SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Medi-Exametazime 500 microgram kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 micrograms exametazime
The radionuclide is not part of the kit.
Excipients(s) with known effect:
Sodium 0.52 mg/vial
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. This is indicated for adults and elderly. For paediatric population see section 4.2.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of technetium (^{99m}Tc) exametazime obtained is indicated for:

Neurology
Technetium (^{99m}Tc) exametazime 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. The following indications are sufficiently documented:
- Evaluation of patients with cerebrovascular disease (specifically acute stroke, chronic ischemia, and transient ischemic attack)
- Presurgical lateralization and localization of epileptogenic foci.
- Evaluation of patients with suspected dementia (specifically Alzheimer’s disease and frontotemporal dementia)
- Evaluation of patients with migraine
- Adjuvant technique in the diagnosis of brain death

Infectious or inflammatory diseases
In infectious or inflammatory diseases, the diagnostic target is tissue or structures in which labeled
leukocytes are retained.

In infectious or inflammatory diseases, the following indications are sufficiently documented:

- Localisation of abnormal foci guiding the aetiologic diagnosis in case of fever of unknown origin
- Diagnosis of infection in case of suspected osteomyelitis (with or without implants) and suspected hip or knee prosthesis infection.
- Detection of the extension of inflammation in case of inflammatory bowel disease.

4.2 Posology and method of administration

Posology

Adults and elderly population

The suggested activity range for intravenous administration to an adult patient of average weight (70 kg) is for:

- Brain perfusion SPECT: 350-500 MBq

- For labelled leukocyte scintigraphy: 200 MBq

Renal/Hepatic impairment

In case of renal or hepatic impairment, exposure to ionising radiation can be increased. This must be taken into account when calculating the activity to be administered.

Paediatric population

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. Safety and efficacy in paediatric population have not been fully established. Alternative techniques which do not involve ionising radiation should be especially considered.

The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity

(for calculation purposes) by the weight-dependent multiples given in the table below.

A[MBq]Administered = Baseline Activity × Multiple

The baseline activity is 51.8 MBq for brain perfusion SPECT, and the minimum activity is 100 MBq.

For labelled leukocyte scintigraphy, the baseline activity is 35 MBq and the minimum activity is 40 MBq.

Weight [kg]	Multiple	**Weight [kg]**	Multiple	**Weight [kg]**	Multiple
3	1	**22**	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57

6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

Method of administration

- Brain perfusion SPECT: intravenous use. The radiopharmaceutical should be injected no sooner than 10 min but not later than 60 min after radioligand reconstitution.

- For labelled leukocyte scintigraphy: Leukocytes are labelled in vitro and subsequently labelled

leukocytes are for intravenous use.

Because of potential tissue damage extravasal injection of this radioactive product has to be strictly

avoided.

For multidose use.

Precautions to be taken before handling or administration of the medicinal product

This medicinal product should be reconstituted before administration to the patient. For instructions on

reconstitution and control of the radiochemical purity of the medicinal product of the medicinal product

before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition

Brain perfusion SPECT

Imaging should be delayed 30-90 min after injection for best image quality. Depending on the imagingdevice, typical scan time for triple head cameras is around 20–25 min (e.g. 120 projections, 40 projections per head, 20–25 s/projection); for dual head cameras it is closer to 30 min (e.g. 120 projections, 60 projections per head, 30 s/projection). Imaging should be completed within 4 hours post injection.

Labeled leukocyte scintigraphy

A large-field-of-view gamma camera with a low-energy high-resolution collimator is usually preferred.

Early imaging of the pelvis and abdomen is essential (bowel activity is seen in 20%–30% of children by 1 h and 2%–6% of adults by 3–4 h after injection). Images of the limbs should be acquired for 10 min/view at 4–8 h and at least 15 min/view at 16–24 h (particularly for osteomyelitis).

SPECT images of the chest, abdomen/pelvis,or spine may be helpful.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occurs, 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 or Hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in paediatric population, see sections 4.2.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

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.

Brain perfusion SPECT
Patients should preferably avoid excessive stimulants (such as caffeine, cola, and energy drinks), alcohol, smoking, and any drugs known to affect cerebral blood flow prior to imaging.

After the procedure
Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium- free’.

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 patient on low sodium diet.

The preparation without reconstitution with sodium ^{99m}Tc-pertechnetate must not be administered to patients.

Reinjected Medi –exametazime labelled leukocytes only

When preparing technetium (^{99m}Tc)-labelled leukocytes, 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.

