HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ga 68 DOTATOC INJECTION safely and effectively. See full prescribing information for Ga 68 DOTATOC INJECTION.

Ga 68 DOTATOC Injection, for intravenous use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2) 12/2021

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

Ga 68 DOTATOC Injection is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients. (1)

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

- Recommended dose for adults is 148 MBq (4 mCi) as a bolus intravenous injection (2.2)
- Recommended dose for pediatric patients is 1.59 MBq/kg (0.043 mCi/kg) with a range of 11.1 MBq (0.3 mCi) to 111 MBq (3 mCi), as a bolus intravenous injection (2.2)
- Initiate imaging 55 to 90 minutes after drug administration (2.4)
- See full prescribing information for additional preparation, administration, imaging and radiation dosimetry information (2)

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

Injection: 18.5 MBq/mL to 148 MBq/mL (0.5 mCi/mL to 4 mCi/mL) of Ga 68 DOTATOC Injection in a multiple-dose glass vial (3)

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

None (4)

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

- Radiation Risk: Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure Advise patients to hydrate before and after administration and to void frequently after administration (2.1, 2.3, 5.1)
- Hypersensitivity Reactions: Most reported reactions were rash and pruritus and reversible either spontaneously or with routine symptomatic management. (5.2)
- Risk for Image Misinterpretation: Uptake of Ga 68 DOTATOC injection can be seen in a variety of tumor types that contain somatostatin receptors, and in other pathologic conditions, and as a normal physiologic variant (e.g. uncinate process of the pancreas) (5.3)

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

Reported adverse reactions include: Nausea, pruritis, and flushing.

To report SUSPECTED ADVERSE REACTIONS, contact the UIHC – P E T Imaging Center at 1-319-356-1092 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (6)

----------DRUG INTERACTIONS----------

Somatostatin Analogs: Somatostatin analogs competitively bind to the same somatostatin receptors as Ga 68 DOTATOC Injection and may affect imaging –Discontinue short-acting somatostatin analogs 24 hours before imaging with Ga 68 DOTATOC and image just prior to dosing with long-acting somatostatin analogs (2.3, 7)

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

Lactation: Breast milk should be pumped and discarded for 8 hours after administration (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ga 68 DOTATOC Injection is indicated for use with positron emission tomography (PET) for the localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety – Drug Handling

Handle Ga 68 DOTATOC Injection with appropriate safety measures to minimize radiation exposure *[see Warnings and Precautions (5.1)]*. Use waterproof gloves, effective radiation shielding and appropriate safety measures when preparing and handling Ga 68 DOTATOC Injection.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

2.2 Recommended Dosage and Administration Instructions

Recommended Dosage

In adults, the recommended amount of radioactivity to be administered for PET imaging is 4 mCi (148 MBq) with a range of 3 mCi to 5 mCi (111 MBq to 185 MBq) administered as an intravenous injection with an injection rate of approximately 10 seconds per mL.

In pediatric patients, the recommended amount of radioactivity to be administered for PET imaging is 0.043 mCi/kg of body weight (1.59 MBq/kg) with a range of 0.3 mCi (11.1 MBq) to 3 mCi (111 MBq) as an intravenous injection with an injection rate of approximately 10 seconds per mL.

Administration

- Use Ga 68 DOTATOC Injection within 3 hours of calibration time.
- Use aseptic technique and radiation shielding when withdrawing and administering Ga 68 DOTATOC Injection.
- Inspect Ga 68 DOTATOC Injection visually for particulate matter and discoloration before administration. Do not use the drug if the solution contains particulate matter or is discolored.
- Calculate the necessary volume to administer based on measured activity, volume, calibration time, and date.
- Measure the patient dose immediately prior to administration in a dose calibrator.
- After injection of Ga 68 DOTATOC Injection, administer an intravenous flush of sodium chloride injection, 0.9% to ensure full delivery of the dose.
- Dispose of any unused drug in a safe manner in compliance with applicable regulations.

