SUMMARY OF PRODUCT CHARACTERISTICS

for

Stabilised Ceretec, kit for radiopharmaceutical preparation

1. NAME OF THE MEDICINAL PRODUCT

Stabilised Ceretec

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains exametazime 500 micrograms.

Stabilised Ceretec is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. (not included in this kit) to prepare stabilised Technetium (^{99m}Tc) Exametazime Injection.

Excipients:
The product before reconstitution contains sodium: 1.77 mg/vial. This needs to be taken into consideration for patients on a controlled sodium diet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabeling with Sodium Pertechnetate (^{99m}Tc) Injection, the solution of technetium (^{99m}Tc) exametazime is indicated in adults for:

Neurology
Technetium (^{99m}Tc) Exametazime Injection is indicated for use with single photon emission tomography (SPECT). In brain perfusion SPECT, the diagnostic target is detection of abnormalities of regional cerebral blood flow, including:

- Evaluation of patients with cerebrovascular disease (specifically acute stroke, chronic ischaemia and transient ischaemic attack);
- Presurgical lateralisation and localisation of epileptogenic foci;
- Evaluation of patients with suspected dementia (specifically Alzheimer's disease and frontotemporal dementia);
- Adjuvant technique in the diagnosis of brain death

4.2 Posology and method of administration

Posology

*Adults*555-1110 MBq by direct intravenous injection

Normally a once-only diagnostic procedure

Paediatric population
Technetium-99m exametazime with the cobalt chloride solution is not recommended for administration to children. Safety and effectiveness of the cobalt solution has not been established in the paediatric population.

Method of administration

This medicinal product should be reconstituted before administration to the patient. For instructions on reconstitution of the medicinal product before administration, see section 12. For patient preparation, see section 4.4

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
The possibility of hypersensitivity including anaphylactic/anaphylactoid reactions should always be considered. If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal impairment and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
Paediatric population, see section 4.2

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Specific warnings

Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol. This should be taken into account in patients on low sodium diet.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed and no drug interactions have been reported to date.

4.6 Pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

No data are available on the use of this product in human pregnancy. Animal reproduction studies have not been performed. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and the foetus.

Breastfeeding

Before administering a radioactive medicinal product to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for 12 hours and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The frequencies of undesirable effects are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

Congenital and familial/genetic disorders Not known	Hereditary defects[1].

Neoplasms benign and malignant (including cysts and polyps) Not known	Cancer induction[1].
Immune system disorders Not known	Hypersensitivity including rash, erythema, urticaria, angiooedema, pruritus.
Nervous system disorders Not known	Headache, dizziness, paraesthesia
Vascular disorder Not known	Flushing
Gastrointestinal disorders Not known	Nausea, vomiting
General disorders and administration site conditions Not known	Asthenic conditions (e.g., malaise, fatigue)

[1] Linked with ionising radiation.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose resulting from the administration of a (maximal recommended) activity of 1110 MBq for an adult weighing 70 kg is about 10.3 mSv, these adverse events are expected to occur with low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Norway
Statens legemiddelverk
Nettside: www.legemiddelverket.no/meldeskjema

4.9 Overdose

In the event of the administration of a radiation overdose frequent micturition and defaecation should be encouraged in order to minimise the absorbed dose to patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Technetium (^{99m}Tc) compounds.
ATC-code: V 09 AA 01

At the chemical concentrations and activities used for diagnostic procedures technetium-99m exametazime does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

The technetium-99m complex of the active ingredient is uncharged, lipophilic and of sufficiently low molecular weight to cross the blood-brain barrier. It is rapidly cleared from the blood after intravenous injection. Uptake in the brain reaches a maximum of 3.5-7.0 % of the injected dose within one minute of injection. Up to 15 % of the cerebral activity washes out of the brain 2 minutes post injection after which there is little loss of activity for the following 24 hours except by physical decay of technetium-99m. The activity not associated with the brain is widely distributed throughout the body particularly in muscle and soft tissue. About 20 % of the injected dose is removed by the liver immediately after injection and excreted through the hepatobiliary system. About 40 % of the injected dose is excreted through the kidneys and urine over the 48 hours after injection resulting in a reduction in general muscle and soft tissue background.

