PRODUCT MONOGRAPH

Drax Exametazime®

Kit for the Preparation of Technetium Tc 99m Exametazime for Leukocyte Labelling
Powder for Solution, 0.5 mg/vial, Intravenous

Reagent for Preparation of a Radiodiagnostic Agent

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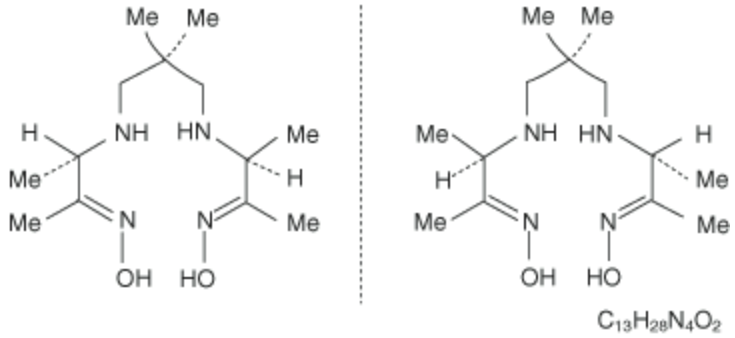
DESCRIPTION

Drax Exametazime® (Kit for the Preparation of Technetium Tc 99m Exametazime for Leukocyte Labelling) is a kit containing five (5) single-dose vials. Each 10 mL, clear glass vial contains a sterile, non-pyrogenic lyophilized mixture of 0.5 mg exametazime (d,l-HMPAO), 7.6 mcg stannous chloride dihydrate (minimum stannous tin 0.6 mcg; maximum total stannous and stannic tin 4 mcg per vial) and 4.5 mg sodium chloride, sealed under nitrogen atmosphere with a rubber closure. The product contains no antimicrobial preservative.

The chemical formula of exametazime is $C_{13}H_{28}N_4O_2$, with the following structural formula:



Prior to publication of the USAN, exametazime [also known as (RR,SS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime] was known as hexamethylpropylene amine oxime (HM-PAO). The name HM-PAO appears in many publications.

Physical Characteristics

Technetium 99m decays by isomeric transition with a physical half-life of 6.02 hours[(9)]. Photons that are useful for detection and imaging studies are listed in Table 1.

Table 1. Principal Radiation Emission Data – Tc 99m

Radiation	Mean %/ Disintegration	Mean Energy (keV)
Gamma-2	87.87	140.5

External Radiation

The specific gamma ray constant for Tc 99m is 206 mcCkg^{-1}/37MBq-hr.(0.78R/millicurie-hr.) at l cm. The first half-value layer is 0.02 cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.02	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions of radioactivity that remain at selected intervals after time of calibration are shown in Table 3.

Table 3. Physical Decay Chart: Technetium 99m, Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
*0	1.000	5	0.562
1	0.891	6	0.501
2	0.794	8	0.398
3	0.708	10	0.316
4	0.631	12	0.251

*Calibration time

CLINICAL PHARMACOLOGY

In vitro Tc 99m leukocyte labelling

Leukocytes are involved in a number of the body's responses to disease including infection, inflammation and infarction. Techniques have been developed to tag leukocytes with a radiolabel using In 111, in order to subsequently assess sites of localization and consequently pathology using a gamma camera. In 111 labelled leukocytes are an established noninvasive means of diagnosing a variety of inflammatory conditions in which granulocyte migration is a prominent feature[1-4].

The superior imaging characteristics of Tc 99m have led to a search for a suitable method to label leukocytes with this nuclide. Labelling by means of complexes such as Tc 99m oxine, Tc 99m pyrophosphate and medronate and the incorporation of Tc 99m colloids by phagocytes have been proposed, but all suffer deficiencies either in label stability or in "activation" or damage to leukocytes during the labelling procedure, leading to an unnatural biodistribution on reinjection[5, 6].

