HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CERETEC safely and effectively. See full prescribing information for CERETEC.

CERETEC (kit for the preparation of technetium Tc 99m exametazime injection) for intravenous use.
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------

Ceretec is a radioactive diagnostic agent, indicated in adults and pediatric patients age 2 to 17 for:

- Leukocyte Labeled Scintigraphy – As an adjunct in the localization of intraabdominal infection and inflammatory bowel disease. (1.1)
- Cerebral Scintigraphy – As an adjunct in the detection of altered regional cerebral perfusion in stroke. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Do not use cobalt stabilizer solution for leukocyte labeled scintigraphy. (2.1)
- Use appropriate radiation safety measures and aseptic technique during preparation and handling. (2.1)
- Leukocyte Labeled Scintigraphy - The recommended adult dose is 185 MBq to 370 MBq (5 mCi to 10 mCi) of Tc 99m exametazime labeled leukocytes by intravenous injection. Administer as soon as possible after labeling, preferably within 20 minutes but no later than 1 hour. (2.2)
- Cerebral Scintigraphy - The recommended adult dose is 555 MBq to 1110 MBq (15 mCi to 30 mCi) by intravenous injection. (2.2)
- See full prescribing information for preparation and administration, interpretation of chromatograms and radiation dosimetry. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Each Ceretec kit consists of 5 units. (3) Each unit contains:

- One vial of Ceretec: A lyophilized mixture of 0.5 mg exametazime and 4.5 mg sodium chloride.
- One vial of cobalt stabilizer solution: 200 mcg cobalt chloride 6-hydrate stabilizer solution in 2 mL of Water for Injection.

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity reactions: Have cardiopulmonary resuscitation equipment and personnel available and monitor all patients for hypersensitivity reactions (5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions include a reversible increase in blood pressure. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy - Advise the pregnant woman of the potential risk to the fetus based on the radiation dose from the Technetium Tc 99m exametazime injection and the gestational timing of exposure. (8.1)
- Lactation – Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 12 to 24 hours after Technetium Tc 99m Exametazime labeled leukocyte administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Leukocyte Labeled Scintigraph

Ceretec, when reconstituted with technetium Tc 99m exametazime (without cobalt stabilizer solution), is indicated in adults and pediatric patients age 2 to 17 for leukocyte labeled scintigraphy as an adjunct in the localization of intraabdominal infection and inflammatory bowel disease.

1.2 Cerebral Scintigraphy

Ceretec, when reconstituted with technetium Tc 99m exametazime (with or without cobalt stabilizer solution), is indicated in adults and pediatric patients age 2 to 17 for cerebral scintigraphy as an adjunct in the detection of altered regional cerebral perfusion in stroke.

2 DOSAGE AND ADMINISTRATION

2.1 Important Preparation and Radiation Safety Instructions

- The Ceretec kit includes a cobalt stabilizer solution, which is optional for cerebral scintigraphy. DO NOT USE COBALT STABILIZER SOLUTION FOR LEUKOCYTE LABELED Scintigraphy [see Dosage and Administration (2.4, 2.6)].
- Technetium Tc 99m exametazime injection is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure [see Warnings and Precautions (5.3)]. Use waterproof gloves and effective shielding, including syringe shields, when preparing and administering technetium Tc 99m exametazime injection.

2.2 Recommended Dosing and Imaging Procedures

Leukocyte Labeled Scintigraphy

Dosing

Adults: The recommended dose is 185 MBq to 370 MBq (5 mCi to 10 mCi) of Tc 99m exametazime labeled leukocytes by intravenous injection. Administer using a 19G needle as soon as possible, preferably within 20 minutes but no later than 1 hour, after preparing the Tc 99m labeled leukocyte suspension.

Pediatric patients age 2 to 17: The recommended dose is 7.4 MBq/kg (0.2 mCi/kg); with a minimum of 74 MBq (2 mCi). Do not exceed the maximum administered activity for an adult.

Imaging Procedures

- Instruct patients to empty their bladder prior to imaging.
- Dynamic imaging may be performed for the first 60 minutes after injection to assess lung clearance and to visualize cell migration.
- Perform static imaging at 0.5-1.5 hours**,** 2-4 hours and if necessary, at 18-24 hours after administration to detect focal accumulation of activity.

