[redacted]

EU Risk Management Plan (RMP) for Emcitate (tiratricol)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 30 June 2024

Date of final sign-off: 11 December 2024

Rationale for submitting an updated RMP: This is the final version of the RMP prepared as part of the initial Marketing Authorization Application (MAA).

Summary of significant changes in this RMP: This is an initial version of the RMP

QPPV name: Panagiota Kontogianni, MSc [redacted]

QPPV signature: [redacted]

Table of contents

Abbreviations 3

Part I: Product(s) overview 5

Part II: Module SI - Epidemiology of the indication(s) and target population(s) 8

Part II: Module SII - Nonclinical part of the safety specification 11

Part II: Module SIII - Clinical trial exposure 12

Part II: Module SIV - Populations not studied in clinical trials 17

Part II: Module SV – Post authorization experience 17

SV.1 Post authorization exposure 17

Part II: Module SVI - Additional EU requirements for the safety specification 18

Part II: Module SVII - Identified and potential risks 18

SVII.1 Identification of safety concerns in the initial RMP submission 18

SVII.2 New safety concerns and reclassification with a submission of an updated RMP 23

SVII.3 Details of important identified risks, important potential risks, and missing information 23

Part II: Module SVIII - Summary of the safety concerns 24

Part III: Pharmacovigilance plan (including post authorization safety studies) 24

III.1 Routine pharmacovigilance activities 24

III.2 Additional pharmacovigilance activities 25

III.3 Summary table of additional pharmacovigilance activities 26

Part IV: Plans for post authorization efficacy studies 29

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities) 30

V.1. Routine risk minimization measures 30

V.2. Additional risk minimization measures 30

V.3 Summary of risk minimization measures 31

Part VI: Summary of the risk management plan 32

II.A List of important risks and missing information 33

II.B Summary of important risks 33

II.C Post authorization development plan 34

II.C.1 Studies which are conditions of the marketing authorization 34

II.C.2 Other studies in post authorization development plan 34

Part VII: Annexes 36

Annex 1 – EudraVigilance interface 36

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program 36

Annex 3 - Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan 36

Annex 4 - Specific adverse drug reaction follow-up forms 36

Annex 5 - Protocols for proposed and ongoing studies in RMP Part IV 36

Annex 6 - Details of proposed additional risk minimization activities (if applicable) 36

Annex 7 - Other supporting data (including referenced material) 36

Annex 8 – Summary of changes to the risk management plan over time 38

Abbreviations

Abbreviation	Definition
AAC	Authorisation d'Accès Compassionnel
AE	Adverse event
ATC	ATC
BERA	Brainstem evoked response audiogram
BSID-III	Bayley scales of infant development III
CSR	Clinical study report
DLP	Data lock point
DSUR	Development safety update report
EAP	Expanded Access Program
EEG	Electroencephalogram
EMA	European Medicines Agency
EMC	Erasmus Medical Centre
EPAR	European public assessment report
EU	European Union
FDA	Food and Drug Administration
GMFM-88	Gross motor function measure 88
INN	International nonproprietary names
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MAA	Marketing authorization applicant
MCT8	Monocarboxylate transporter 8
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NPU	Named patient use
PIL	Package information leaflet
PSUR	Periodic safety update report
PTY	Patient years
RMP	Risk management plan
RTHβ	Resistance to thyroid hormone beta
SmPC	Summary of product characteristics
T3	3,3',5-triiodothyronine
TEP	Treatment extension period
TH	Thyroid hormone
TR	Thyroid receptor
TSH	Thyroid stimulating hormone

Abbreviation	Definition
UK	United Kingdom
US	United States of America
VEP	Visual evoked potentials

Part I: Product(s) overview

Table Part I.1 – Product(s) overview

Active substance(s) **(INN or common name)**	Tiratricol
Pharmacotherapeutic group(s) (ATC Code)	Thyroid hormones (H03AA04)
Marketing authorization applicant (MAA)	Rare Thyroid Therapeutics International AB, Klara Norra Kyrkogata 26, Stockholm, Sweden
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Emcitate
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Tiratricol (3,3',5-triiodothyroacetic acid) is a naturally circulating metabolite of active thyroid hormone (T3)
	Summary of mode of action: Tiratricol is a naturally circulating metabolite of active thyroid hormone (T3) with a high degree of structural similarity and follows the same downward degradation pathway (deamination 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. In patients with MCT8 deficiency, tiratricol can thereby replace T3 in MCT8 dependent tissues and restore normal thyroid hormone activity across tissues.
	Important information about its composition: Emcitate tablets contain lactose. In patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption, special clinical consideration should be taken by the treating physician before initiating treatment.

<table>
<tr><td>Hyperlink to the product information</td><td>Product information is presented in common technical document Module 1 (Module 1.3.1).</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current:

Treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.</td></tr>
<tr><td>Proposed (if applicable):

Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

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 is 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
<table>
<tr><th>Titration</th><th>Total daily dose (micrograms)</th><th>Number of tablets/day</th></tr>
<tr><td>Starting dose</td><td>350</td><td>1</td></tr>
<tr><td>Week 2</td><td>700</td><td>2</td></tr>
</table>
</td></tr>
</table>

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	1.0
Week 4	525	1.5
Week 6	700	2.0
Week 8	875	2.5
Week 10	1050	3.0
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.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): • 350 micrograms 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 halves
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

MCT8 deficiency:

MCT8 deficiency (also known as Allan-Herndon-Dudley syndrome) is a rare, chronic, devastating, and severely debilitating condition caused by the dysfunction of a key TH transporter (MCT8), leading to substantially deranged TH signal across tissues (Visser et al. 2013). There are currently no approved therapies available (orpha.net).

Incidence:

MCT8 deficiency is a genetic X-linked rare disease occurring in less than 1 in 70,000 males or 1 in 140,000 live births (Groeneweg et al. 2020).

Prevalence:

There are currently approximately 320 known cases diagnosed with MCT8 deficiency described in literature (orpha.net). The exact number of patients having MCT8 deficiency is not known, since many patients today likely remain undiagnosed. Based on literature data, MCT8 deficiency prevalence is 1.4% of males with intellectual disability of unknown etiology (orpha.net).

Demographics of the population in the proposed indication:

MCT8 deficiency is an X-linked congenital disease affecting predominantly male patients from their first days of life after apparent normal intrauterine development and birth.