The small lipophilic nature of the Tc 99m exametazime complex facilitates its uptake into leukocytes, following which the Tc 99m is selectively retained in neutrophils. Provided the recommended cell separation and labelling procedures are carried out, the Tc 99m labelled leukocytes do not appear to suffer significant damage or "activation", as evidenced by their *in vivo* recovery and lack of lung and liver uptake. Label elution rate is up to 10% in the first hour, declining thereafter.

Following cell separation and radiolabelling, according to the package insert instructions for CERETEC® (Kit for the Preparation of Technetium Tc 99m Exametazime Injection), a labelling efficiency of around 55% may be expected with around 78% of the label associated with the neutrophil population. Studies of elution rates indicate that Tc 99m exametazime shows relative selectivity for granulocytes[7] and acts as an effective radiolabelling agent. Following reinjection of the Tc 99m labelled leukocytes the functional integrity of the granulocytes appears to be well maintained as the recovery of radiolabelled granulocytes (i.e., the circulatory granulocyte associated activity as a percentage of injected granulocyte associated activity) at 40 minutes after injection gave a mean value of 37%[8] which compares favorably with pure granulocytes labelled with In 111 tropolonate[3]. The initial biodistribution is similar to that of In 111 tropolonate labelled pure granulocytes. During the first hour following injection of Tc 99m labelled leukocytes, 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 gallbladder may also be visualized. 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 substantial colonic activity is seen, in addition to the normal areas visualized in earlier scans.

TOXICOLOGY

Toxicity studies have been performed on intravenously administered technetium 99m exametazime injection in male and female rats and rabbits.

No adverse reactions or mortalities were observed at a dose level equivalent to the single injection of 1200 times the maximum human equivalent dose (MHD). Similarly, 14-day repeat-dose studies in rats and rabbits at a cumulative dose of up to 14,000 times the maximum human equivalent dose resulted in no adverse reactions or mortalities. At termination, thorough histopathology, hematology and blood chemistry revealed no abnormalities.

INDICATIONS AND CLINICAL USES

Tc 99m Exametazime is an effective agent for *in vitro* Tc 99m leukocyte radiolabelling. Tc 99m labelled leukocytes are useful in the detection of sites of focal infection, especially abdominal abscess and as an adjunct in the investigation of pyrexia of unknown origin (PUO), and in the evaluation of inflammatory conditions not associated with infection such as inflammatory bowel disease (IBD).

CONTRAINDICATIONS

There are no specific contraindications.

WARNINGS

The possibility of hypersensitivity including serious signs and symptoms of anaphylaxis should always be considered. Advanced life support facilities should be readily available.

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 Imunodeficiency Virus (HIV) or other infectious agents are absent. All human blood samples should be considered potentially infectious. Precautions for handling are as those for handling radioactive materials.

The contents of the Drax Exametazime® kit are intended for use in the preparation of Tc 99m exametazime injection and are NOT to be directly administered to the patient.

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability should be performed during the first ten days following the onset of menses.

PRECAUTIONS

General

The Tc 99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

Sodium Chloride Injection, USP must be used as the diluent. Do not use bacteriostatic sodium chloride as a diluent for sodium pertechnetate Tc 99m injection because it will increase the oxidation products and adversely affect the biological distribution of Tc 99m exametazime injection.

Radiopharmaceuticals should be used only by those medical practitioners who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

The content of the vials is sterile and non pyrogenic. It is essential that the user follows directions carefully and adheres to strict aseptic technique.

It should also be noted that materials used in cell separation may cause hypersensitivity reactions. It is essential that cells are washed free of sedimentation agents before they are reinjected into the patient.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males and females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

Nursing

Where an assessment of the risk/benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

Pediatric Use

Adequate studies do not exist to support the use in children. As in pregnancy and lactating mothers, the benefits to risk ratio should be assessed before consideration is given to the use of this product in this age group.

Use in Pregnancy

In women of childbearing age the possibility of pregnancy should always be taken into account. It would be prudent to treat as pregnant any woman of reproductive age presenting for a nuclear medicine examination at a time when a menstrual period is overdue or missed, unless there is information that precludes pregnancy. If the menstrual cycle is irregular, a pregnancy test may be indicated before proceeding.