Cerebral Scintigraphy

Dosing

Adults: The recommended dose is 555 MBq to 1110 MBq (15 mCi to 30 mCi) by intravenous injection.

Pediatric patients age 2 to 17: The recommended dose is 14.0 MBq/kg (0.4 mCi/kg); with a minimum of 110 MBq (3.0 mCi). Do not exceed the maximum administered activity for an adult.

Imaging Procedures

Images may be acquired by planar or SPECT imaging techniques.
Perform imaging 30-90 min. after administration and complete imaging within 4 hrs after administration.

2.3 Preparation and Administration Instructions

General Preparation and Administration Instructions

- Use aseptic procedures throughout preparation and handling.
- Visually inspect the reconstituted technetium Tc 99m exametazime injection prior to use and do not use if there is evidence of particulate matter or discoloration.
- Measure patient dose with a dose calibrator immediately prior to administration.
- Instruct patients to maintain adequate hydration, after administration of technetium Tc 99m exametazime labeled white blood cells or Tc 99m exametazime injection and void frequently to minimize radiation dose to the kidneys and bladder *[see Warnings and Precautions (5.3)]*.

Reconstitution Instructions

- Elute the technetium Tc 99m generator according to the manufacturer's instructions.
- Only use eluate from a technetium Tc 99m generator which has been eluted within the previous 24 hours.
- For the highest radiochemical purity reconstitute with freshly eluted technetium 99m generator eluate.
    - To prepare technetium Tc 99m exametazime injection for **white blood cell labeling**, use generator elute that is **not more than 2 hours old.**
    - To prepare technetium Tc 99m exametazime injection **with cobalt stabilizer** for **cerebral imaging**, use generator eluate that is **not more than 4 hours old.**

2.4 Preparation of Autologous Leukocytes

Leukocyte Harvest and Separation

1) Draw up 10 mL acid citrate dextrose solution into a 60 mL 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 of the syringe for 20 seconds.
4) Clamp the syringe barrel to the ring stand in an upright (hub side up) position and tilt the syringe 10-20 degrees from its position perpendicular to the bench.
5) Allow the red cells to sediment 30-60 minutes, until the supernatant [leukocyte rich plasma (LRP)] looks clear of red blood cells.
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 400-450 g for 5 minutes. The plasma will separate out into a liquid [leukocyte poor plasma (LPP)] and a solid (WBC button). (Note: The button often contains a small number of red cells and may appear red).
8) Transfer the supernatant into another sterile tube marked "LPP" leaving enough supernatant to cover the white cell button.

Reserve LPP for later use (steps 11,15,18).

Washing and Radiolabeling

9) Add approximately 5 mL Sodium Chloride Injection, USP (0.9%) to the WBC button. Cap the "WBC" tube and resuspend the button by gently swirling.
10) Centrifuge the capped "WBC" tube at 150 g for 8 minutes and discard all but 0.5 to 1 mL of the supernatant to cover the cells.
11) Add 1 mL of "LPP" (from Step 9) to the white cell button and resuspend the cells by gentle swirling.
12) Reconstitute technetium Tc 99m exametazime from Ceretec with generator eluate *[see Dosage and Administration (2.6)]*.
13) Within 30 minutes of preparation, add the reconstituted Tc 99m exametazime (do not use cobalt stabilizer solution) to the "WBC" tube. Swirl gently to mix.
14) Set a lab timer for 15 minutes and allow the white cells to incubate. Swirl at 30 second intervals during the incubation.
15) After incubation, add 10 mL of the LPP (from Step 9) to the "WBC" tube.
16) Cap the "WBC" tube, gently swirl, and then centrifuge at 450 g for 5 minutes.
17) Transfer the supernatant in the "WBC" tube into the "Wash" tube and leave the labeled white cells in the "WBC" tube.
18) Add approximately 5 mL of LPP (from Step 9) to the "WBC" tube. Gently swirl to resuspend the cells.
19) Draw the labeled cells into a syringe. Cap the syringe and assay the amount of radioactivity in a dose calibrator. Place the syringe in a shielded container.
20) **Verify the identity of the labeled leukocyte recipient.**
21) Administer the Tc 99m labeled leukocyte suspension using a 19G needle as soon as possible, preferably within 1-2 hours after labeling.

