Ceretec™

N109 - 2 vial pack
N109 - 5 vial pack

Kit for the preparation of Technetium [99mTc] Exametazime Injection

Presentation

Each vial of Ceretec™ contains exametazime (HM-PAO or [RR.SS]-4,8-diaza-3.6.6.9-tetramethylundecane-2.10-dione bisoxime) (0.5 mg), stannous chloride dihydrate (7.6µg) and sodium chloride (4,5mg) as a freeze-dried mixture sealed under nitrogen.

Powder for injection following reconstitution with 5ml of sterile Sodium Pertechnetate [^{99m}Tc] Injection Ph.Eur. at a radioactive concentration of 74-222MBq/ml (2-6 mCi/ml).

The pH of the injection is 9.0-9.8. This yields Technetium [^{99m}Tc] Exametazime injection, a diagnostic radio-pharmaceutical imaging agent for single dose use.

Packs of 2 and 5 vials are available. Labels for the reconstituted product and sanitising swabs (containing 70% isopropyl alcohol BP) are provided.

Holder of Marketing Authorisation and Manufacturer

GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire
United Kingdom

Indications

i. Technetium [^{99m}Tc] Exametazime is indicated for brain scintigraphy. The product is to be used for the diagnosis of abnormalities or 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.
ii. Technetium [^{99m}Tc] Exametazime 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.

Contra-indications

There are no specific contra-indications.

Precautions for use

This product is not to be administered directly to the patient. The contents of the vial are intended only for use in the preparation of a radioactive technetium-99m labelled injection, using the procedures described in this pack leaflet.

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides.They may be received, used and administered only by authorised persons in designated clinical settings. Their receipt,

storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.
Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.
The normal precautions for handling radioactive materials should also be observed. A separate leaflet specifying information and instructions relating to the handling, use, storage and disposal of radiopharmaceuticals is enclosed with the product.
For details of the storage, elution, handling and disposal of the Technetium-99m Sterile Generator used as the source of Sodium Pertechnetate [^{99m}Tc] Injection required for reconstitution of Ceretec, the user is referred to the Instructions for Use supplied with the Generator by the manufacturer.
Normal safety precautions for the handling of blood products should be observed in the preparation and adminstration of labelled leucocytes. When preparing technetium-99m-labelled leucocytes it is essential that cells are washed free from sedimentation agents before they are re-injected into the patients as materials used in cell separation may cause hypersensitivity reactions.

Interactions
No drug interactions have been reported to date.

Warnings
As part of the manufacture, the vial of freeze-dried product is filled with an inert nitrogen atmosphere to a pressure just below atmospheric before being sealed with the rubber closure.
The product does not contain an antimicrobial preservative. Technetium [^{99m}Tc]-Exametazime should not be mixed with any substance other than those recommended for reconstitution.
Care should be taken when handling blood specimens to be labelled using this radiopharmaceutical. Even if the subject has been tested, no method can offer complete assurance that Hepatitis B Virus, Human immuno-deficiency Virus (HIV) or other infectious agents are absent. All human blood samples should be considered potentially infectious.
This product is a component for use in the preparation of a radioactive product intended for pharmaceutical use. Because of the small mass of chemical substances present, there is negligible risk to persons handling or administering the material, other than that from the radioactive nature of the reconstituted product.
The administration of radiopharmaceuticals creates risk from other persons form external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Pregnancy and Lactation
Pregnancy: No data are available on the use of this product in human pregnancy. Animal reproductive studies have not been performed. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus. Adminstration of technetium [^{99m}Tc]-exametazime at a dose of 500 MBq (13.5 mCi) results in an absorbed dose the the uterus of 3.6mGy: administration of Technetium-99m-labelled leucocytes at a dose of 200MBq (5.4 mCi) results in an absorbed dose to the uterus of 0.76mGy. A radiation dose above 0.5 mGy (equivalent to that exposure from annual background radiation)

would be regarded as a potential risk to the foetus.
Women of childbearing potential: When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.
Lactation: Before administering a radioactive medicinal product to a mohter who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until 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. Breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.

Dosage and administration:
Normally a once-only diagnostic procedure

i. **Brain scintigraphy. Adults and the elderly**: the recommended dose is 350-500 MBq (9.5-13.5 mCi) by intravenous injection
ii. ***In vivo*** **localization of technetium-99m-labelled leucocytes. Adults and the elderly**: the recommended dose is 200MBq (5mCi) as technetium-99m-labelled leucocytes by intravenous injection.Administer the technetium-99m-labelled leucocyte suspension using a 19G needle as soon as possible after labelling.

Paediatric administration: Technetium [^{99m}Tc] exametazime and technetium-99m-labelled leucocytes prepared using technetium [^{99m}Tc] exametazime are not recommended for administration to children or adolescents as data are not available for these age groups. In the United Kingdom the maximum usual activity per test is specified in the Notes for Guidance published by the Department of Health, Administration of Radioactive Substances Advisory Committee.