Patients with MCT8 deficiency present with a broad spectrum of symptoms, resulting from disrupted or dysfunctional MCT8-mediated TH transport in various tissues. Since both neural cells (e.g., neurons) and endothelial cells forming the blood-brain-barrier are solely depending on

MCT8 for TH transport, MCT8 deficiency leads to impaired neurodevelopment with severe intellectual and motor disability, where affected patients will never gain even basic neurocognitive functions or early developmental milestones. Patients with MCT8 deficiency will only rarely achieve independent sitting and most will not be able to maintain head control. All patients require life-long 24-hour care (Dumitrescu et al. 2004, Friesema et al. 2004, Groeneweg et al. 2020, Schwartz et al. 2005, Schwartz et al. 2007). In addition to the lack of neurodevelopment in childhood, MCT8 deficiency results in a number of non-developmental, chronic, system-wide and severely debilitating symptoms across all ages, caused by dysfunctional TH signaling. Depending on a tissue's dependence on MCT8 or other transporters, such effects may be caused by either a decreased or increased TH signal. In tissues expressing other TH transporters than MCT8, overexposure of T3 is manifested by symptoms such as very low body weight, tachycardia, insomnia, and muscle wasting (Schwartz et al. 2005). The consequences of this chronic TH overexposure in non-MCT8 dependent cells are believed to contribute to the increased mortality and shortened life expectancy in this patient population.

The main existing treatment options:

There are currently no pharmacological treatments approved or routinely used in clinical practice for the treatment of MCT8 deficiency.

Therapeutic measures are primarily supportive to manage symptoms and signs of the disease, including medications to manage seizures and muscle tone, and physical therapy.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The natural history of MCT8 deficiency has been extensively described by Groeneweg et al. 2020 in a retrospective cohort of 151 treatment-naïve patients carrying 73 different underlying MCT8 mutations. The median age at diagnosis in the cohort was 24·months with a median age at onset of first symptoms being approximately 4 months. The median overall survival was 35 years and 30% of patients died during childhood. The median age at time of death was 10.5 years. The main causes of mortality, when known, were pulmonary infection and sudden death. Lack of head control at the age of 1.5 years or being underweight at a young age was associated with increased risk of death. Patients in the cohort commonly suffered from symptoms such as spasticity (80%), urinary or fecal incontinence (80%), impaired swallowing function (71%), and sleep problems (40%). 23% of patients in the natural history study had seizures confirmed by pathological electroencephalogram (EEG) findings.

T3 concentrations were above the age-specific upper reference limit in almost all patients (96 of 101; 95%) and most patients (59 of 83; 71%) were underweight as per World Health Organization definition.

Although most patients were completely immobile, 24-hour ambulatory cardiac monitoring showed a high resting mean heart rate (103 beats per min) with frequent episodes of tachycardia and premature atrial or ventricular contractions. 25 of 47 patients (53%) had a systolic blood pressure above the 90th percentile for the corresponding general age population; 20 of 64 patients (31%) had resting tachycardia; and 34 of 45 patients (76%) had premature atrial contractions present in electrocardiograms.

There were no significant correlations between biological age and neurocognitive developmental age as per the validated/gold standard methods of the GMFM-88 or BSID-III, indicating that motor and cognitive abilities do not improve with age. The patients will not gain even basic

neurocognitive functions and will only rarely achieve independent sitting, and most will not be able to maintain head control.

The Groeneweg et al. 2020 natural history study shows high morbidity and poor survival in untreated MCT8 deficiency. A high prevalence of potentially treatable risk factors was noted, such as tachycardia, arrythmia, hypertension, low body weight, and hypermetabolism attributable to the peripheral chronic thyrotoxicosis. Reducing high T3 concentrations is therefore key to an effective treatment of the clinically manifested risk factors of/in MCT8 deficiency.

The natural history study includes a substantial number of patients in an ultra-rare indication and covers the most important endpoints used in the clinical studies. It is therefore relevant to compare (other) clinical study results with this untreated study population as a control group.

A structured literature review covering the period up to 30 June 2023 identified 37 publications providing additional clinical information on untreated patients with MCT8 deficiency. These case reports support the findings in Groeneweg et al. 2020 (see Module 5.3.5.4, Summary of case reports).

Important comorbidities:

Patients with MCT8 deficiency to a high extent suffer from seizures, arrhythmias, and infections, all intrinsic manifestations of the MCT8-deficiency syndrome.

Relevant data were available from the natural history cohort study to determine the incidence of seizures for 65 treatment-naïve patients with MCT8 deficiency. Of these, 15 patients (23%) had EEG-confirmed seizures which were characterized as generalized absence-like episodes without a clear motor component Groeneweg et al. 2020. The extent of medicinal treatment, including antiepileptic treatment, was not described and neither was the frequency of seizures with or without antiepileptic treatment. Seizures in the MCT8 deficiency population are not always confirmed by EEG, are atypical in characteristics, and are difficult to treat successfully with antiepileptic therapy (Sarret et al. 2020, Masnada et al. 2022).

Recurrent pulmonary infections are reported as a common clinical feature in patients with MCT8 deficiency in the natural history cohort study, reported in 69% of patients (Groeneweg et al. 2020). Patients had several risk factors for pulmonary infections, including immobility, muscular hypotonia, and underweight.

Resting tachycardia was reported for 20 of 64 patients (31%), defined as a resting heart rate above the 90th percentile for the corresponding age. Systolic blood pressure above the 90th percentile was reported for 25 of 47 patients (53%). Premature atrial contractions were reported for 34 of 45 patients (76%). Prolonged QTc interval was above the 98th percentile in 3 of 39 patients (8%) (Groeneweg et al. 2020).

Part II: Module SII - Nonclinical part of the safety specification

The application for authorization of the medicinal product concerned by this RMP is submitted according to the Article 10(3) of Directive 2001/83/EC, (as amended, hybrid application).

Nonclinical studies/data of relevance for this part of the MAA are described below.

The acute toxicity of tiratricol is low as demonstrated after single doses to mice and rats.

When administered orally to non-diseased juvenile rats for up to 3 months there were dose-related effects on organ-weights, clinical chemistry endpoints and bone parameters evidencing that the animals were overall in a hyperthyroid state. Sudden deaths/early sacrifices were observed in all dose groups, a finding consistent with reports from a previously conducted 6 months rat study. Since there were no histopathological correlates to the deaths, they are considered the result of persistent electrophysiological changes of the heart as observed after thyroid hormone administration in this species (Aizawa et al. 2000; Ma et al. 2003; Liu et al. 2021). Since MCT8 deficient patients tolerate higher tiratricol doses than those associated with mortality in the juvenile rat study, the rat mortality and toxicity in this species are considered of limited clinical relevance.