2.3 Use with Somatostatin Analogs and Patient Hydration

Somatostatin Analogs

Somatostatin analogs bind to the same somatostatin receptors as Ga 68 DOTATOC

- Discontinue short-acting somatostatin analogs 24 hours before imaging with Ga 68 DOTATOC Injection.
- Image patients with Ga 68 DOTATOC Injection just prior to dosing with long-acting analogs of somatostatin *[see Drug Interactions (7)]*.

Patient Hydration

Instruct patients to drink water to ensure adequate hydration prior to administration of Ga 68 DOTATOC Injection and to continue to drink and void frequently during the first hours following administration to reduce radiation exposure *[see Warnings and Precautions (5.1)]*.

2.4 Image Acquisition

For Ga 68 DOTATOC PET imaging, a whole-body acquisition from the skull vertex to mid-thigh is recommended. Image acquisition can begin at 60 minutes (range 55 to 90 minutes) after the intravenous administration of the Ga 68 DOTATOC Injection. Adapt Ga 68 DOTATOC Injection uptake time and scan duration according to the equipment used, and the patient and tumor characteristics, to obtain the optimal image quality.

2.5 Image Interpretation

Ga 68 DOTATOC binds to somatostatin receptors. Based upon the intensity of the signals, PET images obtained using Ga 68 DOTATOC Injection indicate the presence and density of somatostatin receptors in tissues, .Uptake can also be seen in a variety of non-NET tumors that contain somatostatin receptors or as a normal physiologic variant *[see Warnings and Precautions (5.2)]*. NET tumors that do not bear somatostatin receptors will not be visualized.

2.6 Radiation Dosimetry

Estimated radiation absorbed doses per injected activity for organs and tissues of adult patients following an intravenous bolus of Ga 68 DOTATOC Injection are shown in Table 1. Estimated radiation effective doses per injected activity for adult and pediatric patients following an intravenous bolus administration of Ga 68 DOTATOC Injection are shown in Table 2.

Table 1: Estimated Radiation Absorbed Dose per Injected Activity in Selected Organs with Ga 68 DOTATOC

Site	**Absorbed Dose (mGy/MBq)**
Urinary bladder wall	0.119 ± 0.058
Spleen	0.108 ± 0.065
Kidney	0.082 ± 0.020
Adrenal gland	0.077 ± 0.028
Liver	0.041 ± 0.014
Red marrow	0.016 ± 0.003
Gallbladder wall	0.015 ± 0.001
Total body	0.014 ± 0.002
Lungs	0.007 ± 0.001
Effective dose (mSv/MBq)	**0.021 ± 0.003**

The effective radiation dose resulting from the administration of 148 MBq (4 mCi) to an adult weighing 75 kg, is about 3.11 mSv. For an administered activity of 148 MBq (4 mCi) the typical radiation dose to the critical organs, which are the urinary bladder wall, the spleen and the kidneys/adrenals, are about 18 mSv, 16 mSv and 12 mSv, respectively. Because the spleen has one of the highest physiological uptakes, higher uptake and radiation dose to other organs or pathologic tissues may occur in patients with splenectomy.

Table 2: Estimated Radiation Effective Dose per Injected Activity after a Ga-68 DOTATOC Injection

Age	Model Weight (kg)	Effective Dose per Injection Activity (mSv/MBq)
Adult	73.7	0.019
15 years	56.8	0.026
10 years	33.2	0.041
5 years	19.8	0.066
1 year	9.7	0.13
Newborn	3.6	0.36

3 DOSAGE FORMS AND STRENGTHS

Injection: Gallium Ga 68 DOTATOC Injection is a clear, colorless solution in a 30 mL multiple-dose vial containing 18.5 MBq/mL to 148 MBq/mL (0.5 mCi/mL to 4 mCi/mL) of Ga 68 DOTATOC Injection at calibration date and time.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risk

Ga 68 DOTATOC Injection contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure 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. Advise patients to hydrate before and after administration and to void frequently after administration *[see Dosage and Administration (2.1, 2.3)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions following administration of somatostatin receptor imaging agents predominantly consisted of cutaneous reactions such as rash and pruritus. Reactions reversed either spontaneously or with routine symptomatic management. Less frequently hypersensitivity reactions included angioedema or cases with features of anaphylaxis.

