

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Stabilised Ceretec 500 micrograms kit for radiopharmaceutical preparation

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains exametazime 500 micrograms.

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

### Excipients with known effect

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.

A white powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

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

#### Neurology

Technetium ( $^{99m}\text{Tc}$ ) 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, exposure to ionising radiation must be justifiable on the basis of 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 Fertility, pregnancy and lactation**

##### Women with 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.

##### Breast-feeding

Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast feeding 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

<b>Congenital and familial/genetic disorders</b> Not known	Hereditary defects <sup>1</sup>
<b>Neoplasms benign and malignant (including cysts and polyps)</b> Not known	Cancer induction <sup>1</sup>
<b>Immune system disorders</b>	Hypersensitivity including rash,

Not known	erythema, urticaria, angiooedema, pruritus.
<b>Nervous system disorders</b> Not known	Headache, dizziness, paraesthesia
<b>Vascular disorder</b> Not known	Flushing
<b>Gastrointestinal disorders</b> Not known	Nausea, vomiting
<b>General disorders and administration site conditions</b> Not known	Asthenic conditions (e.g., malaise, fatigue)

<sup>1</sup> 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 Yellow Card Scheme at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

### 4.9. Overdose

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical for central nervous system, technetium (<sup>99m</sup>Tc), ATC code: V09AA01

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 are 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**

The finished product contains the following excipients:

Ceretec component:

- Sodium chloride Ph. Eur.
- Stannous chloride dihydrate Ph. Eur.

Cobalt stabiliser solution:

- Cobalt (II) chloride 6-hydrate
- Water for injections Ph. Eur.

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

52 weeks from the day of manufacture. The stabilised product must be injected between 30 minutes and 5 hours after preparation.

The stabilised reconstituted product should be stored below 25°C. Do not freeze.

### **6.4 Special precautions for storage**

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

Storage should be in accordance with national regulations for radioactive materials.

### **6.5 Nature and contents of container**

The freeze-dried component of the product is supplied in a glass vial sealed with a chlorobutyl rubber closure and 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**

#### 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 ( $^{99m}\text{Tc}$ ) 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 ( $^{99m}\text{Tc}$ ), 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 Limited  
Pollards Wood  
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United Kingdom

## 8 **MARKETING AUTHORISATION NUMBER(S)**

PL 00221/0136

## 9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 09 September 1998

Date of last renewal: 29 November 2003

## 10 **DATE OF REVISION OF THE TEXT**

05/05/2020

## 11 **DOSIMETRY (IF APPLICABLE)**

Technetium ( $^{99m}\text{Tc}$ ) is produced by means of a ( $^{99}\text{Mo}/^{99m}\text{Tc}$ ) 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 ( $^{99}\text{Tc}$ ) which, in view of its long half-life of  $2.13 \times 10^5$  years can be regarded as quasi stable.

### Brain scintigraphy

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

	<b>Absorbed dose per unit activity administered (mGy/MBq)</b>
<b>Organ</b>	<b>Adult</b>
Adrenals	5.3E-03
Bone surfaces	5.1E-03
Brain	6.8E-03

Breast	2.0E-03
Gallbladder wall	1.8E-02
Gastrointestinal tract	
Stomach wall	6.4E-03
Small intestine wall	1.2E-02
Colon wall	1.7E-02
(Upper large intestine wall	1.8E-02)
(Lower large intestinal wall	1.5E-02)
Heart wall	3.7E-03
Kidneys	3.4E-02
Liver	8.6E-03
Lungs	1.1E-02
Muscles	2.8E-03
Oesophagus	2.6E-03
Ovaries	6.6E-03
Pancreas	5.1E-03
Red marrow	3.4E-03
Skin	1.6E-03
Spleen	4.3E-03
Testes	2.4E-03
Thymus	2.6E-03
Thyroid	2.6E-02
Urinary bladder wall	2.3E-02
Uterus	6.6E-03
Remaining organs	3.2E-03
<b>Effective dose (mSv/MBq)</b>	<b>9.3E-03</b>

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.

## **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.

### **Method of preparation of cobalt stabilised technetium-99m exametazime for intravenous injection:**

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 10ml syringe, inject into the shielded vial 5ml of sterile eluate from a technetium-99m generator (see notes 1 - 6). Before withdrawing the syringe from the vial withdraw 5ml 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 2ml of cobalt stabiliser solution into the shielded vial using a 3ml syringe. Before withdrawing the syringe from the vial, withdraw 2ml 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. [<sup>99m</sup>Tc]pertechnetate complying with the specifications prescribed by the USP and BP/Ph.Eur. monographs on Sodium Pertechnetate (<sup>99m</sup>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 (<sup>99m</sup>Tc) Exametazime Injection. These are a secondary <sup>99m</sup>Tc-exametazime complex, free [<sup>99m</sup>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 2.5cm from the bottom of two Glass Microfiber Chromatography Paper impregnated with Silicic Acid (GMCP-SA) strips (2cm (+ 2 mm) x 20cm). 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 15cm 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 <sup>99m</sup>Tc-exametazime complex and reduced-hydrolysed-technetium-99m remain at the origin.

Lipophilic <sup>99m</sup>Tc-exametazime complex and [<sup>99m</sup>Tc]pertechnetate migrate at Rf 0.8-1.0.

**System 2** (GMCP-SA:0.9% sodium chloride)

Lipophilic  $^{99m}\text{Tc}$ -exametazime complex, secondary  $^{99m}\text{Tc}$ -exametazime complex and reduced-hydrolysed-technetium-99m remain at the origin.

$^{99m}\text{Tc}$ ]pertechnetate migrates at Rf 0.8-1.0.

I. Calculate the percentage of activity due to both secondary  $^{99m}\text{Tc}$  exametazime complex and reduced-hydrolysed-technetium-99m from System 1 (A%). Calculate the percentage of activity due to  $^{99m}\text{Tc}$ ]pertechnetate from System 2 (B%).

II. 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  $^{99m}\text{Tc}$ ]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.