A 3-month study in dogs also showed clear evidence of significant hyperthyroidism particularly in high dose animals. Evidence of hyperthyroidism at this dose consisted, for example, of significant increases in heart rate and myocyte hypertrophy as indicated from an increase in heart-to-brain weight ratios. High dose tiratricol was also associated with a prolongation of the corrected QT interval. However, ECG's taken on Day 1 of the study showed no QTc prolongation although similar exposures were achieved as further on in the study. Since an in vitro hERG assay showed no relevant inhibition of the IKr potassium current at high concentrations of tiratricol, the QTc prolongation should not be the result of a blockade of the hERG potassium channel. Investigations of ion currents in ventricle myocytes collected from tachycardia-induced heart failure dogs have shown electrophysiological changes of the heart including action potential duration prolongation (Akar et al. 2005; Zicha et al. 2004) providing a possible explanation to the observed QTc prolongation in this species. The estimated mean exposure at 20 weeks in the Triac Trial II was 2.1-fold the exposure at NOAEL in female dogs. Since no significant CV abnormalities, have been detected in the Triac Trial II (2 years duration) where the mean dose level was > 4-fold higher than in Triac Trial I, there should be no clinical concern for induction of cardiovascular changes such as observed in the dog toxicity study. Furthermore, slit lamp examinations revealed lens opacities in all high dose dogs. This effect was not reversible when examined one month after end of dosing. In view of the documented propensity of cholesterol lowering drugs, with different mechanisms of action, to induce cataracts in dogs (Peter et al. 1973; Cenedella 1983; Gerson et al. 1990; Pyrah et al. 2001), it would appear likely that the cataractogenic activity of tiratricol is intimately linked to its effect on cholesterol synthesis. Since there is no or minor reductions on cholesterol in MCT8 patients treated with tiratricol, there should be no risk for lens opacities.

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.

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.

In summary, non-clinical toxicity studies in rats and dogs with tiratricol have shown toxicities consistent with exaggerated pharmacological activity i.e. overactivity on tissues/organs expressing TRα and TRβ. Since tiratricol is dosed in MCT8 patients to achieve an euthyroid state,

recommended monitoring of thyroid hormone status should guard against the development of adverse pharmacological activities.

Part II: Module SIII - Clinical trial exposure

In MCT8 deficient patients, 2 investigator-initiated studies have been completed (Triac Trial I and the EMC cohort study). In addition, a sponsor-led study (Triac Trial II) has been completed in patients with MCT8-deficiency. Tiratricol is currently also available for named patient/compassionate use. The data from the clinical trials and from named patient/compassionate use are supporting the MAA for Emcitate.

In view of feedback on the development program by the US FDA, a small short-term, placebo-controlled withdrawal study with tiratricol (ReTRIACt) was initiated, and the study is currently ongoing in the US, UK, and EU (see Module 2.7.3). At the DLP, limited safety data is available from this study (DSUR no. 4).

As summarized in Table SIII.1, in Triac Trial I and the EMC cohort study, a total of 86 patients received at least 1 dose of tiratricol. 27 of the 46 patients who participated in Triac Trial I subsequently continued in the EMC cohort study (EMC Triac Trial I subset). An additional 40 patients who participated in the EMC cohort study had not participated in Triac Trial I (EMC NPU subset). Of the 46 patients who participated in Triac Trial I, 36 patients (78%) received treatment for less than 2 years and 10 patients (22%) received treatment for more than 2 years during the study. 24 of the 27 patients (89%) from Triac Trial I who continued into the EMC cohort study (EMC Triac Trial I subset) had received treatment for at least 2 years. Of the 40 patients who participated in the EMC cohort study (EMC NPU subset), 14 patients (35%) had received treatment for at least 2 years (Table SIII.1). In Triac Trial I, 46 patients received tiratricol, with 40 patients completing the 12-month study period. 6 patients discontinued prior to 12 months of treatment due to decision by the caregiver (2 patients; 1 due to long travel time to the study center and 1 due to severe comorbidity), lost to follow-up, noncompliance, development of Graves' disease, and death due to sepsis (1 patient each). A country-specific protocol amendment in the Netherlands allowed continuation in a treatment extension period (TEP). Of the 40 patients who completed 12 months of treatment, 10 continued and were enrolled in the TEP.

The dose of tiratricol in Triac Trial I was increased following a dose titration schedule of biweekly steps to determine the individual optimal dosing regimen based on serum total T3 levels. The maximum dose administered was 2100 micrograms/day. The target level for serum T3 normalization was between 1.4 and 2.5 nmol/L. Of the 46 patients who participated in Triac Trial I, 5 were <2 years of age with 1 patient being <1 years old (0.8 years old) at the time of the start of treatment (Study MCT8-2014-1 CSR, Listing 16.2.3). The maintenance dose varied between 350 and 2100 micrograms/day with the doses of 350 and 700 micrograms/day (corresponding to 1 or 2 tablets) being the most frequently used. The lowest administered dose during the study was 175 micrograms/day for patients aged <2 years and 350 micrograms/day for adults (Study MCT8-2014-1 CSR, Table 14.1-3). The highest administered dose of 2100 micrograms/day was used by patients aged 11 and 14 years at study entry. Dose titration was not stopped due to AEs in any patient.

In the EMC NPU subset of EMC cohort study, the youngest patient to start treatment with tiratricol was approximately 6 months old. Of the 40 patients in the EMC NPU subset, 7 were <1 years of age, 18 were <2 years, and 20 were <2.5 years of age (Technical Report: EMC cohort study). In the EMC NPU subset, the median duration of treatment was 1.53 years (range: 0.16 to

5.0 years) (Technical Report: EMC cohort study, Table E-1). For patients <2.5 years old (n=20) in the EMC NPU subset, median duration of treatment was 1.35 years (range: 0.16 to 3.59 years) (Technical Report: EMC cohort study, Table E-2). For patients ≥2.5 years old (n=20), median duration of treatment was 2.14 years (range: 0.22 to 5.0 years) (Technical Report: EMC cohort study, Table E-3). For the EMC NPU subset, median dose of tiratricol at the first maintenance dose visit (n=16) was 51.8 micrograms/kg/day (range: 35.71 to 112.2 micrograms/kg/day). The median dose was similar at the 12-month visit (n=26, 48.25 micrograms/kg/day [range: 25.00 to 106.52 micrograms/kg/day]) and at the last visit (n=37, 54.26 micrograms/kg/day [range: 29.91 to 107.9 micrograms/kg/day]) (Technical Report: EMC cohort study, Table A-4). Dose titration was not stopped in any patient due to AEs.

In Triac Trial I, 5 patients were <2.5 years of age; 2 patients (40%) received treatment for <1 year, 1 patient (20%) received treatment for between 3 and 5 years, and 2 patients (40%) received treatment for >5 years (Technical Report: EMC cohort study, Table E-2).

Total exposure (approximately) with tiratricol was 232 PTY in Triac Trial I, EMC cohort study, and Triac Trial II (n=108). The exposure was 123 PTY in Triac Trial I (including patients in TEP and EMC Triac Trial I subset of EMC cohort study) and was 70 PTY in EMC NPU subset of EMC cohort study. Overall, of the total exposure of 232 PTY in Triac Trial I (including patients in TEP, and EMC Triac Trial I subset of EMC cohort study), EMC NPU subset of EMC cohort study, and Triac Trial II, exposure of 150 PTY was observed in patients >2.5 years of age and 82 PTY in patients <2.5 years of age (Table SIII.2).

