinning medicines. This may make you bleed more often. The dose of these medicines may have to be changed.
- Some medicines for epilepsy (such as phenytoin and carbamazepine, phenobarbital and phenytoin) – These may increase how fast your body breaks down Emcitate. Your doctor may need to regularly check your blood levels of T3 if you are starting, changing or stopping treatment with these medicines. The dose of Emcitate may need to be changed.
- Proton pump inhibitors (such as omeprazole, esomeprazole, pantoprazole, rabeprazole and lansoprazole) used to lower the amount of acid produced by the stomach – These may lower the amount of Emcitate that is absorbed by your body. The dose of Emcitate may need to be changed.
- Antimalarial medicines (such as chloroquine, proguanil) – These may cause hypothyroidism when used together with Emcitate. Your doctor may need to regularly check your blood levels of T3 and adjust the dose of Emcitate during and after treatment with antimalarial medicines.

- Antibiotic medicines (used for the treatment of bacterial infections) such as rifampicin and rifabutin. The dose of Emcitate may need to be changed.
- Anti-inflammatory medicines, corticosteroids (such as hydrocortisone) and pain medicines (such as salicylates, acetylsalicylic acid or naproxen, phenylbutazone and aspirin) – These may lower blood levels of Emcitate.
- Herbal medicines (such as St. John's wort (*Hypericum perforatum*)) – This may increase how fast your body breaks down Emcitate. Your doctor may need to regularly check your blood levels of T3 if you are starting, changing or stopping treatment with this medicine.
- Immunosuppressants, medicines used after an organ transplantation (such as ciclosporin, everolimus, sirolimus and tacrolimus) – Emcitate may change how fast these are broken down by your body.
- Medicines for lowering blood cholesterol (such as atorvastatin, lovastatin and simvastatin) – Emcitate may change how fast these are broken down by your body.
- If you are taking oestrogen or products containing oestrogen (such as hormone replacement therapy, but not contraceptives), you may need a higher dose of tiratricol.
- The weight-loss medicine orlistat may lower the amount of tiratricol your body takes in, which can lead to low thyroid hormone levels. Your doctor may need to check your thyroid function if you are taking orlistat with tiratricol.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before taking Emcitate.

Pregnancy and breast-feeding
You must not take Emcitate if you are pregnant, as it is not known if it will be harmful to an unborn baby.
You must not become pregnant while taking Emcitate. If you are able to have a baby, you must use effective contraception (birth control) while taking Emcitate.

If you do become pregnant during your treatment with Emcitate, you must stop treatment and inform your doctor immediately.

Talk to your doctor before taking this medicine if you are breast-feeding. This is because it is not known if it passes into breast milk. You and your doctor must decide whether to stop breast-feeding or to stop taking Emcitate, considering the benefit of breast-feeding for your child and the benefit of Emcitate for you.

Driving and using machines
Emcitate does not affect your ability to drive, cycle or use any tools or machines.
If you think this medicine might be affecting your ability to drive or use machines, do not drive, cycle or use any tools or machines until symptoms have improved.

Emcitate contains lactose
Emcitate contains lactose, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Emcitate

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

Treatment will be started and monitored by doctors who are experienced in treating people with rare genetic diseases such as MCT8 deficiency.

How much Emcitate to take
Your doctor will decide what dose is right for you. Your dose of Emcitate depends on your thyroid hormone levels and body weight.

- Your dose will be increased every two weeks until your levels of T3 are right for your situation.
- When you are taking a stable dose of Emcitate, your blood levels of T3 will be checked regularly. If levels change and are no longer right for you, your doctor may decide to adjust your dose.
- Do not change the dose without talking to your doctor first.

When to take Emcitate
When you start taking 2 or more tablets a day, spread the doses over the day – such as morning, midday and evening.

How to take Emcitate
Emcitate dispersible tablets should always be dispersed in water before use. The dispersion should be given by mouth or through a gastroenteral feeding tube.

