SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceretec 500 micrograms kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains exametazime 500 micrograms.

Ceretec is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection (not included in this kit) to prepare Technetium (^{99m}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 a 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}Tc) Injection, the product is indicated in adults for:

(1) Technetium (^{99m}Tc) Exametazime Injection is indicated for brain scintigraphy. The product is to be used for the diagnosis of abnormalities of regional cerebral blood flow, such as those occurring following stroke and other cerebrovascular disease, epilepsy, Alzheimer's disease and other forms of dementia, transient ischaemic attack, migraine and tumours of the brain.

(2) Technetium (^{99m}Tc) Exametazime Injection is also indicated for *in vitro* technetium-99m leucocyte labelling, the labelled leucocytes subsequently being re-injected and scintigraphy carried out to image the sites of localisation. This procedure may be used in the detection of sites of focal infection (e.g. abdominal abscess), in the investigation of pyrexia of unknown origin and in the evaluation of inflammatory conditions not associated with infection such as inflammatory bowel disease.

4.2 Posology and method of administration

The route of administration is direct intravenous injection for brain scintigraphy studies and intravenous injection of labelled leucocytes post labelling *in vitro*.

Posology

Adults and the elderly population

1. for brain scintigraphy, 350-500 MBq
2. for *in vivo* localisation of technetium-99m-labelled leucocytes, 200 MBq

Normally a once-only diagnostic procedure.

Paediatric population

Technetium-99m exametazime and technetium-99m-labelled leucocytes are not recommended for administration to children.

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.

Re-injected Ceretec labelled leucocytes only:

When preparing technetium-99m-labelled leucocytes it is essential that cells are washed free of sedimentation agents before they are re-injected into the patient as materials used in cell separation may cause hypersensitivity reactions.

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 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 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 as to whether the investigation could be reasonably delayed until after the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, 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)

Immune system disorders

Not known: Hypersensitivity including rash, erythema, urticaria, angioedema, pruritus.

Re-injected Ceretec labelled leukocytes only:

Not known: Hypersensitivity including rash, erythema, urticaria, angioedema, pruritus, anaphylactoid reaction or anaphylactoid shock.

Nervous system disorders

Not known: Headache, dizziness, paraesthesia

Vascular disorders

Not known: Flushing

Gastrointestinal disorders

Not known: Nausea, vomiting

General disorders and administration site conditions

Not known: Asthenic conditions (e.g., malaise, fatigue)

Exposure to ionising radiation is linked with cancer induction and a potential for developing hereditary defects. As the effective dose is 5.2 mSv when the maximal recommended activity of 555 MBq is administered, these adverse events are expected to occur with a 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

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 radiopharmaceuticals, central nervous system, ATC code: V09AA01

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, inflammation and infection detection, ATC code: V09HA02

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

5.2 Pharmacokinetic properties

(i) Direct intravenous injection

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.

(ii) Injection of labelled leucocytes

Technetium-99m-labelled leucocytes distribute between the marginating pools of the liver (within 5 minutes) and spleen (within about 40 minutes), and the circulating pool, (the latter represents approximately 50% of the leucocyte

pool). Approximately 37% of the cell associated technetium-99m is recoverable from the circulating pool 40 minutes after injection. Technetium-99m activity is slowly eluted from the cells and is excreted partly by the kidneys and partly via the liver into the gall bladder. This results in increasing amounts of activity being seen in the intestines.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Stannous chloride dihydrate

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.

Store the reconstituted product below 25°C. Do not freeze or refrigerate. The labelled product must be injected within 30 minutes of reconstitution.

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

10ml Type I Ph.Eur., clear, colourless, borosilicate glass vial sealed with a chlorobutyl rubber closure and oversealed with an aluminium overseal with a blue flip off cap.

Pack sizes: 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 Limited
Pollards Wood
Nightingales Lane
Chalfont St Giles
Buckinghamshire HP8 4SP
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00221/0126

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 October 1995 / 21 March 2006

10 DATE OF REVISION OF THE TEXT

29/03/2023

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.

(1) Brain scintigraphy

The table below shows the dosimetry as calculated according to the Publication 62 of the ICRP (International Commission on Radiological Protection in Biomedical Research, Pergamon Press 1991) following administration of ^{99m}Tc-exametazime to adults.

Organ	**Absorbed dose per unit activity administered (mGy/MBq) Adult**
Adrenals	5.3E - 03
Bladder	2.3E - 02
Bone surfaces	5.1E -03
Brain	6.8E - 03
Breast	2.0E - 03
Gall bladder	1.8E - 02
GI tract	
Stomach	6.4E - 03
SI	1.2E - 02
ULI	1.8E – 02
LLI	1.5E - 02
Heart	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
Uterus	6.6E - 03
Remaining organs	3.2E - 03
Effective dose (mSv/MBq)	**9.3E - 03**

Effective Dose is 4.7 mSv/500 MBq (70 kg individual).