Manipulation of human cells (labelling of leucocytes) carries the risk of potential transmission of infections (HBV, HIV, etc).

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 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

Radionuclide procedures carried out on pregnant women also involve radiation dose 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 foetus

Breastfeeding

Before administering radiopharmaceuticals 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, breastfeeding should be interrupted for 12 hours and the expressed feeds discarded. Breastfeeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1mSv.

Close contact with infants should be restricted during this period.

Fertility
No studies on fertility have been performed.

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 **Re-injected labelled leukocytes only** Not known	Hypersensitivity including rash, erythema, urticaria, angiooedema, pruritus. Hypersensitivity including rash, erythema, urticaria, angiooedema, pruritus, anaphylactoid reaction or anaphylactoid shock
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)

Other disorder
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
As the effective dose is 4.7 mSv when the maximal recommended activity of 500 MBq is administered these adverse reactions 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 United Kingdom Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

In the event of administration of a radiation overdose with technetium (^{99m}Tc) exametazime, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defaecation. It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, Technetium (^{99m}Tc) compounds, ATC code:
V09AA01 and V09HA02.
Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, technetium (^{99m}Tc) exametazime solution
does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Brain perfusion SPECT

Distribution

The technetium (99mTc) 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.

Organ uptake

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 (99mTc).

The activity not associated with the brain is widely distributed throughout the body particularly in muscle and soft tissue.

Elimination

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.

Labeled leukocyte scintigraphy

Technetium (99mTc) -labelled leukocytes distribute between the marginal pools of the liver (within 5 minutes) and spleen (within about 40 minutes), and the circulating pool, (the latter represents approximately 50% of the leukocyte

pool). Approximately 37% of the cell associated technetium (99mTc) is recoverable from the circulating pool 40 minutes after injection. Technetium (99mTc) 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

Toxicological studies with mice have demonstrated that with a single IV injection of 2.5 mg/kg no deaths or pathological alteration were observed. Human safety factor 1750.
Toxicological studies with mice have demonstrated that with a single IV injection of 0.15 mg/kg no deaths or pathological alteration were observed. Human safety factor 105.
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

Stannous chloride dihydrate
Tetrasodium Pyrophosphate Decahydrate
Nitrogen

6.2 Incompatibilities

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

6.3 Shelf life

12 months.
After radiolabelling: 60 minutes
Do not store above 25°C after radiolabelling.
Do not refrigerate or freeze

6.4 Special precautions for storage

Store at 2-8°C.
Do not freeze. Keep the vials in the outer carton in order to protect from light.
For storage conditions of the radiolabelled medicinal product, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

The product is supplied in 8 ml Type I Ph.Eur., clear, colourless, borosilicate glass vial sealed with a chlorobutyl rubber closure and oversealed with an aluminium overseal with a green flip off cap.
1 pack contains 3 multidose vials
1 pack contains 6 multidose vials
Sample package: 1 multidose vial
Bundle pack of 2 packs of 6 multidose vials
Bundle pack of 4 packs of 6 multidose vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Radiopharmaceuticals should 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 licensees of the competent official organization. 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}Tc) exametazime 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 sections 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

The content of the kit before extemporary preparation is not radioactive. However, after *sodium pertechnetate (^{99m}Tc) Injection, 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.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 40129/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/05/2017

10 DATE OF REVISION OF THE TEXT

10/05/2017

11 DOSIMETRY (IF APPLICABLE)

Technetium (99mTc) is produced by means of a (99Mo/99mTc) 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 (99Tc) which, in view of its long half-life of 2.13 x 105 years can be regarded as quasi stable.

Brain perfusion SPECT

The data listed below are from ICRP 80:

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**					
	Adult	**15 years**	**10 years**	**5 years**	**1 years**	**Newborn**
Adrenals	0.0053	0.0067	0.0099	0.014	0.024	0.066
Bladder	0.023	0.028	0.033	0.033	0.056	0.15
Bone surfaces	0.0051	0.0064	0.0094	0.014	0.024	0.073
Brain	0.0068	0.011	0.016	0.021	0.037	0.084
Breast	0.00206	0.0024	0.0037	0.0056	0.0095	0.034