2.5 Preparation of Tc 99m Exametazime Injection with Cobalt Stabilizer Solution

- The preparation may be used in cerebral scintigraphy

1) Add up to 370 MBq to 2000 MBq (10 mCi to 54 mCi) sodium pertechnetate Tc 99m eluate to the shielded Ceretec vial.
2) Before reconstitution, the technetium Tc 99m generator eluate may be adjusted to the correct radioactive concentration [74 to 400 MBq/mL (2 to 10.8 mCi/mL)] by dilution with a volume of 5 mL preservative-free, non-bacteriostatic 0.9% sodium chloride for injection.
3) Between 1 and 5 minutes after reconstitution, inject 2 mL of cobalt stabilizer solution into the vial. Shake the shielded vial for 10 seconds to ensure complete mixing.
4) The cobalt stabilized technetium 99m exametazime is a pale straw-colored solution and the pH is in the range 5 to 8.
5) Use a Sample for Radiochemical Purity measurement.
6) Assay the vial for total radioactivity. Calculate the volume to be injected. Complete the label provided and attach to the vial.
7) Use the stabilized product within 5 hours after preparation. Individual patient doses may be stored aseptically in a capped syringe if required.
8) Discard any unused material.

Radiochemical Purity Measurement Tc 99m Exametazime Injection with Cobalt Stabilizer Solution

Obtain the Following Materials:

- Two GMCP-SA (Glass Microfiber Chromatography Paper impregnated with Silicic Acid) strips (2 cm (±2 mm) x 20 cm)
- Ascending chromatography development tanks
- MEK [methyl ethyl ketone (butanone)]
- 0.9 % sodium chloride

A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection:

- **System 1** GMCP-SA: MEK [methyl ethyl ketone (butanone)]
- **System 2** GMCP-SA:0.9% sodium chloride

Three potential radiochemical impurities may be present in prepared Technetium (^{99m}Tc) Exametazime Injection

- secondary Tc 99m exametazime complex
- free Tc 99m pertechnetate
- reduced-hydrolyzed Tc 99m

Method

1) Perform radiochemical purity testing as soon as possible after preparation.
2) Prepare the two Chromatographic Systems **(System 1** and **System 2).**
3) Apply test samples by needle approximately 2.5 cm from the bottom of each GMCP-SA strip.
4) Immediately place each strip in prepared ascending chromatography development tanks. After the solvent has travelled to the 14 cm mark, remove the strips and mark the solvent fronts.
5) Allow the strips to dry.
6) Determine the distribution of activity determined using suitable equipment.
7) Chromatogram Interpretation:

System 1 (GMCP-SA: MEK [butanone])

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

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

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

8) Calculate the percentage of activity due to both secondary Tc 99m exametazime complex and reduced-hydrolyzed Tc 99m from **System 1 (A %)**.
9) Calculate the percentage of activity due to Tc 99m pertechnetate from **System 2 (B %)**.
10) Calculate the radiochemical purity:

% lipophilic Tc 99m exametazime complex = 100 - (A %+B %)

- **A %** represents the level of secondary Tc 99m exametazime complex plus reduced-hydrolyzed Tc 99m.
- **B %** represents the level of Tc 99m pertechnetate.

11) Do not use if radiochemical purity of lipophilic Tc 99m exametazime is less than 80%.

2.6 Preparation of Technetium Tc 99m Exametazime Injection Without Cobalt Stabilizer Solution

The preparation may be used in cerebral scintigraphy or for use in the preparation of Tc 99m labeled leukocytes.

1) Add 370 MBq to 2000 MBq (10 mCi up to 54 mCi) of sodium pertechnetate Tc 99m eluate.
2) Before reconstitution, the technetium Tc 99m generator eluate may be adjusted to the correct radioactive concentration [74 to 400 MBq/mL (2 to 10.8 mCi/mL)] by dilution with a volume of 5 mL preservative-free, non-bacteriostatic 0.9 % sodium chloride for injection.
3) The pH of the prepared injection is 9 to 9.8.
4) Use a sample for Radiochemical Purity Measurement.
5) Assay the total activity.
6) Calculate the volume to be injected and complete the label provided and attach to the vial shield.
7) Use the preparation within 30 minutes after reconstitution.
8) Discard any unused material.