5.3 Risk for Image Misinterpretation

The uptake of Ga 68 DOTATOC Injection reflects the level of somatostatin receptor density in NETs, however, uptake can also be seen in a variety of other tumors that also express somatostatin receptors. Increased uptake might also be seen in other non-cancerous pathologic conditions that express somatostatin receptors including thyroid disease or in subacute inflammation, or might occur as a normal physiologic variant (e.g. uncinate process of the pancreas) *[see Dosage and Administration (2.5)]*.

A negative scan after the administration of Ga 68 DOTATOC Injection in patients who do not have a history of NET disease does not rule out disease *[see Clinical Studies (14)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity reactions

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Ga-68 DOTATOC injection was evaluated in 334 patients in clinical trials of patients receiving a single dose of Ga-68 DOTATOC injection for imaging known or suspected NET.

The following adverse reactions occurred at a rate of < 2%:
Gastrointestinal Disorders: nausea

The following adverse reactions occurred at a rate of a < 1%
Skin and Subcutaneous Tissue Disorders: pruritus
Vascular Disorders: flushing

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of other somatostatin receptor imaging agents. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug.
***Immune System Disorders*: Hypersensitivity reactions**, predominantly rash, pruritus, less frequently angioedema or features of anaphylaxis

7 DRUG INTERACTIONS

Non-radioactive somatostatin analogs bind to the same somatostatin receptors as Ga 68 DOTATOC Injection. Image patients with Ga 68 DOTATOC Injection just prior to dosing with long-acting analogs of somatostatin. Short-acting analogs of somatostatin can be used up to 24 hours before imaging with Ga 68 DOTATOC Injection *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of Ga 68 DOTATOC Injection in pregnant women to identify a risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Ga 68 DOTATOC. However, all radiopharmaceuticals, including Ga 68 DOTATOC Injection have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering Ga 68 DOTATOC Injection administration to a pregnant woman, inform the patient of the potential for adverse pregnancy outcomes based on the radiation dose from Ga 68 DOTATOC Injection 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 risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information on the presence of Ga 68 DOTATOC in human milk, the effect on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ga 68 DOTATOC Injection and any potential

adverse effects on the breastfed child from Ga 68 DOTATOC Injection or from the underlying maternal condition.

Clinical Considerations

To decrease exposure to the breastfed infant, advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for 8 hours after Ga 68 DOTATOC Injection administration.

8.4 Pediatric Use

The safety and efficacy of Ga 68 DOTATOC Injection have been established in pediatric patients with neuroendocrine tumors. Efficacy is based on data from 14 patients in Study A and B demonstrating the ability of Ga 68 DOTATOC to image NETs *[see Clinical Studies (14)]*. The safety profile of Ga 68 DOTATOC Injection is similar in adult and pediatric patients with somatostatin receptor positive tumors. The recommended Ga 68 DOTATOC injected dose in pediatric patients is weight based *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

Clinical studies of Ga 68 DOTATOC 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.

10 OVERDOSAGE

In the event of a radiation overdose, reduce the absorbed dose to the patient by increasing the elimination of the radionuclide from the body by reinforced hydration, frequent bladder voiding, and diuretics, if needed. If possible, perform an estimate of the radioactive dose given to the patient.