Table SIII.1 Summary of exposure to tiratricol (Triac Trial I, EMC cohort study and Triac Trial II)

Study	Exposure	n (%)
Triac Trial I including TEP **N=46** **n (%)**	<2 years	36 (78%)
	2 to 5 years	10 (22%)
	>5 years	0 (0%)
	Median duration, years	1.1
	Range	0 to 3.6 years
EMC Triac Trial I Subset [a] **N=27** **n (%)**	<2 years	3 (11%)
	2 to 5 years	13 (48%)
	>5 years	11 (41%)
	Median duration, years	4.3
	Range	1.5 to 6.2 years
EMC NPU Subset **N=40** **n (%)**	<2 years	26 (65%)[d]
	2 to 5 years	13 (33%)[c]
	>5 years	1 (3%)[c]
	Median duration, years	1.5
	Range	0.2 to 5.0 years
Triac Trial II **N=22** **n (%)**	<2 years	22 (100%)
	2 to 5 years	1 (0.04%)
	Median duration, years	1.9
	Range	0.4 to 2.1 years

Source: Technical report Triac Trial I Table F-3 and Figure F-1; Technical Report: EMC cohort study Table A-1, Table B-1, Table-E1, Table E-2, and Table E-3; Module 2.7.4, Section 2.7.4.1.2; Triac Trial II: Table 14.1.13.1, Listing 16.2.5.2

CSR=clinical study report; EMC=Erasmus Medical Centre; N=number of patients analyzed; n=number of patients with the event; NPU=named patient use; TEP=treatment extension period.

[a] Patients participated in Triac Trial I prior to the EMC cohort study. Exposure includes treatment in both studies.

In Triac Trial II (part I completed), 22 patients received at least 1 dose of tiratricol (Triac Trial II summary report Module 5.3.5.2 section 4.2.1).

Tiratricol dose escalation continued until target T3 level was achieved in accordance with the dose titration scheme. In order to increase the chances of a positive effect on the neurological phenotype of the disease, the dose escalation continued until patients were receiving approximately 150-200 micrograms/kg/day, provided T3 levels did not drop below 10% of the LLN and while no DLTs were observed.

The dose escalation was not stopped due to DLTs in any patient. The majority of patients in the study achieved T3 levels within the target range and completed their initial dose escalation between week 8 to 16, and were receiving between 150-200 micrograms/kg/day on completion of their dose escalation (Triac Trial II Summary Report, Table 4-5). Reflecting that only 1 patient discontinued the study, overall median exposure to tiratricol during Part I of the study was 97.1 weeks, range 2 to 107 weeks.

At a dose of approximately 70-100 micrograms/kg/day, serum T3 levels had reached a maximum reduction and did not decrease further with increasing dose of tiratricol.

In order to keep a constant dose/kg and avoid an increase in T3 to above the LLN, there were frequent dose increases during the study as patients grew older and gained weight.

Table SIII.2 Exposure in Patient Years

Age Group	All Ages From Birth		<2.5 Years Old		>2.5 Years Old	
Study	N	Exposure in Patient Years	N	Exposure in Patient Years	N	Exposure in Patient Years
Triac Trial I including TEP and EMC Triac Trial I Subset [a]	46	123	5	16	41	107
EMC NPU Subset	40	70	20	27	20	43
Triac Trial II	22	39	22	39	0	0
Total Exposure in Patient Years	108	232	47	82	61	150

Source: Technical Report: EMC cohort study Table-E1, Table E-2, and Table E-3; Tiratricol DSUR no. 3; Module 2.7.4, Section 2.7.4.1.2; Triac Trial II: Listing 16.2.5.2.

CSR=clinical study report; EMC=Erasmus Medical Centre; NA=not available; N=number of patients analyzed; n=number of patients with the event; NPU=named patient use; TEP=treatment extension period.

[a] 27 patients from Triac Trial I were subsequently enrolled in the EMC cohort study. Exposure includes treatment in both studies.

In Turkey, a compassionate use program for tiratricol has been ongoing since September 2021 and a total of 18 patients have received tiratricol in this program (Tiratricol DSUR no. 4 and data on file). A similar program known as the Autorisation d'Accès Compassionnel (AAC) was started in France in July 2023, with 13 patients receiving tiratricol up until the data lock point (DLP) for this RMP (Tiratricol DSUR No. 4, data on file). In the US, an expanded access program (EAP) has been ongoing since January 2023, with a total of 8 patients receiving tiratricol up until the DLP (Tiratricol DSUR No. 4, data on file).

For the patients treated with tiratricol under named patient use (168 patients with MCT8 deficiency, 38 patients with RTHβ and 7 patients with unknown indications) no information on dose or duration of exposure is available (Tiratricol DSUR no. 4 and data on file).

In addition, tiratricol has been used in other indications for over 40 years with an estimated >10,000 PTY exposure to tiratricol from marketing experience of Teatrois between 2007 and 2021 (Module 2.7.4, Section 2.7.4.6).

Age group and gender data for patients who received tiratricol in Triac Trial I and the EMC cohort study are summarized in Table SIII.3. In both studies, all patients were male. The age range of patients was wide (0.8 to 66.8 years at baseline), with patients in Triac Trial I being older (median age 7.1 years) than patients in the EMC NPU subset of the EMC cohort study (median age of 2.7 years). Half of patients in the EMC NPU subset were <2.5 years of age.

In the completed Triac Trial II (part I), of the 22 male patients enrolled, 8 patients were between 5 and 12 months old, 10 patients were between 12 and 24 months, and 4 patients > 24 months old at the start of the study (Triac Trial II Summary Report). Age group and gender data for patients who received tiratricol in Triac Trial II are summarized in Table SIII.3.

No demographic data are available from named patient use of tiratricol. All 18 male patients in the ongoing compassionate use program in Turkey were between 3 and 17 years of age at the time of entry in the program (Module 2.7.4, Section 2.7.4.1.3).

Table SIII.3 Age group and gender

	Triac Trial I N=46	EMC Cohort Study N=67		Triac Trial II (Part I) N=22
Characteristic		**EMC Triac Trial I Subset[a] N=27**	**EMC NPU Subset N=40**	
Median age in years (range)	7.1 (0.8 to 66.8)	6.9 (1.6 to 66.8)	2.7 (0.5 to 27.4)	1.3 (0.4 to 2.3)
Age (groups)				
No. of patients <2.5 years	5 (11%)	3 (11%)	20 (50%)	22 (100%)
No. of patients >2.5 to 5 years	8 (17%)	4 (15%)	9 (23%)	NA
No. of patients >5 to 10 years	17 (37%)	10 (37%)	7 (18%)	NA
No. of patients >10 to 18 years	11 (24%)	7 (26%)	3 (8%)	NA
No. of patients >18 years	5 (11%)	3 (11%)	1 (3%)	NA
Sex, males, n (%)	46 (100%)	27 (100%)	40 (100%)	22 (100%)

Source: Study MCT8-2014-1 CSR, Table 10-2 and Listing 16.2.3; Technical Report EMC Table A-1, Table B-1; Tiratricol Triac Trial II Summary Report Section 4.2.1 and Table 14.1.3.1
CSR=clinical study report; EMC=Erasmus Medical Centre; N=number of patients analyzed; n=number of patients with the event; NA=not applicable; NPU=Named Patient Use; NR=not reported.
Note: All the age groups in this table are presented as used by Investigators across different studies.
[a] Patients participated in Triac Trial I prior to the EMC cohort study. Exposure includes treatment in both studies.