Radiochemical Purity Measurement Tc 99m Exametazime Injection without Cobalt Stabilizer Solution

- Perform radiochemical purity testing of technetium Tc 99m exametazime within 2 minutes of reconstitution.
- The entire procedure takes approximately 15 minutes.

Obtain the Following Materials:

- 2 SA ITLC strips 20 cm x 2 cm
- 1 Whatman No. 1 strips 6 cm x 0.7 cm
- MEK (methyl ethyl ketone [butanone])
- 0.9% aqueous sodium chloride (non-bacteriostatic)
- 50% aqueous acetonitrile
- Dilute with non-bacteriostatic Water for Injection
- Glass test tubes (12 x 75 mm)
- Glass measuring cylinders (100 mL) with covers
- 1 mL syringes with 25-gauge needles
- A combination of 3 chromatographic systems is necessary for the complete definition of the radiochemical composition of the injection.
    - **System 1**: MEK (methyl ethyl ketone [butanone]) + SA ITLC strip
    - **System 2**: 0.9% non-bacteriostatic sodium chloride solution + SA ITLC strip
    - **System 3**: 50% acetonitrile solution + Whatman No. 1 paper strip

Three potential radiochemical impurities may be present in the prepared injection of the lipophilic Tc 99m exametazime complex.

- a secondary Tc 99m exametazime complex
- free Tc 99m pertechnetate
- reduced-hydrolyzed Tc 99m

Method

1) Prepare chromatography tubes (Identify the solvent in each cylinder).
   System 1 - 100 mL cylinder containing a 1 cm depth of fresh MEK.
   System 2 - 100 mL cylinder containing a 1 cm depth of 0.9% sodium chloride.
   System 3 - 1 chromatography tube containing 0.2-0.3 mL of 50% acetonitrile, respectively.
2) Prepare 2 SA ITLC strips and 1 Whatman No. 1 paper strip.
   Mark the SA ITLC strips 2.5 cm from the bottom as the point of origin.
   Mark both the SA ITLC strips at 14 cm above the origin (solvent front).
   Mark the Whatman strip 1 cm from the bottom as the point of origin.
3) Apply at least 5 microliter samples of freshly prepared Tc 99m exametazime solution to the origin of the 3 strips (within 2 minutes of reconstitution). Do not allow to dry.
4) Immediately place 1 SA ITLC strip into the MEK tank (System 1), the second SA ITLC strip into the saline tank (System 2), and the Whatman No. 1 paper strip into the 50% acetonitrile tube (System 3).
5) The SA ITLC MEK strip takes approximately 15 minutes to run. When the eluate has reached the solvent front remove the strip from the tube with forceps and immediately cut 1 cm above the origin.
6) The SA ITLC saline strip takes approximately 15 minutes to run. When the eluate has reached the solvent front remove the strip from the tube with forceps and immediately cut 2.5 cm above the origin.
7) The Whatman No. 1 paper CH3CN strip takes approximately 100 seconds to run. When the eluate has reached the solvent front mark remove the strip from the tube with forceps and immediately cut 0.5 cm above the origin.
8) Chromatogram Interpretation:

System 1 (SA ITLC: MEK (methyl ethyl ketone [butanone])

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

System 2 (SA ITLC: 0.9% sodium chloride)

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

System 3 (Whatman No. 1: 50% aqueous acetonitrile)

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

9) Count the separate sections of each strip to determine the activity distribution. Calculate:
- % origin of saline strip (system 2)
- % origin of MEK strip (system 1)
- % solvent front of saline strip (= % Tc 99m pertechnetate)
- % origin of Whatman No. 1 paper strip (= % reduced-hydrolyzed Tc 99m)

10) Calculate Radiochemical Purity

% lipophilic Tc 99m exametazime complex = % origin of saline strip (system 2) – % origin of MEK strip (system 1)

11) *Do not use if the radiochemical purity of the lipophilic Tc 99m exametazime complex is less than 80%.*

2.7 Radiation Dosimetry

Tc 99m Exametazime labeled leukocytes for leukocyte labeled scintigraphy

Radiation absorbed dose per unit activity (microGy/MBq) administered to average-size adults (70 kg) and pediatric patients from an intravenous injection of Tc 99m Exametazime labeled leukocytes is estimated in Table 1.