Imaging

i. **Brain scintigraphy**. Brain imaging may commence from 2 minutes after injection. Although gross abnormalities of brain distribution may be visualised by planar imaging, it is strongly recommended that SPECTimaging is carried out to maximise the value of the study.
ii. ***In Vivo*** **localisation of technetium-99m-labelled leucocyte.** Dynamic imaging may be performed for the first 60 minutes after injection to assess lung clearance and to visualise immediate cell migration. Static imaging at 0.5-1.5 hours, 2-4 hours and if necessary, at 18-24 hours post injection should be performed to detect focal accumulation of activity. Care should be taken to distinguish between leucocyte localisation and normal biodistribution. During the first hour following injection of technetium-99m-labelled leucocytes, activity is seen in the lungs, liver, spleen, blood pool and bone marrow as well as in the bladder. The kidneys (parenchyma and/or renal pelvis) and gall bladder may also be visualised. This pattern of activity continues to be seen at 4 hours post-injection except that lung activity is greatly reduced and faint bowel activity may be visible. At 24 hours post-injection some colonic activity may be seen, in addition to the normal areas visualised in earlier scans.

Procedure for preparation of technetium [^{99m}Tc] exametazime for intravenous injection or *in vitro* leucocyte labelling

Normal safety precautions for the handling of radioactive materials should be observed in addition to the use of aseptic technique to maintain sterility of the vial contents.

i. Place the vial of Ceretec in a shielding container and swab the closure with the sanitising swab provided.
ii. Using a 10ml 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.
iii. Assay the total activity and calculate the volume to be injected or used for *in vitro* technetium-99m leucocyte labelling.
iv. Complete the label and attach to the vial.
v. Use within a maximum of 30 minutes after reconstitution. Dispose of any unused material and its container via an authorised route.

Notes:

1. For the highest radiochemical purity reconstitute with freshly eluted technetium-99m generator eluate.
2. The technetium-99m generator eluate must be used within two hours of elution and must be obtained from a generator that has already been eluted within the previous 24 hours.
3. 0.37-1.11 GBq (10-30 mCi) 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 (10-30 mCi) in 5ml by dilution with Saline for Injection.
5. Pertechnetate complying with the specifications prescribed by the USP and B.P./Ph. Eur. monographs on Sodium Pertechnetate [99mTc] Injection should be used.
6. 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

i. Draw 9ml of acid-citrate-dextrose (a) into each of two 60ml plastic non-heparinized syringes
ii. Withdraw 51 ml of patient's blood into each syringe, using a 19G Butterfly needle infusion set. Close the syringes with sterile hubs.
iii. Dispense 2 ml sedimentation agent(b) into each of 5 Universal containers or tubes.
iv. 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 20 ml of blood into a tube without sedimentation agent.

TIP to avoid bubbles and frothing run the blood gently down the sides of the tubes.

v. 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.

vi. 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 temperatur, for use as a cell labelling and re-injection medium.
vii. When sufficient red cell sedimentation has taken place [see (v)] 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.

viii. Centrifuge the LRPRP at 150g for 5 minutes to give supernatant, platelet-rich plasma (PRP) and a pellet of "mixed" leucocytes.
ix. Remove as much of the PRP as possible into clean Universal tubes and further centrifuge at 2000g for 10 minutes to give more supernatant, cell-free plasma (CFP) containing sedimentation agent. This will be used to wash the cells after labelling.
x. 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 vi) and gently swirl to resuspend.
xi. Reconstitute a vial of Ceretec with 5ml of technetium-99m generator eluate containing approximately 500 MBq (13.5 mCi) of 99mTcO4-(using the procedure described above).
xii. Immediately following reconstitution add 4ml of the resulting technetium [99mTc] exametazime solution to the "mixed" leucocytes in CFP (from x)
xiii. Gently swirl to mix and incubate for 10 minutes at room temperature.
xiv. If required, immediately spot the chromatography strips for assessment of radiochemical purity of the technetium [99mTc] exametazime, as instructed overleaf.
xv. On completion of incubation carefully add 10 ml of CFP containing sedimentation agent (from ix) to the cells, in order to stop labelling. Gently invert the cells to mix.
xvi. Centrifuge at 150g for 5 minutes.
xvii. Remove and retain all of the supernatant.

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

xviii. Gently resuspend the technetium-99m labelled mixed leucocyte preparation in 5-10ml of CFP containing ACD from (vi). Gently swirl to mix.
xix. Measure the radioactivity in the cells and in the supernatant from (xvii). 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 (ii), a LE of about 55% might be expected.

xx. 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.

xxi. 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 Ph.Eur. 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. 6% hydroxyethyl starch should be manufactured under aseptic conditions. Commercial preparations of the product are 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 manufacturer.

Radiochemical purity measurement

Three potential radiochemical impurities may be present in the prepared exametazime injection. These are a secondary technetium [^{99m}Tc] exametazime complex, free 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 Gelman ITLG/SG strips (2.5 cm 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 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 (ITLC: butan-2-one(MEK))
Secondary technetium [^{99m}Tc] exametazime complex and reduced-hydrolised-technetium-99m remain at the origin.
Lipophilic technetium [^{99m}Tc] exametazime complex and pertechnetate migrate at Rf 0.8-1.0.