Gall bladder	0.018	0.021	0.028	0.048	0.14	0.32
GI tract						
Stomach	0.0064	0.0085	0.012	0.019	0.036	0.14
Small intestine	0.012	0.015	0.024	0.036	0.065	0.21
Colon	0.017	0.022	0.035	0.055	0.1	0.29
Upper large intestine	0.018	0.024	0.038	0.06	0.11	0.31
Lower large intestine	0.015	0.019	0.031	0.048	0.09	0.27
Heart	0.0037	0.0047	0.0067	0.0097	0.016	0.05
Kidneys	0.034	0.041	0.057	0.081	0.14	0.36
Liver	0.0086	0.011	0.016	0.023	0.04	0.092
Lungs	0.011	0.016	0.022	0.034	0.063	0.17
Muscles	0.0028	0.0035	0.005	0.0073	0.013	0.045
Oesophagus	0.0026	0.0033	0.0047	0.0069	0.011	0.041
Ovaries	0.0066	0.0083	0.012	0.017	0.027	0.081
Pancreas	0.0051	0.0065	0.0097	0.014	0.023	0.069
Red marrow	0.0034	0.0041	0.0059	0.008	0.014	0.042
Skin	0.0016	0.0019	0.0029	0.0045	0.0083	0.032
Spleen	0.0043	0.0054	0.0082	0.012	0.02	0.059
Testes	0.0024	0.003	0.0044	0.0061	0.011	0.039
Thymus	0.0026	0.0033	0.0047	0.0069	0.011	0.041
Thyroid	0.026	0.042	0.063	0.14	0.26	0.37
Uterus	0.0066	0.0081	0.012	0.015	0.025	0.075
Remaining organs	0.0032	0.004	0.006	0.0092	0.017	0.053
Effective dose (mSv/MBq)	**0.0093**	**0.011**	**0.017**	**0.027**	**0.049**	**0.12**

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

The effective dose resulting from the administration of a maximal recommended activity of 500 MBq of technetium (99mTc) exametazime for an adult weighing 70 kg is about 4.7 mSv.

For an administered activity of 500 MBq the typical radiation dose to the target brain is 3,4 mGy and the typical radiation dose/doses to the critical organs kidneys and thyroid are 34 mGy and 13 mGy,

respectively.

Labeled leukocyte scintigraphy

The data listed below are from ICRP 80:

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.010	0.012	0.018	0.026	0.043
Bladder	0.0026	0.0035	0.0052	0.0078	0.014
Bone surfaces	0.016	0.021	0.034	0.061	0.15
Brain	0.0023	0.0029	0.0044	0.0070	0.013

Breast	0.0024	0.0029	0.0049	0.076	0.013
Gall bladder	0.0084	0.010	0.016	0.025	0.036
GI-tract					
Stomach	0.0081	0.0096	0.014	0.020	0.032
Small intestine	0.0046	0.0057	0.0087	0.013	0.021
Colon	0.0043	0.0054	0.0084	0.012	0.021
Upper large intestine	0.0047	0.0059	0.0093	0.014	0.023
Lower large intestine	0.0037	0.0048	0.0073	0.010	0.018
Heart	0.0094	0.012	0.017	0.025	0.044
Kidneys	0.012	0.014	0.022	0.032	0.054
Liver	0.020	0.026	0.038	0.054	0.097
Lungs	0.0078	0.0099	0.015	0.023	0.041
Muscles	0.0033	0.0041	0.0060	0.0089	0.016
Oesophagus	0.0035	0.0042	0.0058	0.0086	0.015
Ovaries	0.0039	0.0050	0.072	0.011	0.018
Pancreas	0.013	0.016	0.023	0.034	0.053
Red marrow	0.023	0.025	0.040	0.071	0.14
Skin	0.0018	0.0021	0.0034	0.0055	0.010
Spleen	0.15	0.21	0.31	0.48	0.85
Testes	0.0016	0.0021	0.0032	0.0051-	0.0092
Thymus	0.0035	0.0042	0.0058	0.0086	0.015
Thyroid	0.0029	0.0037	0.0058	0.0093	0.017
Uterus	0.0034	0.0043	0.0065	0.0097	0.016
Remaining organs	0.0034	0.0042	0.0063	0.0095	0.016
Effective dose (mSv/MBq)	**0.011**	**0.014**	**0.022**	**0.034**	**0.062**

The effective dose resulting from the administration of a maximal recommended activity of 200 MBq of technetium (99mTc) exametazime for an adult weighing 70 kg is about 2.2 mSv.

For an administered activity of 200 MBq the typical radiation dose/doses to the critical organ/organs spleen and red marrow are 30 mGy and 4.6 mGy respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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.