Cumulative subject exposure by race to tiratricol from completed Triac Trial I and the EMC cohort study, the completed Triac Trial II (part I) clinical trial, and the Emcitate (tiratricol) compassionate use program in Turkey, are presented in Table SIII.4.

Table SIII.4 Race

	Triac Trial I	EMC Cohort Study[a]		Triac Trial II (Part I)	Emcitate (tiratricol) Compassionate Use Program in Turkey[b]
Race, n (%)	**N=46**	**EMC Triac Trial I Cohort N=27**	**EMC NPU Cohort N=40**	**N=22**	**N = 17**
Caucasian	44 (96%)	NR	NR	19 (86%)	17 (100%)
Asian	1 (2%)	NR	NR	0	0
Mixed	NR	NR	NR	2 (9%)	0
Other	1 (2%)	NR	NR	1 (4%)	0

Source: Study MCT8-2014-1 CSR, Table 10-2; Technical Report EMC; Tiratricol DSUR no. 3, Table 5 and Table 7.
CSR=clinical study report; N=number of patients analyzed; n=number of patients with the event; NR=not reported; NPU=named patient use.
[a] Race of study patients was not reported in EMC cohort study
[b] Information on race was only available for 17 of 18 patients in Compassionate Use Program in Turkey

Part II: Module SIV - Populations not studied in clinical trials

The application for authorization of the medicinal product concerned by this RMP is submitted according to the Article 10(3) of Directive 2001/83/EC, (as amended hybrid application).

Populations studied within the clinical trials and studies are considered fully representative of the population of the planned indication. No clinically relevant exclusion criteria from the very limited MCT8-deficient male patient population have been applied in the studies.

MCT8 deficiency is an ultra-rare disease. MCT8-deficient subpopulations with concurrent renal or hepatic impairment have not been identified and consequently, not further studied or presented in the data supporting the marketing authorisation application. Considering the rarity of the disease, it is considered unfeasible to include sufficient patients with renal or hepatic impairment in future clinical studies or in additional pharmacovigilance activities. Post marketing safety information regarding patients with such comorbidities will be collected through routine pharmacovigilance activities and analysed to gain, and when relevant communicate, knowledge about such populations.

Part II: Module SV – Post authorization experience

Teatrois is a medicinal product with the same composition, strength, and pharmaceutical form as Emcitate – tiratricol 350 microgram tablets. The Applicant has patient exposure information based on PSURs submitted for regulatory purposes.

SV.1 Post authorization exposure

Tiratricol was originally approved and marketed in France in 1974 (as Teatrois) for the indication "Situations requiring suppression of TSH secretion, in particular TH resistance syndromes and differentiated thyroid cancers" with an estimated average of 500 individuals treated in the country each year. Teatrois was available in France for more than 40 years. The marketing application was transferred to Rare Thyroid Therapeutics International AB on 16 May 2018. Teatrois was mainly used as a TH substitute for patients with no or low endogenous T3 production. It was used in this patient population for chronic therapy. As use in France was at a low level (the product was rarely used, use under the approved indication was not recommended in modern clinical guidelines, and alternative treatments for TH resistance syndromes were available), Teatrois was withdrawn from the market by Rare Thyroid Therapeutics International AB on 01 April 2020. Teatrois is not authorized in any other European country.

SV.1.1 Method used to calculate exposure

The recommended dosage for Teatrois was 2 to 5 tablets daily, in 3 to 4 doses, the duration of the treatment being adapted to each individual case. In these conditions, it is not possible to evaluate the number of treated patients during the period, but it is possible to estimate the number of PTY.

Total number of tablets sold were divided by mean daily dose and calculated number of patient-days was divided by 365 to calculate the exposure in PTY. As no actual mean dosage was known, a mean daily dosage of 3.5 tablets was used for this calculation based on the recommended dosage of 2 to 5 tablets daily.

SV.1.2 Exposure

The accumulated patient exposure of Teatrois from available PSURs covering the period 2007 to 2021 is approximately 10,000 PTY (Module 2.7.4, Section 2.7.4.6).

In the most recently submitted PSUR for Teatrois (tiratricol), covering the years 2018 to 2021, 565,200 (Teatrois) tablets and 169,980 (Emcitate) tablets were sold/distributed. Considering a mean daily dosage of 3.5 tablets, the total of units sold during the period 01 November 2018 until 31 October 2021 corresponds to approximately 575 PTY (Tiratricol PSUR 2018-2021, Table 5).

Additionally, tiratricol is currently prescribed on a named patient and compassionate use basis for MCT8 deficiency or RTHβ. At DLP (30 June-2024), there had been 213 patients treated with tiratricol under named patient use (MCT8 deficiency: 168, RTHβ: 38, unknown indication: 7) in 25 different countries (mainly France, Netherlands, Spain, UK, US, and Australia) (Clinical database).

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable. The application for authorization of the medicinal product concerned by this RMP is submitted according to Article 10(3) of Directive 2001/83/EC (as amended, hybrid application).

Part II: Module SVII - Identified and potential risks

The application for authorization of the medicinal product concerned by this RMP is submitted according to Article 10(3) of Directive 2001/83/EC (as amended hybrid application).

The reference medicinal product Teatrois was authorized before the establishment of EU RMP guidelines. There is consequently no approved RMP available for the reference medicinal product.

The active substance related to the current application was on the French market for more than 40 years.

The indication and the target population for Emcitate differ from the reference medicinal product due to the different aims of the therapy. This RMP and described risks concern Emcitate and the target population for the sought indication for this application.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Hyperhidrosis, diarrhoea, irritability, anxiety, and nightmare are adverse drug reactions reported in clinical trials with tiratricol. These adverse reactions are listed in Section 4.8 in the SmPC and are not associated with a relevant risk as these reactions were mild, usually occurred at the start of treatment and/or when the dose was increased and were transient in nature. The SmPC also includes a warning in Section 4.4 stating that at initiation of treatment and/or during dose titration, new onset or worsening of hypermetabolic signs and symptoms, such as hyperhidrosis, irritability, anxiety, insomnia, nightmare, hyperthermia, tachycardia, transient elevations in systolic blood pressure (SBP), or diarrhoea, may occur. 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. Following the resolution of hypermetabolic signs and symptoms, dose titration may be resumed, as clinically appropriate (Emcitate EU SmPC).

In tissues expressing alternative means of TH transport than MCT8, a long-term overexposure to T3 is clinically manifested by typical thyrotoxic symptoms such as very low body weight,

tachycardia, insomnia, and muscle wasting (Schwartz et al 2005). The consequences of this chronic TH overexposure in non-MCT8 dependent cells are believed to contribute to the increased mortality and shortened life expectancy in this patient population; however, no such signs of thyrotoxicosis have been observed in clinical trials—on the contrary, improvement of these signs have been noted in patients with MCT8 deficiency associated with the normalization of serum T3 levels by treatment with Emcitate.