Table 1: Estimated Radiation Absorbed Dose for Tc 99m exametazime labeled white blood cells (leukocytes)

Organ	**Absorbed dose per unit activity administered (microGy / MBq)**				
	Adult	15 years	10 years	5 years	1 year
Adrenals	12	12	18	26	43
Bone surfaces	16	21	34	61	150
Brain	2.3	2.9	4.4	7	13
Breast	2.4	2.9	4.9	7.6	13
Gallbladder wall	8.4	10	16	25	36
Gastrointestinal tract					
• Esophagus	3.5	4.2	5.8	8.6	15
• Stomach wall	8.1	9.6	14	20	32
• Small intestine wall	4.6	5.7	8.7	13	21
• Colon wall	4.3	5.4	8.4	12	21
• Upper large intestine wall	4.7	5.9	9.3	14	23
• Lower large intestine wall	3.7	4.8	7.3	10	18
Heart wall	9.4	12	17	25	44
Kidneys	12	14	22	32	54
Liver	20	26	38	54	97
Lungs	7.8	9.9	15	23	41
Muscles	3.3	4.1	6	8.9	16
Ovaries	3.9	5	7.2	11	18
Pancreas	13	16	23	34	53
Red marrow	23	25	40	71	140
Skin	1.8	2.1	3.4	5.5	10
Spleen	150	210	310	480	850
Testes	1.6	2.1	3.2	5.1	9.2
Thymus	3.5	4.2	5.8	8.6	15
Thyroid	2.9	3.7	5.8	9.3	17
Urinary bladder wall	2.6	3.5	5.2	7.8	14
Uterus	3.4	4.3	6.5	9.7	16
Remaining organs	3.4	4.2	6.3	9.5	16
Effective dose per unit activity	**9.3 microSv/MBq**	**11 microSv/MBq**	**17 microSv/MBq**	**27 microSv/MBq**	**49 microSv/MBq**

**International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances, Ann ICRP 2015)., ICRP Publication 128, Ann ICRP 2015).*

Tc 99m Exametazime Injection for Cerebral Scintigraphy

Based on human data, the radiation absorbed doses to average sized adults (70kg) and pediatric patients from an intravenous injection of Tc 99m exametazime injection are estimated in Table 2.

Table 2: Estimated Radiation Absorbed Dose for Tc 99m Exametazime Injection

Organ	Absorbed dose per unit activity administered (microGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	5.3	6.7	9.9	14	24
Bone surfaces	5.1	6.4	9.4	14	24
Brain	6.8	11	16	21	37
Breast	2	2.4	3.7	5.6	9.5
Gallbladder wall	18	21	28	48	140
Gastrointestinal tract					
• Esophagus	2.6	3.3	4.7	6.9	11
• Stomach wall	6.4	8.5	12	19	36
• Small intestine wall	12	15	24	36	65
• Colon wall	17	22	35	55	100
• Upper large intestine wall	18	24	38	60	110
• Lower large intestine wall	15	19	31	48	90
Heart wall	3.7	4.7	6.7	9.7	16
Kidneys	34	41	57	81	140
Liver	8.6	11	16	23	40
Lungs	11	16	22	34	63
Muscles	2.8	3.5	5	7.3	13
Ovaries	6.6	8.3	12	17	27
Pancreas	5.1	6.5	9.7	14	23
Red marrow	3.4	4.1	5.9	8	14
Skin	1.6	1.9	2.9	4.5	8.3
Spleen	4.3	5.4	8.2	12	20
Testes	2.4	3	4.4	6.1	11
Thymus	2.6	3.3	4.7	6.9	11
Thyroid	26	42	63	140	260
Urinary bladder wall	23	28	33	33	56
Uterus	6.6	8.1	12	15	25
Remaining organs	3.2	4	6	9.2	17

**International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances, Ann ICRP 2015)., ICRP Publication 128, Ann ICRP 2015).*

The effective dose resulting from the administration of a (maximal recommended) activity of 1110 MBq for an adult weighing 70 kg is about 10.3 mSv. For an administered activity of 740 MBq the typical radiation dose to the target organ (brain) is 5 mGy and the typical radiation dose to the critical organ (kidneys) is 25 mGy.