(2) *In vivo* localisation of technetium-99m-labelled leucocytes

The table below shows the dosimetry as calculated according to the Publication 80 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1998).

Organ	**Absorbed dose per unit activity administered (mGy/MBq**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	1.0E-02	1.2E-02	1.8E-02	2.6E-02	4.3E-02
Bladder	2.6E-03	3.5E-03	5.2E-03	7.8E-03	1.4E-02
Bone surfaces	1.6E-02	2.1E-02	3.4E-02	6.1E-02	1.5E-01
Brain	2.3E-03	2.9E-03	4.4E-03	7.0E-03	1.3E-02
Breast	2.4E-03	2.9E-03	4.9E-03	7.6E-03	1.3E-02
Gall bladder	8.4E-03	1.0E-02	1.6E-02	2.5E-02	3.6E-02
GI-tract					
Stomach	8.1E-03	9.6E-03	1.4E-02	2.0E-02	3.2E-02
SI	4.6E-03	5.7E-03	8.7E-03	1.3E-02	2.1E-02
Colon	4.3E-03	5.4E-03	8.4E-03	1.2E-02	2.1E-02
ULI	4.7E-03	5.9E-03	9.3E-03	1.4E-02	2.3E-02
LLI	3.7E-03	4.8E-03	7.3E-03	1.0E-02	1.8E-02
Heart	9.4E-03	1.2E-02	1.7E-02	2.5E-02	4.4E-02
Kidneys	1.2E-02	1.4E-02	2.2E-02	3.2E-02	5.4E-02
Liver	2.0E-02	2.6E-02	3.8E-02	5.4E-02	9.7E-02
Lungs	7.8E-03	9.9E-03	1.5E-02	2.3E-02	4.1E-02
Muscles	3.3E-03	4.1E-03	6.0E-03	8.9E-03	1.6E-02
Oesophagus	3.5E-03	4.2E-03	5.8E-03	8.6E-03	1.5E-02
Ovaries	3.9E-03	5.0E-03	7.2E-03	1.1E-02	1.8E-02
Pancreas	1.3E-02	1.6E-02	2.3E-02	3.4E-02	5.3E-02
Red marrow	2.3E-02	2.5E-02	4.0E-02	7.1E-02	1.4E-01
Skin	1.8E-03	2.1E-03	3.4E-03	5.5E-03	1.0E-02
Spleen	1.5E-01	2.1E-01	3.1E-01	4.8E-01	8.5E-01
Testes	1.6E-03	2.1E-03	3.2E-03	5.1E-03	9.2E-03
Thymus	3.5E-03	4.2E-03	5.8E-03	8.6E-03	1.5E-02
Thyroid	2.9E-03	3.7E-03	5.8E-03	9.3E-03	1.7E-02
Uterus	3.4E-03	4.3E-03	6.5E-03	9.7E-03	1.6E-02
Remaining organs	3.4E-03	4.2E-03	6.3E-03	9.5E-03	1.6E-02
Effective dose (mSv/MBq)	**1.1E-02**	**1.4E-02**	**2.2E-02**	**3.4E-02**	**6.2E-02**

Effective Dose is 2.2 mSv/200 MBq (70 kg individual).

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 technetium-99m exametazime for intravenous injection or *in vitro*

leucocyte labelling

Use aseptic technique throughout.

(1) Place the 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) Assay the total activity and calculate the volume to be injected or used for *in vitro* technetium¬99m-leucocyte labelling

(4) Complete the label provided and attach to the vial.

(5) Use within a maximum of 30 minutes after reconstitution. Discard any unused material. Note:

a) For the highest radiochemical purity reconstitute with freshly eluted technetium-99m generator eluate.

b) Use only eluate which was eluted less than 2 hours previously from a generator which was eluted within 24 hours.

c) 0.37-1.11 GBq (10-30 mCi) technetium-99m may be added to the vial.

d) 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.

e) Pertechnetate complying with the specifications prescribed by the USP and BP/Ph.Eur. Monographs on Sodium Pertechnetate (^{99m}Tc) Injection should be used.

f) The pH of the prepared injection/labelling agent is in the range 9.0-9.8.

Procedure for separation of leucocytes and subsequent *in vitro* labelling with technetium-99m exametazime

Use aseptic technique throughout.

(1) Draw 9 ml of acid-citrate-dextrose (ACD) (see note a) into each of two 60 ml plastic non-heparinized syringes.

(2) Withdraw 51ml of patient's blood into each syringe, using a 19G Butterfly needle infusion set. Close the syringes with sterile hubs.

(3) Dispense 2ml sedimentation agent (see note b) into each of 5 Universal containers or tubes.

(4) Without attaching a needle to the syringes dispense 20 ml of blood into each of the 5 Universal tubes containing sedimentation agent. Dispense the remaining 20ml of blood into a tube without sedimentation agent.

TIP: *To avoid bubbles and frothing run the blood gently down the sides of the tubes*.