<u>To give by mouth</u>
1. Make the dispersion in a small glass. This glass should not be used for anything else.
   - Mix the tablet or tablets (not more than 4 tablets at once) in 30 mL of drinking water. Only use drinking water – do not use any other liquids.
   - If you need half a tablet – break the tablet along the score line in the middle of the tablet.
   - Stir with a teaspoon for 1 minute. The dispersion should look cloudy white. The teaspoon should not be used for anything else.
2. Use a syringe to pull up the dispersion from the glass. The syringe should only be used for Emcitate.
3. Slowly and gently push the plunger down to gently squirt the medicine into the inside of your cheek and swallow it.
4. Then put 10 mL more drinking water into the glass to mix any remaining medicine
   - Stir with the teaspoon for around 5 seconds to make sure any dispersion left is mixed in.
   - Pull up the dispersion from the glass with the same syringe.
5. Take Emcitate as described under step 3.

<u>To give through a gastroenteral feeding tube</u>
1. Make the dispersion in a small glass. This glass should not be used for anything else.
   - Mix the tablet or tablets (not more than 4 tablets at once) in 30 mL of drinking water. Only use drinking water – do not use any other liquids.
   - If you need half a tablet – break the tablet along the score line in the middle of the tablet.
   - Stir with a teaspoon for 1 minute. The dispersion should look cloudy white. The teaspoon should not be used for anything else.
2. Use a syringe to pull up the dispersion from the glass. The syringe should only be used for Emcitate.
3. Please read instructions on the use of the feeding tube carefully before giving Emcitate and use the tube exactly as prescribed.
4. Then put 10 mL more drinking water into the glass to mix any remaining medicine
   - Stir with the teaspoon for around 5 seconds to make sure any dispersion left is mixed in.
   - Pull up the dispersion from the glass with the same syringe.
5. Give Emcitate as prescribed for the tube.
6. Flush and rinse as prescribed for the tube. A 3 mL flush volume (water) is recommended.

If you take more Emcitate than you should
If you take more Emcitate than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

The following effects may happen: fast heartbeat, sweating, body overheating, feeling nervous, not being able to sleep or diarrhoea (signs of a hypermetabolic state).
- Your doctor may lower your dose or pause treatment.

If you forget to take Emcitate
- If you forget a dose, you can take it if there are more than 4 hours to the next dose.

- If the next dose is planned within 4 hours, skip the missed dose and take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Emcitate
Do not stop taking Emcitate without talking to your doctor.

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.

The following side effects may happen with this medicine:

Common (may affect up to 1 in 10 people)
- feeling irritable
- anxiety
- nightmares
- diarrhoea
- excessive sweating (hyperhidrosis)

Not known (frequency cannot be estimated from the available data)
- trouble sleeping (insomnia)
- a faster heartbeat (tachycardia)
- feeling too warm (hyperthermia)

Emcitate can cause so-called hypermetabolic symptoms when starting treatment or when the dose is changed. The symptoms usually do not last more than a few days, but you should inform your doctor immediately if you have symptoms that could be a sign of hypermetabolism such as feeling irritable, anxiety, nightmares, excessive sweating, trouble sleeping, feeling too warm, a faster heartbeat, temporary rises in blood pressure, or diarrhoea. See section 2, Warnings and precautions.

Tell your doctor or nurse if you notice any of the side effects listed above. Also tell them if you think you have any other side effects not in this list.

Reporting of side effects
If you get any side effects, talk to your doctor 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. Like all medicines, this medicine can cause side effects, although not everybody gets them.

5. How to store Emcitate

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 blister foil. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Store in the original package in order to protect from light.

After dispersion:

The 30 mL dispersion can be stored below 25 °C for up to 4 hours in the glass, and then be resuspended by stirring for 1 minute with a teaspoon prior to administration.

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 to protect the environment.

6. Contents of the pack and other information

What Emcitate contains
- Each tablet contains 350 micrograms of the active substance tiratricol.
- The other ingredients are lactose monohydrate (see section 2, 'Emcitate contains lactose'), calcium hydrogen phosphate, maize starch, and magnesium stearate.

What Emcitate looks like and contents of the pack
Emcitate is a white, oblong tablet (size: 10 mm long, 5 mm wide) with score lines on both sides.

Emcitate is supplied in PVC/aluminium blisters, inserted into an outer carton.
Emcitate is available in packs containing 60 dispersible tablets.

Marketing Authorisation Holder
Rare Thyroid Therapeutics International AB
Klara Norra Kyrkogata 26
111 22 Stockholm
Sweden

Manufacturer
Cenexi
17 Rue De Pontoise
95529 Osny
France

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. There are also links to other websites about rare diseases and treatments.