3 DOSAGE FORMS AND STRENGTHS

The Ceretec Kit is supplied as a five-unit package. Each unit contains:

- One (10 mL, multiple-dose) vial of Ceretec: A lyophilized mixture of 0.5 mg exametazime, sealed under nitrogen atmosphere with a rubber closure.
- One vial cobalt stabilizer solution: 200 mcg cobaltous chloride 6-hydrate stabilizer solution in 2 mL of Water for Injection.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported following the administration of Tc 99m exametazime injection and Tc 99m exametazime labeled leukocytes including serious signs and symptoms of anaphylaxis following administration *[see Adverse Reactions (6)]*. Always have cardiopulmonary resuscitation equipment and personnel available and monitor all patients for hypersensitivity reactions.

5.2 Risk for Image Interpretation Errors

The interpretation of images for leukocyte labeled imaging can be affected by the presence of other pathophysiological processes such as: tumor, infarction, trauma, and inflammatory conditions.

5.3 Radiation Exposure Risk

Technetium Tc 99m contributes to a patient's overall long-term cumulative radiation exposure, which is associated with an increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Encourage patients to drink fluids and instruct patients to void when the examination is completed and as often thereafter as frequently as possible after administration *[see Dosage and Administration (2.1, 2.3)]*. Radiation risks associated with the use of Tc 99m exametazime injection and Tc 99m exametazime labeled leukocytes are greater in pediatric patients than in adults due to greater radiosensitivity and longer life expectancy.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*.

The following adverse reactions associated with the use of Ceretec were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular disorders: Reversible increase in blood pressure, flushing
Gastrointestinal disorders: Nausea, vomiting
General disorders and administration site conditions: Malaise, fatigue, fever
Immune system disorders: Hypersensitivity reactions: anaphylactic reactions including shock, facial edema, rash, pruritus or erythema
Nervous system disorders: Headache, dizziness, paresthesia

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with technetium Tc 99m exametazime use in pregnant women are insufficient to inform any drug associated risks for major birth defects and miscarriage. Technetium Tc 99m exametazime is transferred across the placenta *[see Data]*. Animal reproduction studies with technetium Tc 99m exametazime have not been conducted. However, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering technetium Tc 99m exametazime administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from technetium Tc 99m exametazime and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Limited published literature describes Tc 99m exametazime crossing the placental barrier and visualization of radioactivity in the fetal liver. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 10 mGy fetal doses.

8.2 Lactation

Risk Summary

There are limited data available in the scientific literature on the presence of technetium Tc 99m exametazime in human milk. There are no data available regarding the effects of technetium Tc 99m exametazime on the breastfed infant or on milk production. Exposure of technetium Tc 99m exametazime to a breast fed infant can be minimized by temporary discontinuation of breastfeeding [*see Clinical Considerations*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ceretec and any potential adverse effects on the breastfed child from Ceretec or from the underlying maternal condition.

Clinical Considerations

To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of technetium Tc 99m exametazime injection or technetium Tc 99m exametazime-labeled leukocytes for 12 to 24 hours, where the duration corresponds to the typical range of administered activity, 259 MBq to 925 MBq (7 mCi to 25 mCi).

8.4 Pediatric Use

Ceretec is indicated for use in pediatric patients from 2 to 17 years of age for leukocyte labelled scintigraphy and brain scintigraphy. The use of Ceretec for leukocyte labelled scintigraphy and brain scintigraphy is supported by extrapolation from clinical effectiveness in adults. The safety and dosing recommendations are based on clinical experience.

Safety and effectiveness in pediatric patients less than 2 years of age have not been established.

8.5 Geriatric Use

Clinical studies of Ceretec did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

This drug is known to be substantially excreted by the kidney, and radiation exposure may be greater in patients with impaired renal function. A reduction in administered Tc 99m can be considered provided an adequate number of leukocytes are administered.

11 DESCRIPTION

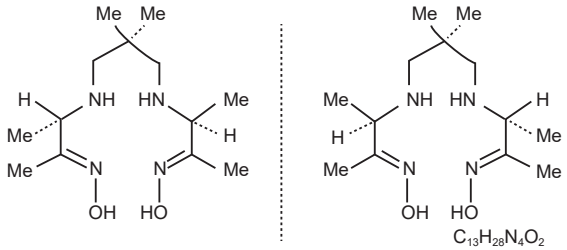
11.1 Chemical Characteristics

Ceretec (kit for the preparation of technetium Tc 99m exametazime injection) prepares a radioactive diagnostic agent for intravenous use.

