Information notice for the prescribers and the patients

1. NAME OF THE MEDICINAL PRODUCT

Emcitate 350 microgram tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 350 micrograms tiratricol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of monocarboxylate transporter 8 (MCT8) deficiency genetically confirmed upon diagnosis in children or in adults.

4.2 Posology and method of administration

Posology

Adults and the elderly

The daily dose is individual and should be based on serum levels of T_3, (F)T_4 and TSH. Recommended starting dose is 350 micrograms once daily which is gradually increased in increments every two weeks during a titration period. The individualised daily dose should be divided to optimise the TSH-reducing effect. The dose escalation should be stopped when the patient´s T_3 levels are within normal age-specific range or undesired side-effects occur.

A common dose for adults is 700-2100 micrograms (2-6 tablets of 350 micrograms) per day divided into 1-3 administrations.

Tiratricol interferes with all common T_3 assays, expert advice is therefore recommended to properly monitor dose response, see section 4.4.

Paediatric population

The principles applicable to adults are equally applicable to children.

A common dose for paediatric patients is 350-1400 micrograms (1 to 4 tablets of 350 micrograms) daily divided into 1-3 administrations.

Hepatic impairment

No information on the treatment of hepatically impaired patients with tiratricol is available.

Renal impairment

No information on the treatment of renally impaired patients with tiratricol is available.

Method of administration

Tablets for oral administration.

The patient population is unlikely to be capable of taking whole tablets. Tablets should be crushed and administered with food (e.g. mashed fruit) or via a nasogastric tube / percutaneous endoscopic gastrostomy. The system should then be rinsed with water.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings
In case of signs of a hypermetabolic state due to hyperthyroidism (tachycardia, nervousness, insomnia, hyperthermia, sweating, rapid weight loss, diarrhoea) treatment should be suspended for 24 to 48 hours. Treatment should then be resumed at a lower dose.

Precautions for use

Tiratricol interferes with T_3 determination, which needs to be taken into account when interpreting the results of the routine assay. Caution should be taken when prescribing, titrating and adjusting the dose with Emcitate. Special guidelines should be followed for T_3 assay interpretation when the dose of Emcitate is determined or changed.

Exercise caution in patients with diabetes or a history of cardiovascular disease.

No information is available from treatment with tiratricol in patients with renal and/or hepatic impairment.

The tablets contains 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

Major interactions

Other T_3 analogues and LT_4

Taking tiratricol along with other thyromimetics may increase the risk of thyrotoxic symptoms.

Minor interactions

Antacids, charcoal, calcium, cationic resins (e.g. cholestyramine), iron, sucralphate, and gastro-intestinal topical agents may interfere with the gastro-intestinal absorption of tiratricol. Adjustment of the tiratricol dose may be required to obtain the desired effects. These treatments should be taken some time before or after thyroid hormones (more than 2 hours if possible). In the case of cholestyramine, tiratricol should be taken 1 hour before or 4 hours after the resin dose. The timing of tiratricol administration relative to antacid use should be optimised.

Sevelamer

Decrease in concentrations of thyroid hormones, with risk of decline in efficacy. Take sevelamer some time before or after thyroid hormones (more than 2 hours if possible).

Oral anticoagulants

Increase in the effect of the oral anticoagulant and in the risk of bleeding (increase in metabolism of thrombin complex factors).

More frequent checking of INR. Possible adjustment of dosage of oral anticoagulant on commencement of treatment of hypothyroidism or thyroid hormone overdose. Such a check is not necessary in patients on stable thyroid replacement therapy.

Enzyme-inducing antiepileptic drugs

Risk of clinical hypothyroidism in patients with underactive thyroid, through an increase in T_3 and T_4 metabolism.

Monitoring of serum concentrations of T_3 and T_4 and adjustment, if necessary, of the dosage of thyroid hormones during treatment with the inducer and after it is stopped.

Chloroquine, proguanil

Risk of clinical hypothyroidism in patients on thyroid hormone replacement therapy.