Caution in patients with diabetes is advised in Section 4.4 of the SmPC (Emcitate EU SmPC). This originates from a general caution during TH substitution therapy but is not considered to be associated with a relevant risk for the target population due to very low prevalence of diabetes in patients with MCT8 deficiency.

Section 4.4 of the SmPC advises caution during dose titration in patients with cardiac disease, as there is a potential increased risk of adverse reactions associated with a hypermetabolic state. These adverse reactions are most often transient, mild and manageable through dose adjustment.

Information on the cross-reactivity of tiratricol and T3 if assessed by immunoassay is included in Section 4.2 and 4.4 of the SmPC. A clear recommendation is provided to use an LC/MS/MS method for measuring T3 levels or to follow specific guidelines when interpreting results obtained via immunoassay. This guidance aims to mitigate the potential risk of unreliable test results. Adherence to the recommendations in the SmPC is expected to be high, and the potential risk and impact on the overall benefit-risk balance of the medicinal product are considered minimal.

Information on misuse for weight reduction, as included for other thyroid hormone medicinal products, is addressed in Section 4.4 of the SmPC. It is stated that Tiratricol should not be taken for weight reduction since it may cause serious or life-threatening undesirable effects, particularly in combination with orlistat. The risk of misuse for weight reduction is considered low in the target patient population.

No clinical interaction studies have been performed evaluating the effect of other medicinal products on tiratricol. Potential interactions listed in Section 4.5 of the SmPC (Emcitate EU SmPC) 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.

Section 4.5 of the SmPC includes information on the effect of other medicinal products on the pharmacokinetics of tiratricol, recommending concomitant use with caution for certain medicinal products, as detailed below.

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

The anti-obesity drug orlistat may decrease tiratricol absorption which may result in hypothyroidism (changes in thyroid function should be monitored).

Section 4.5 of the SmPC includes the following information regarding the effect of tiratricol on the pharmacokinetics of other medicinal products, advising caution with concomitant use.

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.

Section 4.5 of the SmPC provides information on pharmacodynamic interactions, with a recommendation against concomitant use as outlined below.

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.

Additionally, Section 4.5 includes the below information on pharmacodynamic interactions, with a recommendation for 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.

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.

No individual case reports of drug interactions have been reported (Tiratricol PSUR 2018-2021 Table 8). The potential interactions mentioned above are based on known pharmacodynamic and pharmacokinetic interactions of thyromimetic agents with other medicinal products and were not specifically studied with tiratricol.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known theoretical risks based on interactions of other known thyromimetic agents that require no further characterization are:

- Risk of bleeding due to interaction between oral anticoagulants and tiratricol
- Risk of decreased effect of tiratricol due to concomitant use of enzyme-inducing antiepileptic drugs
- Risk of thyrotoxicosis due to concomitant use of other thyromimetics
- Risk of decreased blood glucose due to concomitant use of antidiabetic agents

These risks are followed up via routine pharmacovigilance (signal detection and adverse reaction reporting), and the risk minimization messages for them are adhered by prescribers in the product information (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized).

These risks are not included as an identified or potential risk in the list of safety concerns in the RMP, as these are theoretical and based upon interactions of other thyromimetic agents. Further, Emcitate is titrated against response and serum T3 level which is assessed regularly during treatment so the risk to patients is negligible.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk:

None identified.

Important potential risk:

None identified.

Missing information 1: Use in infants (≤1 year of age)

Risk-benefit impact: Diagnosis and treatment of patients with MCT8 deficiency at a very young age are considered to be key in improving their long-term prognosis, e.g., through amelioration of deleterious cardiovascular and hypermetabolic effects of high T3 levels observed in untreated disease. A large part of brain development and maturation occurs very early in life; however, with MCT8 deficiency, there is a lack of normal neurodevelopment during and after infancy. Therefore, the strongest putative therapeutic effects on brain development from treatment with tiratricol would be expected when treatment is started as early as possible in life. Diagnosis of MCT8 deficiency is based on clinical presentation, specific hormonal and laboratory analyses including biomarker analyses, brain imaging, and genetic testing. Early diagnosis of MCT8 deficiency is difficult as developmental delays or absence of achieving developmental milestones are nonspecific clinical signs in infancy that may be due to numerous pathological mechanisms.

In Triac Trial I, 5 of 46 patients were <2 years of age with 1 patient being <1 years old (0.8 years old) at the time of start of treatment. The youngest patient to start treatment with tiratricol in the EMC cohort study/EMC NPU cohort was approximately 6 months old; a total of 7 of the 40 patients were <1 years of age, and 20 of the 40 patients were <2.5 years of age. Efficacy and safety data available among these patients do not indicate any safety concerns related to treatment at an early age (Module 2.7.4).

The Triac Trial II is an early intervention study investigating effects of tiratricol in young patients with MCT8 deficiency (up to 30 months at enrolment), assessing potential benefits and risks of early treatment on neurodevelopment as well as cardiovascular and other secondary effects of thyrotoxicosis. All patients (22) enrolled in the study were <2.5 years of age with median age (age range) being 16 (5 to 28) months. Safety data available from this study do not indicate any clinically relevant differences in this younger population compared to other age groups (Triac Trial II Summary Report section 4.6 and table 14.3).

Triac Trial II confirmed the well-tolerated safety profile of tiratricol seen in previous clinical studies, despite higher dosing per kg body weight compared to previous trials and adds important data from treatment of a very young patient population.

There is no data available in infants <5 months of age. Clinical safety of Emcitate is being investigated further in Triac Trial II (Part I and Part II) where patients ≤1 year of age at time of enrolment (n=8) are followed long-term (up to 5 years of treatment). All safety reports describing safety in infants will be collected and summarized to gain knowledge about this young population.

Missing information 2: Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)

Risk-benefit impact: MCT8 deficiency is a chronic disease requiring life-long treatment for patients. Treatment with Emcitate (tiratricol) is therefore expected to be long-term for patients with this chronic disease.

Considering that MCT8 deficiency is an ultra-rare disease with an estimated prevalence of 1 in 70 000 male individuals, safety data available from 86 patients treated with tiratricol in Triac Trial I and EMC cohort study for up to 6 years and the additional long-term safety data of up to 5 years of treatment that will come from Triac Trial II, including the part II extension, will allow for further assessment of long-term safety in this patient population.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable. This is an initial submission of RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

None identified.