In-vitro stabilisation of technetium-99m exametazime injection with cobalt (II) chloride does not appear to affect the *in vivo* pharmacokinetics of the complex.

5.3 Preclinical safety data

There is no additional preclinical safety data of relevance concerning exametazime for the prescriber in recognising the safety profile of the product used for the authorised indication.

There are no indications that the gross toxicity profile of the stabilised formulation of technetium-99m exametazime is significantly different from that of the non-stabilised formulation.

In-vitro mutagenicity studies indicate that the stabilised formulation of technetium-99m exametazime is weakly mutagenic in the Ames (bacterial mutation) test, human lymphocyte chromosome aberration assay and mouse lymphoma thymidine kinase assay. The stabilised formulation is found not to be mutagenic in two *in-vivo* assays (rat bone marrow micronucleus and rat liver micronucleus).

At quantities such as those encountered in stabilised technetium-99m exametazime preparations, cobalt (II) ions or complexed forms of cobalt have no known adverse effects and are rapidly eliminated from the circulation by urinary excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ceretec component:
Sodium chloride
Stannous chloride dihydrate

Cobalt stabiliser solution:
Cobalt (II) chloride 6-hydrate

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

Kit before reconstitution: 52 weeks from the day of manufacture.

Stabilised reconstituted product: must be injected between 30 minutes and 5 hours after preparation.
Store below 25ºC. Do not freeze.

6.4 Special precautions for storage

Storage should be in accordance with national regulations for radioactive materials.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of the container

The freeze-dried component of the product is supplied in a glass vial sealed with a chlorobutyl rubber closure, aluminium overseal, and blue flip off cap.
The cobalt stabiliser solution is supplied in a glass vial with a chlorobutyl rubber closure and metal overseal.

Pack sizes: each kit contains 2 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Contents of the vial are intended only for use in the preparation of technetium **(**99mTc) exametazime injection and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on reconstitution of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before reconstitution is not radioactive. However, after sodium pertechnetate (^{99m}Tc), Ph. Eur. is added, adequate shielding of the final preparation must be

maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare AS
P.O.Box 4220 Nydalen
NO-0401 Oslo
Norway

8. MARKETING AUTHORISATION NUMBER

00-4795

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02.04.2001/02.04.2006

10. DATE OF REVISION OF THE TEXT

13.03.2019

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable.

The table below shows the dosimetry according to ICPR Publication 128 (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances., Ann ICPR 2015).

	Absorbed dose per unit activity administered (mGy/MBq)
Organ	**Adult**
Adrenals	0.0053
Bone surfaces	0.0051
Brain	0.0068

Breast	0.0020
Gallbladder wall	0.018
Gastrointestinal tract	
Stomach wall	0.0064
Small intestine wall	0.012
Colon wall	0.017
Upper large intestine wall	0.018
Lower large intestinal wall	0.015
Heart wall	0.0037
Kidneys	0.034
Liver	0.0086
Lungs	0.011
Muscles	0.0028
Oesophagus	0.0026
Ovaries	0.0066
Pancreas	0.0051
Red marrow	0.0034
Skin	0.0016
Spleen	0.0043
Testes	0.0024
Thymus	0.0026
Thyroid	0.0026
Urinary bladder wall	0.023
Uterus	0.0066
Remaining organs	0.0032
Effective dose (mSv/MBq)	**0.0093**

The effective dose resulting from the administration of a (maximal recommended) activity of 1110 MBq for an adult weighing 70 kg is about 10.3 mSv. For an administered activity of 740 MBq the typical radiation dose to the target organ (brain) is 5.0 mGy and the typical radiation dose/doses to the critical organ (kidneys) is 25.2 mGy.

The biodistribution and hence the radiation dosimetry of technetium-99m exametazime is not significantly altered by *in vitro* cobalt stabilisation.

Technetium-99m disintegrates with the emission of gamma radiation with an energy of 140 keV and a half-life of 6 hours to technetium-99 which can be regarded as quasi-stable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system. If the integrity of this vial is compromised, the product should not be used

<u>Method of preparation of cobalt stabilised technetium-99m exametazime for intravenous injection:</u>

Use aseptic technique throughout.