System 2 (ITLC:0.9% sodium chloride)
Lipophilic technetium [^{99m}Tc] exametazime complex, secondary technetium [^{99m}Tc] exametazime complex and reduced-hydrolysed-technetium-99m remain at the origin.
Pertechnetate migrates at Rf 0.8-1.0.

i. Calculate the percentage of activity due to both secondary technetium [^{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%).
ii. The radiochemical purity (as percentage lipophilic technetium [^{99m}Tc] exametazime complex) is given by:

    100-(A%+B%) where :

    A% represents the level of secondary technetium [^{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.

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 the patient.

Side-effects
A very few cases of mild hypersensitivity, evidenced by the development of an urticarial erythematous rash have been reported following direct intravenous injcetion of the reconstituted product.

A very few reports have also been received of hypersensitivity reactions, possibly anaphylactic in nature, following administration of technetium-99m-labelled leucocytes prepared using technetium [^{99m}Tc]-exametazime. It should also be noted that materials used in cell separation may cause hypersensitivity reactions.

In case of side-effects following adminstration of radiopharmaceuticals, users should ensure the availability of appropriate medical treatment at the time of administration of any radiopharmaceutical to the patient. Users are requested to report to GE Healthcare Limited or the local subsidiary company any instances of suspected adverse drug reactions or side-effects associated with the use of this product.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered mus be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with negligible frequency because of the low radiation dose incurred. For most diagnostic investigations using a nuclear medicine procedure the radiation dose (EDE) delivered is less than 20mSv. Higher doses may be justified in some clinical circumstances.

PHARMACOLOGICAL PARTICULARS

Pharmacodynamic properties
At the chemical concentrations and activities used for diagnostic procedures technetium [^{99m}Tc]-exametazime and technetium-99m-labelled leucocytes do not appear to exert any pharmacodynamic effects.

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 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**

The 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.

Preclinical Safety Data
There are no additional preclinical safety data of relevance for the prescriber in recognising the safety profile of the product used for the authorised indications.

Radiation Dosimetry
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.

i. Brain scintigraphy

According to ICRP 62 (International Commision on Radiological Protection) the estimated absorbed radiation doses to various organs following administration of technetium [^{99m}Tc]-exametazime to adults are as follows:

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 equivalent (mSv/MBq)	**1.1E - 02**

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

ii. *In vivo* localisation of technetium[^{99m}Tc]-labelled leucocytes

The estimated absorbed radiation dosed to various organs following the intravenous administration of technetium-99m-labelled leucocytes to adults given by ICRP 53 are as follows:

Organ	Absorbed dose per unit activity administered (mGy/MBq) Adult
Adrenals	8.9E - 03
Bladder wall	2.6E - 03
Brain	3.1E - 03
Breast	3.1E - 03
GI tract	
Stomach wall	8.0E - 03

Small intestine	4.9E - 03
ULI wall	4.9E - 03
LLI wall	3.9E - 03
Heart	9.0E - 03
Kidneys	9.9E - 03
Liver	2.0E - 02
Lungs	6.9E - 03
Ovaries	4.2E - 03
Pancreas	1.4E - 02
Red marrow	2.2E - 02
Spleen	1.5E - 01
Testes	1.7E - 03
Thyroid	2.4E - 03
Uterus	3.8E - 03
Other tissue	3.4E - 03
Effective dose equivalent (mSv/MBq)	**1.7E - 02**

Effective dose (E) is 2.2 mSv/200 MBq (70 kg individual)

To convert the figures in the tables above to non-S1 Units the following factors should be used:
1 mSv=0.1 rem
1Mbq=0.027 mCi
1mGy=0.1 Rad

Nuclear data for Technetium-99m
Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. is produced by a [^{99m}Mo/^{99m}Tc] generator. Technetium-99 disintegrates with the emission of gamma radiation (energy 141keV, 88.5%: 143 keV, 0.03%) with a half life of 6.02 hours. The decay product, technetium-99, may be regarded as quasi-stable. The dose rute at 0.5m from 1.1GBq technetium-99m shielded with 3 mm of lead is 0.03µSv/hr.

Availability
The product is available from stock.

Expiry
The product must not be used after the expiry date which is stated on the packaging.

Storage
Storage at any temperature in the range of 2-25ºC. Store the reconstituted product at 15 - 25ºC and use within 30 minutes of preparation.

Date of preparation

April 2006

Marketing authorisations
UK: PL 0221/0126
Denmark: DK R.10
Sweden: 80004
Norway: MTNr 8343
Finland: 11217
Ireland: PA/240/4/1

European Patent Numbers 1230504 and 194843 BI

L/5657/01

GE Healthcare

TECHNICAL INFORMATION

CERETEC™

Kit for the preparation

of Technetium
[^{99m}Tc] Exametazime
Injection

N109 2 vial pack
N109 5 vial pack

Harus dengan Resep Dokter
No Reg:
Manufacturing date:

Imported and distributed by :
PT Medikon Utama Pharmalab
Jakarta, Indonesia