SVII.3.2. Presentation of the missing information

Missing information: Use in infants (≤1 year of age)

Evidence source:

Safety data was evaluated in 41 patients between 10 months and 18 years of age in Triac Trial I and in an additional 39 patients between 6 months and 18 years of age in the EMC retrospective cohort study. Of this, 1 patient in Triac Trial I (0.8 years old) and an additional 7 patients in the EMC retrospective cohort study were ≤1 years of age, with the youngest patient being 6 months old. There is no data available in children less than 6 months of age. However, there is no indication from clinical study data that the safety profile in infants (≤1 year of age) is different from the safety profile in pediatric patients older than 1 year or the safety profile in adults. Considering limited safety data is available from a small sample size of 8 infants (≤1 year of age), safety in this age group will be investigated further in the ongoing Triac Trial II study (Module 2.7.4, Emcitate EU SmPC).

Triac Trial II with its long-term extension part assesses long-term efficacy and safety of tiratricol in children between 0 to 28 months of age at enrolment for up to 5 years. All patients (22) enrolled in the study were <2.5 years of age with median age at time of enrolment of 16 months, range: 5 to 28 months. Currently, the safety data available at the DLP from this study do not indicate any clinically relevant differences in this younger population compared to other age groups (Triac Trial II Summary Report).

Population in need of further characterization:

Infants (≤1 years of age) with MCT8 deficiency.

Anticipated risk/consequence of the missing information:

None.

Missing information: Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)

Evidence source:

Safety data was evaluated in 41 patients between 10 months and 18 years of age in Triac Trial I and in an additional 39 patients between 6 months and 18 years of age in the EMC retrospective cohort study, enabling assessment of long-term safety of up to 6 years of treatment.

Additional long-term safety data post-marketing will become available from the final analysis of Triac Trial II. This will provide up to an additional 3 years of follow-up on tiratricol treatment (in addition to the 96 weeks of treatment in Part I) for 18 patients who continued into the long-term extension. The safety objective is to evaluate the long-term safety of up to a total of 5 years of tiratricol treatment. Safety assessments include monitoring of adverse events, safety labs (which will allow assessment of markers of thyrotoxicosis), physical examination including vital signs, 24-hour Holter ECGs at the final visit, and 12-lead ECGs at interim visits (to monitor cardiovascular safety).

In addition, safety data is also collected in the ongoing compassionate use program (CUP) in Turkey, a similar program in France (AAC), and the expanded access program in the US (EAP). Eighteen patients have been treated in the Turkish CUP since it began in 2021. Adverse events are collected regularly, and 6-monthly listings are provided to the Turkish MoH. Since July 2023, 13 patients with MCT8 deficiency have been included in the French AAC, with periodic reports submitted to the ANSM every six months. The US EAP, initiated in January 2023, has included 8 patients at the DLP, with adverse events collected routinely.

Safety data will also be collected as a part of routine pharmacovigilance post-approval.

Population in need of further characterization:

Patients of all ages with MCT8 deficiency.

Anticipated risk/consequence of the missing information:

None.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	• Use in infants (≤1 year of age) • Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)

Part III: Pharmacovigilance plan (including post authorization safety studies)

III.1 Routine pharmacovigilance activities

The Applicant will conduct routine pharmacovigilance activities for monitoring the safety of Emcitate (tiratricol) 350 microgram tablets and gathering missing information. The pharmacovigilance activities will be conducted as per the available pharmacovigilance system master file and are as per Directive 2010/84/EU of the European Parliament and of the Council of 15 Dec 2010 amending, as regards Pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

III.2 Additional pharmacovigilance activities

One open-label, multicenter study (Triac Trial II) is currently ongoing to evaluate the effect of tiratricol treatment in young patients with MCT8 deficiency. Eligible patients will be treated with tiratricol for 96 weeks followed by a long-term extension part with treatment for an additional 3 years, which will address the missing information of safety of tiratricol in infants (≤1 year of age), long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart) and will provide a cumulative 5 years of exposure data.

Triac Trial II summary

Study short name and title:

Tiratricol treatment of children with monocarboxylate transporter 8 deficiency: Triac Trial II.

Study description and objectives:

This study will investigate the effect of treatment with tiratricol in young boys (≤30 months at enrolment) with MCT8 deficiency. The hypothesis tested is that treatment with tiratricol will have a beneficial effect on the hypothyroid state in the brain as well as the hyperthyroid state in peripheral organs and tissues in these patients. Patients will be treated for 96 weeks with tiratricol; treatment effect on neurodevelopment impairment caused by hypothyroidism and peripheral symptoms caused by thyrotoxicosis will be evaluated after 96 weeks treatment. After the 96-week treatment period, patients will enter Part II of the trial, evaluating long-term treatment. Patients will be followed for an additional 3 years, with safety assessments conducted 4 and 5 years after the start of treatment.

Part I

Primary Objective:

Evaluate the effects of tiratricol on neurodevelopment in young MCT8-deficient patients, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain.

Secondary Objectives:

1. Evaluate the effect of tiratricol treatment at Week 96 on specific motor development milestones.
2. Evaluate the effect of tiratricol treatment on neurodevelopment in young MCT8-deficient patients as measured by the BSID-III.
3. Evaluate the effect of tiratricol at Week 96 on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of TH action).

Exploratory objectives:

1. Evaluate the effects of tiratricol treatment on quality of life for patients and parents.
2. Evaluate the effect of tiratricol treatment on neurological status.
3. Evaluate the effect of tiratricol treatment on brain function/brain imaging (EEG, BERA, VEP and MRI/MRS) (optional).
4. Study the pharmacokinetic profile of tiratricol in young children (optional and provided a medical reason prevails).
5. Evaluate the effect of tiratricol on cardiovascular features of the thyrotoxicosis.

Safety objective:

1. Evaluate the safety of tiratricol treatment in patients 0-30 months of age.

Part II

Primary Objective:

Evaluate the effects of long-term treatment (up to 4 years of total treatment) with tiratricol on neurodevelopment in young boys (≤30 months) with MCT8 deficiency, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain.

Secondary Objectives:

1. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol on specific motor development milestones.
2. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol as measured by the BSID-III.
3. Evaluate the long-term treatment effect (up to 5 years of total treatment) of tiratricol on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of TH action).