ADVERSE REACTIONS

Reports of hypersensitivity reactions, possibly anaphylactic in nature, following administration of Tc 99m labelled leukocytes prepared using Tc 99m exametazime have been received.

Immune system disorders
Hypersensitivity (including rash, erythema, urticaria, angioedema, pruritus), anaphylactoid reaction or anaphylactoid shock

Nervous system disorders
Headache, dizziness, paraesthesia

Vascular disorders
Flushing

Gastrointestinal disorders
Nausea, Vomiting

General disorders and administration site conditions
Asthenic conditions (e.g. malaise, fatigue)

In case of side effects following administration 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 Jubilant DraxImage Inc. any instances of suspected adverse drug reactions or side effects associated with the use of this product.

DOSAGE AND ADMINISTRATION

For adults (70 kg), the usual administered activity is 185 to 370 MBq (5 to 10 mCi)[10, 11] of Tc 99m labelled leukocytes by intravenous injection. Administer the Tc 99m labelled leukocyte suspension using a 19G needle as soon as possible after labelling. Dynamic imaging may be performed for the first 60 minutes after injection to assess lung clearance and to visualize immediate cell migration.

Static imaging at 0.5 to 1.5 hours, 2 to 4 hours and if necessary, at 18 to 24 hours post injection should be performed to detect focal accumulation of activity. Care should be taken to distinguish between leukocyte localization and normal biodistribution.

INSTRUCTIONS FOR PREPARATION

Important Administration Instructions

- Use strict aseptic procedures throughout preparation and handling.
- Visually inspect the reconstituted Tc 99m exametazime solution for particulate matter and discoloration prior to radiolabelling of white blood cells. Do not use the reconstituted solution if there is evidence of particulate matter or discoloration.
- Follow the directions of drug preparation carefully to ensure efficient leukocyte labelling.
- Measure patient dose with a suitable radioactivity calibration system immediately prior to administration.

Preparation of Autologous Leukocytes

IMPORTANT - Label all syringes and tubes used in this labelling procedure with the patient's name and unique identification number.

Leukocyte Harvest and Separation

1. Draw 2 mL of Heparin and 8 mL of 6% Hydroxyethyl starch into a 60 mL plastic syringe.
2. Withdraw approximately 40 mL whole blood from the patient into the syringe using a 19-gauge Butterfly needle infusion set. Close the syringe with a sterile hub.
3. Gently mix the contents for 2 minutes.
4. Clamp the syringe barrel to the ring stand in an upright (hub side up) position and tilt the syringe approximately 10 to 20 degrees from its position perpendicular to the bench.
5. Allow the syringe to stand a minimum of 60 minutes until the red blood cells sediment and the supernatant looks clear.
6. Using an infusion set, transfer the leukocyte-rich plasma (LRP), the supernatant, from the previous step, into a sterile, conical centrifuge tube marked "WBC" (white blood cell) and assure that only a minimum amount of red cells enter the centrifuge tube.

7. Immediately centrifuge the capped WBC tube at 400 g to 450 g for 5 minutes. The plasma will separate out into a liquid [leukocyte poor plasma (LPP)] and a solid (WBC button). The WBC button often contains a small number of red blood cells and may appear red.
8. Transfer the leukocyte poor plasma (LPP) into another sterile centrifuge tube marked as "Plasma" tube, without disturbing the WBC button. Save the LPP in the Plasma tube for later use (Steps 16 and 19).

Red Blood Cell Lysis and Washing

9. Add 1 mL Sodium Chloride (NaCl) Injection, USP (0.9%) to the WBC button and suspend.
10. Add the following to the WBC suspension in succession and swirl the centrifuge tube (WBC tube) for 5 to 30 seconds after each addition:
    a) 9 mL sterile water;
    b) 2 mL of 5% NaCl; and
    c) 10 mL of 0.9% NaCl.
    Note: Attention to timing is important as exposing leukocytes to a hypotonic solution for a prolonged period will damage leukocytes and result in poor leukocyte labelling results.
11. Cap the WBC tube and centrifuge at 400 g for 5 to 7 minutes. Draw off the supernatant into the "Waste" tube.
12. Add 1.5 mL of 0.9% Na Cl and re-suspend the WBC button by gentle shaking.
13. Reconstitute Tc 99m exametazime with generator eluate (See Preparation of Tc 99m Exametazime). Measure the radioactivity and record as item (1) on the Labelling Efficiency Worksheet. Use for radiolabelling WBC within 30 minutes.