Each unit consists of the following:

- One 10 mL vial of exametazime containing a sterile, non-pyrogenic, lyophilized mixture of 0.5 mg 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, sealed under nitrogen atmosphere with a rubber closure. The product contains no antimicrobial preservative.
- One vial of cobalt stabilizer containing a sterile, non-pyrogenic solution of 200 mcg cobaltous chloride 6-hydrate in 2 mL of Water for Injection.

The chemical name for Exametazime is [(RR,SS)-4.8-diaza-3,6,6,9-tetramethylundecane-2, 10-dione bisoxime]. The molecular formula of exametazime is $C_{13}H_{28}N_4O_2$, with the following structural formula:



Prior to publication of the USAN, exametazime was known as hexamethylpropylene amine oxime (HM-PAO). The name HM-PAO appears in many publications.

When sterile pyrogen-free sodium pertechnetate Tc 99m in isotonic saline is added to the vial of exametazime, a Tc 99m complex of exametazime is formed.

11.2 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6 hours. Photons that are useful for imaging studies are listed in Table 3.

Table 3: Principal Radiation Emission Data-technetium Tc 99m

Radiation	Mean % Disintegration	Mean Energy (keV)
Gamma 2	88.5	140.5

11.3 External Radiation

The air-kerma-rate (exposure-rate) constant for technetium Tc 99m is 5.23 $m^2 \cdot pGy \cdot (MBq)^{-1} \cdot s^{-1}$ [0.795 $cm^2 \cdot R \cdot (mCi)^{-1} \cdot h^{-1}$]. The first half-value thickness of lead (Pb) for technetium Tc 99m is 0.25 mm. 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 4. For example, the use of a 3 mm thickness of Pb will decrease the external radiation exposure by a factor of approximately 1,000.

Table 4: Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0.25	0.5
1	10^{-1}
2	10^{-2}
3	10^{-3}
4	10^{-4}
5	10^{-5}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals relative to the time of calibration are shown in Table 5.

Table 5: Physical Decay Chart – Tc 99m half-life 6.03 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1	7	0.447
1	0.891	8	0.399
2	0.795	9	0.355
3	0.708	10	0.317
4	0.631	11	0.282
5	0.563	12	0.252
6	0.502	24	0.063

*Calibration time (time of preparation)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

General

When technetium Tc 99m pertechnetate is added to exametazime in the presence of stannous reductant, a lipophilic technetium Tc 99m complex is formed. This lipophilic complex is the active moiety and is able to cross the blood-brain barrier as well as penetrate cell membranes to label leukocytes. It converts to a polar hydrophilic species at approximately 12% per hour. The polar hydrophilic species is unable to cross the blood-brain barrier or cell membranes.

Mechanism for Labeling Leukocytes

When incubated with leukocytes, which have been isolated from whole blood, the technetium Tc 99m exametazime complex, being lipid-soluble, penetrates the cell membrane of the leukocytes by passive diffusion. The lipophilic complex is then converted to a polar hydrophilic species, in a process possibly involving intracellular glutathione, thus trapping the technetium Tc 99m label within the cells.

Mechanism for Brain Uptake

The agent localizes in the brain as a function of regional cerebral perfusion. Technetium Tc 99m exametazime is primarily extracted and trapped by cerebral gray matter and the basal ganglia during the first pass through the brain. It has been proposed that the retention in the brain of technetium Tc 99m exametazime results from *in vivo* conversion of the primary complex to a less lipophilic complex, which is unable to cross the blood-brain barrier.

12.2 Pharmacodynamics

The relationship between Tc 99m exametazime plasma concentrations and successful imaging is not known.

12.3 Pharmacokinetics

Distribution

Leukocytes Labeled with Tc 99m Exametazime

During the first hour following injection of Tc 99m labeled leukocytes, activity is seen in the lungs, liver, spleen, blood pool, bone marrow, kidneys, gall bladder, and urinary bladder. At 4 hours following injection, lung radioactivity was decreased and bone marrow radioactivity was increased.

The lipophilic Tc 99m exametazime complex (that is not stabilized by cobalt chloride) is taken up by leukocytes and selectively retained in neutrophils. Label elution rate is up to 10% in the first hour.