1) Place the exametazime vial in a shielding container and swab the closure with the sanitising swab provided.
2) Using a 10 ml syringe, inject into the shielded vial 5 ml of sterile eluate from a technetium-99m generator (see notes 1 - 6). Before withdrawing the syringe from the vial withdraw 5 ml of gas from the space above the solution to normalise the pressure in the vial. Shake the shielded vial for 10 seconds to ensure complete dissolution of the powder.
3) Between 1 and 5 minutes after reconstitution, inject 2 ml of cobalt stabiliser solution into the shielded vial using a 3 ml syringe. Before withdrawing the syringe from the vial, withdraw 2 ml of gas from the space above the solution to normalise the pressure in the vial. Shake the shielded vial for 10 seconds to ensure complete mixing.
4) Assay the total radioactivity and calculate the volume to be injected.
5) Complete the label provided and attach to the vial.
6) Use the stabilised product between 30 minutes and 5 hours after preparation. Individual patient doses may be stored aseptically in a capped syringe if required (see note 7).
7) Discard any unused material.

Note:

1) For the highest radiochemical purity reconstitute with freshly eluted technetium-99m generator eluate.
2) The technetium-99m generator eluate must be used within 4 hours of elution from a generator that has already been eluted within the previous 24 hours.
3) 0.37 - 1.11 GBq technetium-99m may be added to the vial.

4) Before reconstitution the generator eluate may be adjusted to the correct radioactive concentration (0.37 - 1.11 GBq in 5 ml) by dilution with sodium chloride for injection.
5) (^{99m}Tc) pertechnetate complying with the specifications prescribed by the USP and BP/Ph.Eur. Monographs on Sodium Pertechnetate (^{99m}Tc) Injection should be used.
6) The cobalt stabilised technetium-99m exametazime is a pale straw-coloured solution and the pH is in the range 5.0 - 8.0.
7) When Stabilised Ceretec preparations are transferred to individual patient syringes, a small volume of the headspace gas must be withdrawn from the vial into the syringe after solution transfer to ensure that no solution remains in contact with the syringe needle prior to administration to the patient.
8) The shelf life of the reconstituted Ceretec component without the addition of the cobalt stabiliser is only 30 minutes.

Quality control
Three potential radiochemical impurities may be present in prepared Technetium (^{99m}Tc) Exametazime Injection. These are a secondary ^{99m}Tc-exametazime complex, free (^{99m}Tc)-pertechnetate and reduced-hydrolysed-technetium-99m. A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection.
Test samples are applied by needle approximately 2.5 cm from the bottom of two Glass Microfiber Chromatography Paper impregnated with Silicic Acid (GMCP-SA) strips (2 cm (±2 mm) x 20 cm).
The strips are then immediately placed in prepared ascending chromatography development tanks, one containing butan-2-one and the other 0.9 % sodium chloride (1cm depth fresh solvent).
After a 14 cm elution the strips are removed, solvent fronts marked, the strips dried and the distribution of activity determined using suitable equipment.

Interpretation of chromatograms
System 1 (GMCP-SA:butan-2-one(methyl ethyl ketone))
Secondary ^{99m}Tc-exametazime complex and reduced-hydrolysed-technetium-99m remain at the origin.
Lipophilic ^{99m}Tc-exametazime complex and (^{99m}Tc)-pertechnetate migrate at R_f 0.8-1.0.

System 2 (GMCP-SA:0.9% sodium chloride)
Lipophilic ^{99m}Tc-exametazime complex, secondary ^{99m}Tc-exametazime complex and reduced-hydrolysed-technetium-99m remain at the origin.
(^{99m}Tc)-pertechnetate migrates at R_f 0.8-1.0.

1) Calculate the percentage of activity due to both secondary ^{99m}Tc exametazime complex and reduced-hydrolysed-technetium-99m from System 1 (A %). Calculate the percentage of activity due to (^{99m}Tc)-pertechnetate from System 2 (B %).
2) The radiochemical purity (as percentage lipophilic technetium-99m exametazime complex) is given by:

100 - (A %+B %) where:

A % represents the level of secondary technetium-99m exametazime complex plus reduced-hydrolysed technetium-99m.

B % represents the level of (^{99m}Tc)-pertechnetate.

A radiochemical purity of at least 80 % may be expected provided the test samples have been taken and analysed within 5 hours of the preparation of the stabilised product.