Monitoring of serum concentrations of T_3 and T_4 and adjustment, where necessary, of the dosage of thyroid hormones during treatment with the antimalarial after it has been stopped.

Non-contraceptive oestrogens

Risk of clinical hypothyroidism in the case of oestrogen replacement therapy.

Rifabutin, rifampicin

Risk of clinical hypothyroidism in patients with underactive thyroid, through an increase in the metabolism of T_3 and T_4.

Monitoring of serum concentrations of T_3 and T_4 and adjustment, where necessary, of the dosage of thyroid hormones during treatment with rifampicin or rifabutin and after it has been stopped.

Orlistat
Risk of imbalance of thyroid replacement therapy in treatment with orlistat.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

There are limited data on the use of tiratricol in pregnant patients. It is known that tiratricol crosses the placenta to a greater extent than T_3 and T_4. As a precautionary measure it is preferable to avoid the use of Emcitate in pregnancy. In the event of exposure during pregnancy, foetal and neonatal monitoring is desirable.

Lactation

It is unknown whether tiratricol is excreted in human breast milk. As a precaution, Emcitate is not recommended during lactation.

Fertility

The effect of tiratricol on fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

The effect of tiratricol on the ability to drive or operate machinery has not been investigated.

4.8. Undesirable effects

Signs of hypermetabolism by hyperthyroidism (tachycardia, hypernervosity, insomnia, hyperthermia, sweating, rapid weight loss, diarrhea may occur). The occurence of these symptoms leads to the treatment being interrupted for 24 to 48 hours. It can be taken in lower doses.

Reporting of suspected adverse reactions

Healthcare
professionals are asked to report any suspected adverse reactions via the national system of declaration : Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : www.ansm.sante.fr.

4.9 Overdose

Signs of hypermetabolic state may appear in case of overdose. Due to the short half-life of tiratricol, reducing the daily dose will rapidly relieve symptoms of overdosing in most cases. In severe cases, tiratricol treatment should be stopped. Supportive care should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: thyroid hormones, ATC code: H03AA04

Mechanism of action
Thyroid hormone (TH) is crucial for the development and metabolic state of virtually all tissues. TH signalling is regulated at the tissue level by intracellular conversion of the prohormone thyroxine (T_4) to receptor-active 3,3’,5-triiodothyronine (T_3) or receptor-inactive 3,3’,5’-triiodothyronine (rT_3) by deiodinases. Since T_3 receptors are located in the nucleus, TH transport across the plasma membrane is required for both TH metabolism and action. This process is facilitated by TH transporters, the most specific of which is monocarboxylate transporter 8 (MCT8) which gene is located at the X-chromosome. MCT8 is critical for the transport of TH in a number of tissues, in particular the brain. Hemizygous mutations of MCT8 in males cause the MCT8 deficiency, a severe syndrome involving both neurological and peripheral symptoms that is caused by abnormal TH levels, due to the impaired transport of TH into the brain. MCT8 deficiency patients suffer from low TH levels in the brain and peripheral thyrotoxicosis.

Tiratricol (3,3',5-triiodothyroacetic acid) is a structural analogue to triiodothyronine (T_3). Due to the preserved 3,3’,5-iodination pattern, tiratricol holds very similar physiological activity as T_3, with similar affinity for the TRα receptor and slightly higher for the TRβ receptor. While T_3 is dependent on active transport by the MCT8 transporter protein to pass the blood-brain-barrier (BBB), tiratricol can enter the brain without the MCT8 transporter protein.

In tiratricol, the alanine side chain moiety of T_3 is replaced by acetic acid. It is hypothesized that biosynthesis of endogenous tiratricol involves the decarboxylation and successive oxidative deamination of T_3, which is mainly processed in the liver. Tiratricol is naturally present in humans at ~50-fold lower concentrations than T_3. Serum levels of 2.6 – 15.2 ng/dL (42 – 244 pmol/L) in healthy

human subjects have been reported whereas others reported levels below the assay detection limit of ~4 ng/dL (64 pmol/L).