Exploratory objectives:

1. Evaluate the effect of tiratricol treatment on neurological status.

Safety objective:

1. Evaluate the safety of long-term tiratricol treatment.

Study population:

Male patients diagnosed with MCT8 deficiency from newborn to 30 months of age. 12 to 22 patients will be included in the study from countries where potentially eligible patients will be identified. Participating countries include the Netherlands, Czech Republic, Germany, and the US.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study: Tiratricol treatment of children with MCT8 deficiency, Triac Trial II. An Open-Label Multicenter Phase 2 Trial. Ongoing	Part I Primary objective: Evaluate the effects of tiratricol on neurodevelopment in young MCT8-deficient patients, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain. Secondary objectives: 1. Evaluate the effect of tiratricol treatment at Week 96 on specific motor development milestones. 2. Evaluate the effect of tiratricol treatment on neurodevelopment in young MCT8-deficient patients as measured by the BSID-III. 3. Evaluate the effect of tiratricol at Week 96 on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of thyroid hormone action). Exploratory objectives: 1. Evaluate the effects of tiratricol treatment on quality of life for patients and parents. 2. Evaluate the effect of tiratricol treatment on neurological status. 3. Evaluate the effect of tiratricol	• Use in infants (≤1 year of age) • Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	*Part I* First patient first visit Database lock Final Clinical Study Report *Part II* Interim Report (4-year) Final Clinical Study Report (5-year)	 Dec 2020 Jun 2024 Oct 2024 Q4 2026 Q4 2027

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	treatment on brain function/brain imaging (EEG, BERA, VEP and MRI/MRS) (optional). 4. Study the pharmacokinetic profile of tiratricol in young children (optional and provided a medical reason prevails). 5. Evaluate the effect of tiratricol on cardiovascular features of the thyrotoxicosis. Safety objective: 1. Evaluate the safety of tiratricol treatment in patients 0-30 months of age. Part II Primary Objective: Evaluate the effects of long-term treatment (up to 5 years of total treatment) with tiratricol on neurodevelopment in young boys (≤30 months at time of enrolment) with MCT8 deficiency, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain. Secondary Objectives: 1. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol on specific motor development milestones. 2. Evaluate the effect of long-term			

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	treatment (up to 5 years of total treatment) with tiratricol as measured by the BSID-III. 3. Evaluate the long-term treatment effect (up to 5 years of total treatment) of tiratricol on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of thyroid hormone action). Exploratory objectives: 1. Evaluate the effect of tiratricol treatment on neurological status. Safety objective: 1. Evaluate the safety of long-term tiratricol treatment.			

BERA = Brainstem evoked response audiogram; BSID-III = Bayley Scales of Infant Development III; EEG = Electroencephalogram; GMFM-88 = Gross Motor Function Measure-88; MRI = Magnetic resonance imaging; MRS = Magnetic resonance spectroscopy; VEP = Visual evoked potentials.

Part IV: Plans for post authorization efficacy studies

There are no planned or ongoing post authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk minimization plan

V.1. Routine risk minimization measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Use in infants (≤1 year of age)	**Routine risk communication:** Information in SmPC section 4.8 Undesirable effects **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicinal product under supervision of a specialist
Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	**Routine risk communication:** Information in SmPC section 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicinal product under supervision of a specialist

LC-MS/MS = Liquid chromatography with tandem mass spectrometry; PIL = package information leaflet; SmPC = Summary of Product Characteristics

V.2. Additional risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Removal of additional risk minimization activities:

Not applicable.

V.3 Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in infants (≤1 year of age)	**Routine risk minimization measures**: Information in SmPC section 4.8 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II, including part II extension.
Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	**Routine risk minimization measures**: Information in SmPC sections 4.4 and 5.1 Prescription only medicine **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II including part II extension.

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = package information leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for Emcitate (tiratricol)

This is a summary of the risk management plan (RMP) for Emcitate. The RMP details important risks of Emcitate, how these risks can be minimized, and how more information will be obtained about Emcitate's risks and uncertainties (missing information).

Emcitate's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Emcitate should be used.

This summary of the RMP for Emcitate should be read in the context of all this information, including the assessment report of the evaluation and its plain language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current concerns will be included in updates of Emcitate's RMP.

I. The medicine and what it is used for

Emcitate is authorized for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth (see the SmPC for the full indication). It contains tiratricol as the active substance and it is given by oral route of administration or by use of a gastroenteral feeding tube.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Emcitate, together with measures to minimize such risks and the proposed studies for learning more about Emcitate's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and analyzed regularly, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Emcitate is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Emcitate are risks that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Emcitate. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	• Use in infants (≤1 year of age) • Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)

II.B Summary of important risks

Missing information Use in infants (≤1 year of age)	
Risk minimization measures	**Routine risk minimization measures** Information in SmPC section 4.8 Prescription only medicine **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II including part II extension. See Part II.C of this summary for an overview of the post authorization development plan.
Missing information Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	
Risk minimization measures	**Routine risk minimization measures** Information in SmPC sections 4.4 and 5.1 Prescription only medicine **Additional risk minimization measures**

	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II including part II extension. See Part II.C of this summary for an overview of the post authorization development plan.

II.C Post authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Emcitate.

II.C.2 Other studies in post authorization development plan

Tiratricol treatment of children with MCT8 deficiency: Triac Trial II

This study will investigate the effect of treatment with tiratricol in young boys (≤30 months at time of enrolment) with MCT8 deficiency. The hypothesis tested is that treatment with tiratricol will have a beneficial effect on the hypothyroid state in the brain as well as the hyperthyroid state in peripheral organs and tissues in these patients. Patients will be treated for 96 weeks with tiratricol; treatment effect on neurodevelopment impairment caused by hypothyroidism and peripheral symptoms caused by thyrotoxicosis will be evaluated after 96 weeks treatment. After the 96 week treatment period, patients will enter Part II of the trial, evaluating long-term treatment. Patients will be followed for an additional 3 years, with safety assessments conducted 4 and 5 years after the start of treatment.

Part I

Primary Objective:

Evaluate the effects of tiratricol on neurodevelopment in young MCT8 deficiency patients, as measured by the Gross Motor Function Measure (GMFM)-88 and Bayley Scales of Infant Development (BSID)-III Gross Motor Skill Domain.

Secondary Objectives:

1. Evaluate the effect of tiratricol treatment at Week 96 on specific motor development milestones.
2. Evaluate the effect of tiratricol treatment on neurodevelopment in young MCT8-deficient patients as measured by the BSID-III.
3. Evaluate the effect of tiratricol at Week 96 on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of thyroid hormone action).

Exploratory objectives:

1. Evaluate the effects of tiratricol treatment on quality of life for patients and parents.
2. Evaluate the effect of tiratricol treatment on neurological status.

3. Evaluate the effect of tiratricol treatment on brain function/brain imaging (electroencephalogram [EEG], brainstem evoked response audiogram [BERA], visual evoked potentials [VEP], and magnetic resonance imaging [MRI]/magnetic resonance spectroscopy [MRS]) (optional).
4. Study the pharmacokinetic profile of tiratricol in young children (optional and provided a medical reason prevails).
5. Evaluate the effect of tiratricol on cardiovascular features of the thyrotoxicosis.

Safety objective:

1. Evaluate the safety of tiratricol treatment in patients 0-30 months of age at time of enrolment.

Part II

Primary Objective:

Evaluate the effects of long-term treatment (up to 5 years of total treatment) with tiratricol on neurodevelopment in young boys (≤30 months at time of enrolment) with MCT8 deficiency, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain.

Secondary Objectives:

1. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol on specific motor development milestones.
2. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol as measured by the BSID-III.
3. Evaluate the long-term treatment effect (up to 5 years of total treatment) of tiratricol on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of TH action).

Exploratory objectives:

1. Evaluate the effect of tiratricol treatment on neurological status.

Safety objective:

1. Evaluate the safety of long-term tiratricol treatment.