(5) Mix the blood and sedimentation agent with one gentle inversion. Remove the cap of the Universal tube and burst the bubble formed at the top using a sterile needle. Replace the cap and allow the tubes to stand for 30-60 minutes for erythrocyte sedimentation to take place.

TIP: *The period of time for erythrocyte sedimentation depends on the patient's condition. As a guideline it should be stopped when the blood has sedimented to give approximately half the volume as sedimented red cells.*

(6) Meanwhile centrifuge the tube containing 20 ml of blood and no sedimentation agent at 2000g for 10 minutes. This will yield supernatant cell-free plasma (CFP) containing ACD which is retained, at room temperature, for use as a cell labelling and re-injection medium.

(7) When sufficient red cell sedimentation has taken place [see (5)] carefully transfer 15 ml aliquots of the cloudy straw-coloured supernatant into clean Universal tubes. Take care to avoid withdrawing any sedimented erythrocytes. The supernatant is leucocyte-rich, platelet-rich plasma [LRPRP].

TIP: *Do not use needles on sampling syringes to avoid unnecessary cell damage.*

(8) Centrifuge the LRPRP at 150g for 5 minutes to give supernatant, platelet-rich plasma (PRP) and a pellet of "mixed" leucocytes.

(9) Remove as much of the PRP as possible into clean Universal tubes and further centrifuge at 2000g for 10 minutes to give more supernatant, CFP containing sedimentation agent. This will be used to wash the cells after labelling.

(10) Meanwhile loosen the pellets of "mixed" leucocytes by very gently tapping and swirling the Universal tubes. Using a syringe, without an attached needle, pool all the cells into one tube then, using the same syringe, add 1ml of cell-free plasma containing ACD (from 6) and gently swirl to resuspend.

(11) Reconstitute a vial of Ceretec with 5 ml of technetium-99m generator eluate containing approximately 500 MBq (13.5 mCi) of 99mTcO4- (using the procedure described above).

(12) *Immediately* following reconstitution adds 4 ml of the resulting technetium-99m exametazime solution to the "mixed" leucocytes in CFP (from 10).

(13) Gently swirl to mix and incubate for 10 minutes at room temperature.

(14) If required, immediately spot the chromatography strips for assessment of radiochemical purity of the technetium-99m exametazime, as instructed overleaf.

(15) On completion of incubation carefully add 10ml of CFP containing sedimentation agent (from 9) to the cells, in order to stop labelling. Gently invert the cells to mix.

(16) Centrifuge at 150g for 5 minutes.

(17) Remove and retain all of the supernatant.

TIP: *It is critical that all the supernatant which contains unbound technetium-99m exametazime is removed at this stage. This can be best achieved using a syringe with a wide-bore [19G] needle.*

(18) Gently resuspend the technetium-99m labelled mixed leucocyte preparation in 5-10 ml of CFP containing ACD from (6). Gently swirl to mix.

(19) Measure the radioactivity in the cells and in the supernatant from (17). Calculate the labelling efficiency [LE] which is defined as the activity in the cells as a percentage of the sum of the activity in the cells and the activity in the supernatant.

TIP: *Labelling efficiency depends on the patient's leucocyte count and will vary according to the volume of the initial blood sample. Using the volumes in (2), a LE of about 55% might be expected.*

(20) Without attaching a needle, carefully draw up the labelled cells into a plastic, non-heparinised syringe and close it with a sterile hub. Measure the radioactivity.

(21) Labelled cells are now ready for re-injection. This should be performed without delay.

Note:

a) Acid-citrate-dextrose (ACD) should be made up as follows:
NIH Formula A. For 1 litre add 22g trisodium citrate, 8g citric acid, 22.4g dextrose and make up to 1 litre with Water for injections. The product should be manufactured under aseptic condition. Commercial preparations of the product are also available. The product should be stored under the conditions recommended by the manufacturer and should be used only up to the expiry date given by the manufacturer.

b) Sedimentation agents should be manufactured under aseptic conditions. Commercial sedimentation agents are available. Handling and use of sedimentation agents should be in accordance with the recommendation and instructions of the manufacturer.

Quality control

Three potential radiochemical impurities may be present in the prepared exametazime injection. These are a secondary ^{99m}Tc exametazime complex, free pertechnetate and educed-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 (2 cm (± 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% aq. sodium chloride (1cm depth fresh solvent). After a 14cm 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

remain at the origin. Lipophilic ^{99m}Tc exametazime complex and

pertechnetate migrate at Rf 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-Tc remain at the origin.

Pertechnetate migrates at Rf 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 pertechnetate from System 2 (B%).

(2) The radiochemical purity (as percentage lipophilic ^{99m}Tc exametazime complex) is given by:

100- (A%+B%) where:

A% represents the level of secondary ^{99m}Tc exametazime complex plus reduced-hydrolysed technetium-99m

B% represents the level of pertechnetate.

A radiochemical purity of at least 80% may be expected provided the test samples have been taken and analysed within 30 minutes of reconstitution.