Precautions related to the labeling of leukocytes

During the labelling procedure, blood and blood components from the patient, who could potentially be infected with pathogens, need to be handled. To prevent contamination of the operator who is performing the labelling, waterproof gloves should be worn throughout the procedure. Special caution should be taken when handling needles.
Since technetium (^{99m}Tc) exametazime labeled leukocytes have to be reinjected into the patient, strict aseptic conditions are required for the labelling procedure. For this purpose, only sterile reagents and disposable plastic-ware should be used, and sterile gloves, cap and mask should be worn. Usually, the labelling of leukocytes is performed in a laminar flow cabinet or cell isolator, installed according to local regulations.

Simultaneous labelling of leukocytes from multiple patients is discouraged in order to prevent possible cross-contamination.
Labelling of leukocytes from different patients should be carried out at physically separated locations unless closed devices are used. At all times correct identification of the patient's blood products should be guaranteed. All syringes, tubes and any material in contact with the patient's blood components should be clearly labelled with the patient's name, bar-code and/or colour code.
During the labelling of leukocytes with technetium (^{99m}Tc) exametazime care should be taken that leucocytes are not damaged, as this would result in leakage of the radioactivity from the cells, adhesion of labelled leucocytes to the vascular endothelium (especially in the microvasculature of the lungs) and loss of motility. To avoid degradation of the radiopharmaceutical and radiation damage to labelled cells, technetium (^{99m}Tc) exametazime labeled leukocytes should be reinjected as soon as possible, but not later than 1 h after labelling.

Procedure for preparation of technetium (^{99m}Tc) exametazime for intravenous injection or *in- vitro* leukocyte labelling:

Use aseptic technique throughout.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.

(1) Place the 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}Tc) generator (see notes a - f). 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) Assay the total activity and calculate the volume to be injected or used for *in vitro* technetium (^{99m}Tc)-leukocyte labelling.
(4) Complete the label provided and attach to the vial.
(5) Use within a maximum of 60 minutes after reconstitution. Discard any unused material.

Note:

a) For the highest radiochemical purity reconstitute with freshly eluted technetium (^{99m}Tc) generator eluate.
b) Use only eluate which was eluted less than 2 hours previously from a generator which was eluted within 24 hours.
c) 0.37-2.2 GBq (10-60 mCi) technetium (^{99m}Tc) may be added to the vial.
d) Before reconstitution the generator eluate may be adjusted to the correct radioactive concentration (0.37-2.2 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 7.0-10.0

Procedure for separation of leukocytes and subsequent in-vitro labelling with ^{99m}Tc-Medi-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 51 ml of patient's blood into each syringe, using a 19G Butterfly needle infusion set. Close the syringes with sterile hubs.
3) Dispense 2 ml 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 20 ml of blood into a tube without sedimentation agent.
   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.
   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 2000 g 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 leukocyte-rich, platelet-rich plasma (LRPRP). Do not use needles on sampling syringes to avoid unnecessary cell damage.
8) Centrifuge the LRPRP at 150 g for 5 minutes to give supernatant, platelet-rich plasma (PRP) and a pellet of "mixed" leukocytes.
9) Remove as much of the PRP as possible into clean Universal tubes and further centrifuge at 2000 g 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" leukocytes 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 Medi-Exametazime with 5 ml of technetium (^{99m}Tc) generator eluate containing approximately 500 MBq (13.5 mCi) of $^{99m}TcO_4^-$ (using the procedure described above).
12) *Immediately* following reconstitution add 4 ml of the resulting technetium (^{99m}Tc) exametazime solution to the "mixed" leukocytes 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}Tc) 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 150 g for 5 minutes.
17) Remove and retain all of the supernatant.
    It is critical that all the supernatant which contains unbound technetium (^{99m}Tc) 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}Tc) labelled mixed leukocyte 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. Labelling efficiency depends on the patient's leukocyte 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 22 g trisodium citrate, 8 g citric acid, 22.4 g 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) 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 the manufacturer.

Quality control

1. Radiochemical purity measurement of ^{99m}Tc-Medi-Exametazime (Method I)

Method I.

Radiochemical purity measurement

Three potential radiochemical impurities may be present in the prepared exame-tazime injection. These are a secondary ^{99m}Tc exametazime complex, free pertechnetate and reduced-hydrolysed-technetium (^{99m}Tc). A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection.

5 µl test samples are applied by needle approximately 2.5 cm from the bottom of two ITLC/SG strips (2.5 cm 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 % aq. sodium chloride (1cm depth fresh solvent). After a 15 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 (ITLC: 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 (ITLC: 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}Tc) 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}Tc).

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 60 minutes of reconstitution.