Labelling of Autologous Leukocytes with Tc 99m Exametazime

14. Carefully add the reconstituted Tc 99m exametazime to the WBC tube containing the WBC button isolated in Step 12.
15. Incubate the WBCs at room temperature for 15 minutes. Swirl during the incubation every 5 minutes.
16. Add 5 mL of LPP (from Step 8) to the WBC tube. Cap the WBC tube and centrifuge at 400 g for 5 minutes.
17. Carefully remove the supernatant and place into the tube labelled “Wash.” Keep the labelled white cells in the WBC tube.
18. Measure the radioactivity of the Wash tube and record as item (2) on the Labelling Efficiency Worksheet.
19. Add 5 to 10 mL of LPP (from Step 8) to the Tc 99m labelled leukocyte preparation (WBC tube). Gently swirl to mix.
20. Draw up the labelled cells into a non-heparinized syringe with a large bore needle (no smaller than 19-gauge) and cap it with a sterile hub. Measure the radioactivity of the cells and record as item (3) on the Labelling Efficiency Worksheet.
21. **Verify the identity of the leukocyte recipient.**

22. Labelled cells are now ready for administration. Administer as soon as possible and preferably within 1 to 2 hours after labelling.
23. Calculate the labelling efficiency from the Labelling Efficiency Worksheet:

$$\frac{\text{Radioactivity of the cells [item (3)]}}{\text{Radioactivity of the cells [item (3)] + activity in the supernatant [item (2)]}}$$

A labelling efficiency of about 55% might be expected.

Preparation of Tc 99m Exametazime

The Tc 99m labelling reaction involved in preparing the agent depends on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m may adversely affect the radiolabelling efficiency.

- Elute the Tc 99m generator according to the manufacturer's instructions.
  - Use only eluate from a Tc 99m generator which was eluted within the previous 24 hours.
  - Prepare the Tc 99m exametazime with eluate that is not more than 2 hours old.
- Before reconstitution, add up to 5 mL preservative-free, non-bacteriostatic Sodium Chloride Injection USP (0.9%) to the generator eluate to achieve a radioactive concentration no greater than 74 to 370 MBq/mL (2 to 10 mCi/mL).
- Add 370 MBq up to 2000 MBq – recommended 1 110 MBq (10 mCi up to 54 mCi – recommended 30 mCi) of sodium pertechnetate Tc 99m to Drax Exametazime® vial.
- Measure the radioactivity and record as item (1) on the Labelling Efficiency Worksheet.
- Use a sample for Quality Control.
- Maintain reconstituted product at 20°C to 25°C.
- Use for WBC labelling within 30 minutes following reconstitution.
- Discard any unused material according to local radiation safety procedures.

Radiochemical Purity Measurement - Quality Control of Tc 99m Exametazime

Obtain the Following Materials:
SG ITLC strips 6 cm x 0.7 cm
Whatman Grade 31ET chromatographic paper strip 6 cm x 0.7 cm
MEK (methyl ethyl ketone [butanone]) (HPLC Grade)
0.9% aqueous sodium chloride (non-bacteriostatic)
50% aqueous acetonitrile (HPLC Grade)
Glass test tubes (12 x 75 mm) with covers
1 mL syringes with 25-gauge needles
Collimated radiation detector