Pharmacodynamic effects

To exert its biological function, tiratricol has to cross the cell membrane and bind to nuclear thyroid hormone receptors (TR) and subsequently to responsive elements on the DNA resulting in the transcriptional regulation of thyroid hormone target genes. Thyroid hormones are actively transported across the cellular membrane transporters. Tiratricol has higher affinity and transcriptional activation potency for TRβ than TRα and, thus, may exert stronger thyromimetic effects in TRβ-expressing tissues. Effects may be similar or even higher than with T_3. Importantly, despite its higher affinity for TRβ than T_3, it is not entirely clear to what extent this leads to higher transcriptional activation levels.

Thyroid hormones play a key role in metabolic regulation in the body and regulate gene expression in almost all vertebrate cells. Tiratricol is an endogenous substance, in humans conversion to tiratricol accounts for about 14 % of T_3 metabolism. This production is increased under certain physiological conditions, such as fasting. In addition, its presence in serum from several other species has been suggested.

In most clinical studies, tiratricol was administered with the intention to reduce serum TSH levels. Therefore, serum TSH levels and other thyroid hormone parameters have been used to determine the dose-effect relationship for tiratricol.

The effect of a single dose of 1050 µg tiratricol was studied in eight healthy subjects. TSH levels decreased significantly from 1.75 ± 0.40 mU/l to a nadir of 0.72 ± 0.14 mU/l six hours after tiratricol administration. Thereafter, TSH levels returned to baseline levels 24 hours after tiratricol ingestion.

The effects of different tiratricol doses were analysed in 34 subjects, nine hours after a single oral administration of the indicated tiratricol doses. During this study no adverse effects occurred. A significant decrease in serum TSH was already observed after a single oral dose of 350 micrograms tiratricol.

Tiratricol has a relatively short half-life which has important implications for the dosing scheme necessary to maintain stable tiratricol levels and a consistent suppression of serum TSH levels. No studies have been conducted to determine optimal dosing frequency to maintain stable serum tiratricol levels, but due to the short half-life of tiratricol, frequent dosing has been shown to increase the TSH suppressive effect..

5.2 Pharmacokinetic properties

Endogenous serum tiratricol concentrations in healthy human subjects have been reported to be 42 – 140 pmol/L, while also levels below the detection limit of the assay of 50 pmol/L have been reported. The free fraction of tiratricol in serum is lower than that of T_3 due to higher binding to plasma proteins.

Absorption	67 % of the oral dose
Distribution volume	114 L/ 70 kg (SD 9)
Plasma clearance rate	Ranged from 222 L/70 kg/day (SD 37) to 298 L/70 kg/day (SD 9)
Plasma half life	6 h 22 min (SD 29 min)
Route of metabolism	Deiodination

Bioavailability	Oral administration of 1050 µg Tiratricol resulted in peak serum levels 60 nmol/L, 40 minutes after ingestion.
Plasma protein binding	In rat: plasma binding ratio 100 – 200 (= 1-dialysable fraction / dialysable fraction). In humans not described.

Pharmacokinetic data were obtained in healthy male subjects (between 30 and 50 years; mean weight 69 kg; SD 9 kg) without known impaired organ function. Some characteristics have not been tested in humans, in this case animal data or in vitro data are mentioned.

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 T_3, TSH and (F)T_4 levels

5.3 Preclinical safety data

No non-clincial studies specifically investigating the toxicity of tiratricol have been performed. The notable safety-relevant effects of tiratricol in non-clinical studies described in the literature can best be described as secondary or exaggerated pharmacodynamic effects, in line with physiological effects of tiratricol. No direct toxic effects have been described. Since tiratricol is an endogenous substance in animals and humans, classical toxicity studies are not warranted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/TE/PVDC/Aluminium blister, 60 tablets.