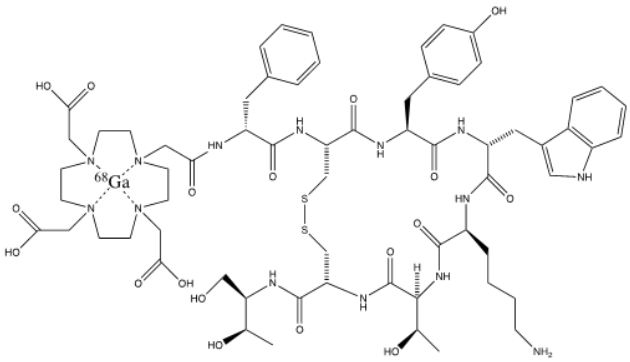
11 DESCRIPTION

11.1 Chemical Characteristics

Ga 68 DOTATOC Injection is a radioactive diagnostic agent for intravenous administration. It contains 3.6 mcg/mL (DOTA-0-Phe1-Tyr3) octreotide, 18.5 MBq/mL to 148 MBq/mL (0.5 mCi to 4 mCi/mL) of Ga 68 DOTATOC at calibration time, and ethanol (10% v/v) in sodium chloride (9 mg/mL) solution (approximately 14 mL volume). Ga 68 DOTATOC Injection is a sterile, pyrogen free, clear, colorless, buffered solution, with a pH between 4 to 8.

Ga 68 DOTATOC, also known as Gallium-68 (DOTA0-Phe1-Tyr3) octreotide, is a cyclic 8 amino acid peptide with a covalently bound chelator (DOTA). The peptide has the amino acid sequence: H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH, and contains one disulfide bond. Ga 68 DOTATOC has a molecular weight of 1489.65 g/mol and its chemical structure is shown in Figure 1.

Figure 1: Chemical Structure of Ga 68 DOTATOC



Gallium-68 labeled 2-[4-[2-[[(2R)-1-[[(4R,7S,10S,13R,16S,19R)-10-(4-aminobutyl)-4-[[(2R,3R)-1,3-dihydroxybutan-2-yl]carbamoyl]-7-[(1R)-1-hydroxyethyl]-16-[(4-hydroxyphenyl)methyl]-13-(1H-indol-3-ylmethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicos-19-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-2-oxoethyl]-7,10-bis(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetic acid.

11.2 Physical Characteristics

Table 3 and Table 4 display the principal radiation emission data and physical decay of Ga 68.

Gallium-68 (Ga 68) decays with a half-life of 68 minutes to stable Zn 68:

- 89% through positron emission with a mean energy of 836 keV followed by emission of two 511 keV annihilation photons (178%),
- 10% through orbital electron capture (with associated X-ray or Auger emissions), and
- 3% through 13 gamma transitions from 5 excited levels of the daughter Zn 68 nucleus. The most probable prompt gamma emission is a 1088 keV gamma with a 3.2% per decay probability.

Table 3: Principal Radiation Emission Data (>1%)

Radiation/ Emission	% Disintegration	Mean Energy (MeV)
beta+	88%	0.8360
beta+	1.1%	0.3526
gamma	178%	0.5110
gamma	3%	1.0770
X-ray	2.8%	0.0086
X-ray	1.4%	0.0086

Table 4: Physical Decay Chart for Gallium Ga-68

Minutes	Fraction Remaining
0	1.000
15	0.858
30	0.736
60	0.541
90	0.398
120	0.293
180	0.158
360	0.025

11.3 External Radiation

Gamma constant: 1.8 X 10^{-4} mSv/hr per MBq at 1 meter [0.67 mrem/hr per mCi at 1 meter]
Table 5 displays the radiation attenuation by lead shielding of Ga 68.

Table 5: Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
6	0.5
12	0.25
17	0.1
34	0.01
51	0.001

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ga 68 DOTATOC binds to somatostatin receptors, with highest affinity (K_i = 2.5± 0.5 nanomolar) for subtype 2 receptors (sstr2). Ga 68 DOTATOC binds to cells that express somatostatin receptors including malignant neuroendocrine cells, which overexpress sstr2 receptors. Gallium 68 is a β+ emitting radionuclide with associated 511 keV annihilation photons that allow positron emission tomography (PET) imaging.