- Perform radiochemical purity testing of Tc 99m exametazime before leukocyte labelling and within 2 minutes of reconstitution.
- This entire radiochemical purity testing procedure takes approximately 15 minutes.
- A combination of 3 chromatographic systems is necessary for the complete definition of the radiochemical composition of the injection.
    - **System 1:** methyl ethyl ketone (MEK) + SG ITLC strip
    - **System 2:** 0.9% non-bacteriostatic sodium chloride solution + SG ITLC strip
    - **System 3:** 50% acetonitrile solution + Whatman 31ET paper strip
- Three potential radiochemical impurities may be present in the prepared injection of the lipophilic Tc 99m exametazime complex:
    - secondary Tc 99m exametazime complex
    - free Tc 99m pertechnetate
    - reduced-hydrolyzed Tc 99m

Method

1. Prepare three chromatographic systems using 12 mm × 75 mm chromatographic tubes with the following solvents (identify the solvent in each tube):
   System 1: 0.3 mL of fresh methyl ethyl ketone (MEK)
   System 2: 0.9% non-bacteriostatic sodium chloride solution
   System 3: 50% acetonitrile solution, prepared with non-bacteriostatic water
2. Apply 5 mcL of freshly prepared Tc 99m exametazime solution (within 2 minutes of reconstitution) about 1 cm from the bottom of three strips: two 6 cm × 0.7 cm instant thin-layer chromatographic strips and one 6 cm × 0.7 cm strip of chromatographic paper. **Do not allow to dry.**
3. Place one SG ITLC strip into the MEK tube (**System 1**), the second SG ITLC strip into the saline tube (**System 2**) and the Whatman 31ET paper strip into the 50% acetonitrile tube (**System 3**). Make sure strips are not adhering to the sides of the tube.
4. Allow the chromatograms to develop until the solvent front has moved to the top of the strips. Remove the strips from the tubes, and allow the solvents to evaporate.
5. Determine the radioactive distribution by scanning the strip sections, using a suitable collimated radiation detector.

Interpretation of Chromatograms

6. Using the Radiochemical Purity Worksheet, record the following counts:

System 1 (SG ITLC: MEK [butanone])

Migrate at R_f 0.8 to 1	Lipophilic Tc 99m exametazime complex and Tc 99m pertechnetate
Origin	Secondary Tc 99m exametazime complex and reduced-hydrolyzed Tc 99m

System 2 (SG ITLC: 0.9% sodium chloride)

Migrate at R_f 0.8-1	Tc 99m pertechnetate
Origin	Lipophilic Tc 99m exametazime complex, secondary Tc 99m exametazime complex and reduced-hydrolyzed Tc 99m

System 3 (Whatman 31ET: 50% aqueous acetonitrile)

Migrate at R_f 0.8 to 1	Lipophilic Tc 99m exametazime complex, secondary Tc 99m exametazime complex and Tc 99m pertechnetate
Origin	Reduced-hydrolyzed Tc 99m

7. Determine and record on the Radiochemical Purity Worksheet:
   % at the origin of saline strip (D)
   % at the origin of MEK strip (B)
   % at the solvent front of saline strip (C) [% Tc 99m pertechnetate]
   % at the origin of Whatman 31ET paper strip (F) [% reduced-hydrolyzed Tc 99m]

8. Calculate the radiochemical purity:
   % lipophilic exametazime complex = % at the origin of saline strip (D) – % at the origin of MEK strip (B)

9. ***Do not use if radiochemical purity of Lipophilic Tc 99m Exametazime is less than 80%***

RADIATION DOSIMETRY

Table 4. Estimated Absorbed Radiation Dose[12] for *in vivo* localization of Tc 99m labelled leukocytes

Target Organ	Absorbed dose per unit activity	
	mcGy/MBq	rad/mCi
Adrenals	12.0	0.044
Bone surfaces	16.0	0.059
Brain	2.3	0.009
Breast	2.4	0.009
Gallbladder wall	8.4	0.031
Gastrointestinal tract		
Stomach wall	8.1	0.030
Small intestine wall	4.6	0.017
Colon wall	4.3	0.016
(Upper large intestine wall)	4.7	0.017
(Lower large intestine wall)	3.7	0.014
Heart wall	9.4	0.035
Kidneys	12.0	0.044
Liver	20.0	0.074
Lungs	7.8	0.029
Muscles	3.3	0.012
Esophagus	3.5	0.013
Ovaries	3.9	0.014
Pancreas	13.0	0.048
Red marrow	23.0	0.085
Skin	1.8	0.007
Spleen	150.0	0.555
Testes	1.6	0.006
Thymus	3.5	0.013
Thyroid	2.9	0.011
Urinary bladder wall	2.6	0.010
Uterus	3.4	0.013
Remaining organs	3.4	0.013
Effective dose	**11.0 mcSv/MBq**	**407 mcSv/mCi**

The effective dose resulting from the administration of a (maximal recommended) activity of 370 MBq for an adult weighing 70 kg is about 4.1 mSv.