Tc 99m Exametazime Injection

Studies in normal volunteers have shown that the technetium Tc 99m exametazime is rapidly cleared from the blood after intravenous injection. Uptake in the brain reaches a maximum of 3.5 to 7% of the injected dose within one minute of injection. Up to 15% of the activity is eliminated from the brain by 2 minutes post injection, after which little activity is lost for the following 24 hours except by physical decay of technetium Tc 99m.

Elimination

Excretion

Leukocytes Labeled with Tc 99m Exametazime

Following injection of Tc 99m labeled leukocytes, over the first 1 to 6 hours, the Tc 99m is visualized in the bowel. At 24 hours post-injection substantial colonic activity is seen, implying that excretion of radioactivity takes place through bowel.

Tc 99m Exametazime Injection

About 30% of the injected dose is found in the gastrointestinal tract immediately after injection and about 50% of this is excreted through the intestinal tract over 48 hours. About 40% of the injected dose is excreted through the kidneys and urine over the 48 hours after injection.

The use of cobalt stabilizer solution for stabilization prior to injection does not appear to affect the pharmacokinetic handling or distribution of Tc 99m exametazime.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ceretec without cobalt stabilizer solution

Long term animal studies have not been performed to evaluate carcinogenic potential or whether exametazime affects fertility in males or females. When evaluated in the Ames test, exametazime increased the apparent rate of gene mutation in the TA100 strain of S. typhimurium. Exametazime did not cause chromosomal aberrations *in vitro* (Chinese Hamster Ovary cells) or *in vivo* (rat bone marrow).

Ceretec with cobalt stabilizer solution

In-vitro mutagenicity studies indicate that the stabilized formulation of technetium-99m exametazime is weakly mutagenic in the Ames (bacterial mutation) test, human lymphocyte chromosome aberration assay and mouse lymphoma thymidine kinase assay.

The stabilized formulation is not mutagenic in two *in-vivo* assays (rat bone marrow micronucleus and rat liver micronucleus).

14 CLINICAL STUDIES

Two clinical trials were performed in a total of 88 patients who had suspected intra-abdominal infection or inflammation. Subjects received both Tc 99m labeled leukocytes and a radiolabeled comparator. Images were obtained at 2 and 30 minutes and at 2 and 4 hours and 24 hours. In two other clinical trials, in a total of 127 patients with suspected abdominal inflammation or infection received Tc 99m labeled leukocytes. Imaging was at 24 hours in one study and at 1, 3 and 24 hours in the other. In all four studies images were blindly evaluated and the findings were confirmed by surgery, biopsy or other clinical data.

Based on the above 4 studies, between 2 to 4 hours Tc 99m labeled leukocytes had 95-100% sensitivity and 62-85% specificity. In all studies, the false positive and false negatives relate to the bowel background, the location of the site of infection/inflammation and whether or not it is contiguous with the bowel. Images obtained at 24 hours can be unreliable because of a high bowel background; false negatives were noted in both Tc 99m and the radiolabeled comparator.

Other studies suggest that the interpretation of the images could be affected by the presence of tumors, infarction and peritonitis; liver abscess may be missed because of the bowel background.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

Each Ceretec Kit (NDC 17156-025-05) contains:

- Five 10 mL vials of 0.5 mg exametazime
- Five 10 mL vials of 200 mcg Cobalt stabilizer solution
- Ten radiation labels
- One package insert

Sodium Pertechnetate Tc 99m is not part of the Ceretec kit. Before reconstitution and radiolabeling with Tc 99m, the contents of the kit are not radioactive.

16.2 Storage and Handling

Store Ceretec kits at controlled room temperature 15°C to 25°C (59°F to 77°F).

This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission or the relevant Agreement State. Store and dispose of technetium Tc 99m exametazime in compliance with the regulations of the government agency authorized to license the use of this radionuclide.

17 PATIENT COUNSELING INFORMATION

Administration Instructions

Instruct patients to remain hydrated and void frequently following administration to decrease radiation exposure *[see Dosage and Administration (2.3)]*.

Pregnancy

Advise pregnant women of the risk of fetal exposure to radiation doses if they undergo a radionuclide imaging study *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a lactating woman to pump and discard breast milk for 12-24 hours (based on injection dose) after administration to minimize radiation exposure to the breastfed infant *[see Use in Specific Populations (8.2)]*.

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CERETEC with Cobalt Chloride/BK