12.2 Pharmacodynamics

The relationship between Ga 68 DOTATOC plasma concentrations and successful imaging was not explored in clinical trials.

12.3 Pharmacokinetics

Distribution

Ga 68 DOTATOC distributes to all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. Uptake in the lung and lymph nodes are lower as compared to other sstr-2 expressing organs.

Elimination

Radiotracer elimination is exclusively via urine. Approximately 16% of the injected dose is excreted in urine in the first two to four hours post-injection.

14 CLINICAL STUDIES

The safety and efficacy of Ga-68 DOTATOC Injection were established in two single-center, open-label studies (Study A and Study B) in which 282 patients with known or suspected SSTR-positive NETs received a single dose of Ga-68 DOTATOC. A total of 238 of the 282 patients (84%) had a history of neoplasm at the time of Ga-68 DOTATOC imaging. Among the 282 patients, 59% were female and 95% white; the mean age was 54 years (range from 4 to 82 years).

The Ga-68 DOTATOC images were rated by two independent readers blinded to clinical information as either positive or negative for NET within each patient. The imaging results were compared to a composite reference consisting of histopathology and imaging (MR, CT, or In-111 pentetreotide imaging) acquired within 1 year of the Ga-68 DOTATOC imaging, as well as chromogranin A and pancreastatin levels. The proportion of patients positive for NET per composite reference who were identified as positive by the Ga-68 DOTATOC image was used to quantify positive percent agreement. The proportion

of patients without NET per composite reference who were identified as negative by the Ga-68 DOTATOC image was used to quantify negative percent agreement.

Study A (NCT: 01619865) included 220 subjects with known or suspected SSTR positive tumors referred for diagnosis or evaluation of disease extension before or after treatment. A total of 178 of the 220 patients (81%) had a history of neoplasm at the time of Ga-68 DOTATOC imaging. In 177 of the 220 patients, sufficient data to establish NET status per composite reference was available for efficacy evaluation. Table 6 shows the performance of Ga-68 DOTATOC in the detection of NETs for Study A.

Table 6: Study A. Performance of Ga-68 DOTATOC in the detection of NET by reader

N = 177	**NET status as identified by reader**	**Reference**	
		Positive	Negative
Reader 1	Positive	121	5
	Negative	12	39
	Agreement (%)* (95% CI)**	91 (85, 95)	89 (75, 96)
Reader 2	Positive	120	6
	Negative	13	38
	Agreement (%)* (95% CI)**	90 (84, 95)	86 (73, 95)

N: number of patients, CI: confidence interval, *Percent reader agreement with reference; **Exact method

Study B (NCT: 01869725) included 62 patients with histologically positive NET or other SSTR positive tumor referred for evaluation of disease before or after treatment. In 59 of the 62 patients, sufficient data to establish NET status per composite reference was available for efficacy evaluation. The estimated positive and negative percent agreements were 92% and 75% for reader 1 and 90% and 75% for reader 2, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ga 68 DOTATOC Injection is supplied in a multiple-dose, capped 30 mL glass vial containing 18.5 MBq/mL to 148 MBq/mL (0.5 mCi/mL to 4 mCi/mL) of Ga 68 DOTATOC at calibration time in approximately 14 mL of solution (NDC 24417-681-30).

Store Ga 68 DOTATOC Injection upright in a lead shielded container at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Receipt, transfer, handling, possession or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate. Store and dispose of Ga 68 DOTATOC Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

17 PATIENT COUNSELING INFORMATION

Radiation Risk

Advise patients to drink water to ensure adequate hydration prior to their PET study and recommend they drink and urinate as often as possible during the first hours following the administration of Ga 68 DOTATOC Injection, in order to reduce radiation exposure *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Lactation

Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for 8 hours after Ga 68 DOTATOC Injection administration in order to minimize radiation exposure to a breastfed infant *[see Use in Specific Populations (8.2)]*.

Manufactured and Distributed by:

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