HOW SUPPLIED

Each Drax Exametazime® kit is supplied as one package containing:

5 Single-dose vials (0.5 mg/vial). Each vial contains a non-radioactive sterile, non-pyrogenic lyophilized mixture of: 0.5 mg of exametazime, 7.6 mcg stannous chloride dihydrate (minimum stannous tin 0.6 mcg; maximum total stannous and stannic tin 4 mcg per vial), and 4.5 mg sodium chloride;

10 Radioassay information labels with radiation warning symbol;

10 Patient identification labels;

5 Sheets of Labelling Efficiency/Radiochemical Purity Testing Worksheets;

1 Leukocyte Labelling Schematic;

1 Package Insert.

Sodium Pertechnetate Tc 99m is not part of Drax Exametazime® kit. Before reconstitution and radiolabelling with Tc 99m, the contents of the kit are not radioactive.

STORAGE

Before reconstitution, store the kit at room temperature (15°C to 30°C).
After reconstitution, store the reconstituted product at 20°C to 25°C using appropriate radiation shielding.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

EXPIRY

Kit before reconstitution: 12 months at room temperature (15°C to 30°C).

Do not use the kit beyond the expiration date stamped on the box. After reconstitution, the Tc 99m exametazime injection should be used, within 30 minutes for leukocyte radiolabelling. Protect from freezing.

REFERENCES

1. Thakur, M.L. et al., Indium-111-labelled Autologous Leukocytes in Man, Journal of Nuclear medicine, 18, 1014-1021, 1977.

2. Knochel, J.Q. et al., Diagnosis of Abdominal Absesses with Computed Tomography, Ultrasound, and ^{111}In Leukocyte Scans, Radiology, 137, 425-432, 1980.

3. Peters, A.M. et al., Imaging of Inflammation with Indium-111 Tropolonate Labeled Leukocytes, Journal of Nuclear Medicine, 24, 39-44, 1983.

4. Becker, W. et al., Three-phase White Blood Cell Scan: Diagnostic Validity in Abdominal Inflammatory Diseases, Journal of Nuclear medicine, 27, 1109-1115, 1986.

5. Coleman, R.E., Radiolabelled Leukocytes, Nuclear Medicine Annual, 119-141, 1982.

6. Kelbaek, H. and Fogh, J., Technetium-99m Labelling of Polymorphonuclear leukocytes: Preparation with Two Different Stannous Agents, Journal of Nuclear Medicine, 26, 68-71, 1985.

7. Danpure, H.J. et al., The Development of a Clinical Protocol for the Radiolabelling of Mixed Leucocytes with ^{99m}Tc-hexamethylpropyleneamine Oxime, Nuclear Medicine Communications, 9, 465-475, 1988.

8. Peters, A.M. Granulocyte Kinetics and Methods of Evaluation Cell Performance, Nuclear Medicine Communications, 9, 687-692, 1988.

9. Dillman, L.T. et al., MIRD Pamphlet No. 10, page 62, 1975.

10. ACR-SPR Practice parameter for the performance of scintigraphy for inflammation and infection, 2014.

11. Guidelines for the labelling of leucocytes with ^{99m}Tc-HMPAO. Eur J Nucl Med Mol Imaging 37:842-848, 2010.

12. 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.

13. Product Monograph for CERETEC® (Kit for the Preparation of Technetium-99m Exametazime Injection). GE Healthcare Canada Inc. Submission Control No. 216123; Date of Revision: December 21, 2018.