6.6 Special precautions for disposal

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

PACKAGE LEAFLET

Package leaflet: Information for the user

Emcitate 350 micrograms 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, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Emcitate is and what it is used for

The active ingredient of Emcitate is tiratricol. This medicine is used to treat a rare disease called Monocarboxylate Transporter 8 (MCT8) Deficiency, also known as Allan-Herndon-Dudley syndrome, in adults and children.

MCT8 deficiency is caused by a non-functioning protein that normally transports thyroid hormone into cells in the body. This causes low levels of thyroid hormone in cells dependent on this transporter, e.g., nerve cells, and high levels of thyroid hormone in other body tissues. This medicine enters into the body and relieves some of the following symptoms: weight loss, increased heart rate and blood pressure, muscle weakness, involuntary movements and abnormal muscle development.

You must talk to a doctor if you do not feel better or if you feel worse when taking Emcitate.

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).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Emcitate.

Tell your doctor if you have or have had diabetes or cardiovascular disease.

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

Some medicines, including medicines obtained without a prescription, may affect the way your treatment works:

- other medicines containing thyroid hormones
- medicines to treat seizures in epilepsy
- medicines to prolong the blood clotting time
- medicines to treat gastric ulcer or heartburn (antacids)
- cholesterol lowering medicines, so-called resins (e.g., cholestyramine)
- phosphate lowering medicines containing sevelamer carbonate
- chloroquine or proguanil used to prevent or treat malaria
- rifabutin or rifampicin which are antibiotics
- orlistat used to treat obesity
- medicines containing calcium, iron or charcoal
- medicines containing the hormone oestrogen

Emcitate with food and drink
Emcitate can be taken with food and drink, see section "How to take Emcitate".

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

This medicine is not recommended during pregnancy or breastfeeding.

Driving and using machines
There is no known effect of this medicine on the ability to drive or operate machines.

Emcitate contains lactose
This medicine contains 20 mg of lactose in each tablet.
Lactose is a source of glucose and galactose. If you have one of the rare genetic disorders galactosaemia, or glucose-galactose intolerance or congenital lactase deficiency you must talk to your doctor or pharmacist before taking this medicine.
The small amount of lactose in each dose is unlikely to cause symptoms in adults with lactose intolerance.

3. How to take Emcitate

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

Your doctor will decide what dose is necessary for you.
The recommended starting dose is 1 tablet per day. The dose is then gradually increased every two weeks as recommended by your doctor.

Adults
The usual dose for adults is 2-6 tablets per day in divided doses (1 to 3 times daily).

Use in children and adolescents
The usual dose for children is 1-4 tablets per day in divided doses (1 to 3 times daily).

Method of administration
Swallow the tablets with a sufficient amount of water. Avoid taking these tablets while lying down.
If you or your child is not able to swallow tablets, crush the tablets and give them with drink or mashed fruit, or through a feeding tube. Check with your doctor or pharmacist if you are not sure how to do it.

If you take more Emcitate than you should
Contact your doctor immediately.

If you forget to take Emcitate
Do not take a double dose to make up for a forgotten tablet.

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, or 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 have been observed:

Common side effects (may affect up to 1 in 10 people): temporary irritability, temporarily increased sweating.

Side effects of not known frequency (cannot be estimated from the available data): diarrhoea, the sensation of rapid, irregular, or forceful heart beat, trembling, sleeplessness, nervousness, weight loss, headache, increased blood pressure, hot flushes or heat intolerance.

These symptoms usually disappear when the dose is reduced or treatment is stopped. Contact your doctor who will adjust your dose.

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

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 after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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

6. Contents of the pack and other information

What Emcitate contains
- The active substance is tiratricol. Each tablet contains 350 micrograms tiratricol.
- The other ingredients are calcium hydrogen phosphate, maize starch, lactose monohydrate and magnesium stearate.

What Emcitate looks like and contents of the pack

Emcitate tablets are white round, tablets. Available in packs of 60 tablets in blisters.

Exploitant
Rare Thyroid Theraputics International AB
Teatergatan 3
111 48 Stockholm
Sweden

Manufacturer
Cenexi
17, Rue De Pontoise
95520 Osny
France