CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208547Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NETSPOT safely and effectively. See full prescribing information for NETSPOT.

NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
NETSPOT, after radiolabeling with Ga 68, 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----------
- After reconstitution and radiolabeling, handle Ga 68 dotatate injection with appropriate safety measures to minimize radiation exposure (2.1)
- Instruct patients to drink a sufficient amount of water before administration, during the first hours following administration and to void frequently (2.1)
- Recommended dose is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi) administered as intravenous bolus injection (2.2)
- See the Full Prescribing Information for detailed instructions on how to prepare Ga 68 dotatate injection (e.g., reconstitution, radiolabeling) (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
NETSPOT is supplied as a single dose kit containing:
- **Vial 1** (reaction vial with lyophilized powder) containing 40 mcg of dotatate (3)
- **Vial 2** (buffer vial) containing 1 mL of reaction buffer solution (3)
- One accessory cartridge (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Radiation Risk: Ga 68 dotatate contributes to a patient's overall long-term cumulative radiation exposure. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure (5.1)
- Risk for Image Misinterpretation: The uptake of Ga 68 dotatate can be seen in a variety of tumor types other than NETs (e.g. those derived from neural crest tissue), in other pathologic conditions, and as a normal physiologic variant (e.g. uncinate process of the pancreas). (5.2)

To report SUSPECTED ADVERSE REACTIONS, contact Advanced Accelerator Applications USA, Inc. at 1-212-235-2380 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Somatostatin Analogs: Somatostatin analogs competitively bind to the same somatostatin receptors as Ga 68 dotatate and may affect imaging – image just prior to dosing with long-acting somatostatin analogs (7)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breast milk should be pumped and discarded for 12 hours after administration (8.2).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NETSPOT, after radiolabeling with Ga 68, is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety

Drug Handling

After reconstitution and radiolabeling, handle the Ga 68 dotatate 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 dotatate 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.

Patient Preparation

Instruct patients to drink a sufficient amount of water to ensure adequate hydration prior to administration of Ga 68 dotatate. Drink and void frequently during the first hours following administration to reduce radiation exposure.

2.2 Recommended Dosage and Administration Instructions

In adults and pediatric patients, the recommended amount of radioactivity to be administered for PET imaging is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi).

After reconstitution with Ga 68 chloride eluate from an Eckert & Ziegler GalliaPharm Germanium 68/Gallium 68 (Ge 68/Ga 68) generator and buffer [see Drug Preparation (2.3)], administer Ga 68 dotatate by intravenous injection (bolus).

Verify the injected radioactivity by measuring the radioactivity of the vial containing the Ga 68 dotatate injection with a dose calibrator before administration to the patient *[see Administration (2.4)]*. Ensure that the injected radioactivity is within ±10% of the recommended dose.

2.3 Drug Preparation

The NETSPOT kit is supplied as 2 vials and an accessory cartridge *[see Dosage Forms and Strengths (3)]* which allows for direct preparation of Ga 68 dotatate injection with the eluate from an Eckert & Ziegler GalliaPharm Germanium 68/Gallium 68 (Ge 68/Ga 68) generator. The Eckert & Ziegler GalliaPharm Ge 68/Ga 68 generator ("GalliaPharm generator") is not supplied with the NETSPOT kit. The safety and efficacy of the Ga 68 dotatate injection drug product prepared from the NETSPOT kit has been established only when using a Ga 68 chloride solution eluted from the GalliaPharm generator.

Components of the kit:

- **Vial 1** (reaction vial with lyophilized powder) contains: 40 mcg dotatate, 5 mcg 1,10-phenanthroline; 6 mcg gentisic acid; 20 mg mannitol.

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- **Vial 2** (buffer vial) contains: 60 mg formic acid; 56.5 mg sodium hydroxide and water for injection.
- Accessory cartridge contains: 660 mg porous silica. The accessory cartridge reduces the amount of Ge 68 potentially present in generator eluate.

Prepare Ga 68 dotatate for intravenous injection according to the following aseptic procedure (Figure 1):

a. Use suitable shielding to reduce radiation exposure.
b. Wear waterproof gloves.
c. Set the temperature of the shielded dry bath to 203 °F (95 °C), and wait for the temperature to reach the set point and stabilize.
d. Prepare a syringe containing 5 mL of 0.1 N sterile HCl, to be used for elution of the GalliaPharm generator. Use 0.1N sterile HCl supplied by the generator manufacturer. Test periodically (weekly) the Ga 68 chloride eluate for Ge 68 breakthrough by suitable method. Ge 68 breakthrough and other gamma emitting radionuclides should be ≤ 0.001%. The Ga 68 chloride is sterile as eluted from the GalliaPharm generator.
e. Remove the cap from **Vial 1** (reaction vial), swab the top of the vial with alcohol to disinfect the surface, and allow the stopper to dry.
f. Pierce the **Vial 1** septum with a sterile needle connected to a 0.22 micron sterile vented filter (not supplied) to maintain atmospheric pressure within the vial during the reconstitution process.
g. Remove the cap from the **Vial 2** (buffer vial), swab the top of the vial with alcohol to disinfect the surface, and allow the stopper to dry.
h. Using a 1 mL sterile syringe, withdraw the required volume of the reaction buffer from **Vial 2**. Calculate the volume (in mL) by multiplying the volume of HCl used for the elution of the generator in mL by its molarity:

   Reaction buffer volume in mL = HCl volume in mL x HCl molarity (for the GalliaPharm generator eluate, 5 mL x 0.1 N = 0.5 mL of reaction buffer).

i. Connect the top of the cartridge to the male luer of the outlet line of the GalliaPharm generator. Connect the bottom of the cartridge with a sterile needle.
j. Connect **Vial 1** to the outlet line of the GalliaPharm generator by pushing the needle through the rubber septum and place the vial in a lead shield container.
k. Elute the generator directly into the **Vial 1** through the cartridge and the needle according to the instructions for use of the GalliaPharm generator that are supplied by Eckert & Ziegler, in order to reconstitute the lyophilized powder with 5 mL of eluate. Perform the elution manually or by means of a pump.
l. At the end of the elution, disconnect the generator from **Vial 1** by removing the needle from the rubber septum, and immediately (do not delay buffer addition more than 10 min) add the kit reaction buffer in the 1 mL sterile syringe (the amount of reaction buffer was determined from Step h). Withdraw the syringe and the 0.22 micron sterile air venting filter, and then using a tong, move **Vial 1** to the heating hole of the dry bath, and leave the vial at 203 °F (95 °C, not to exceed 98 °C) for at least 7 minutes (do not exceed 10 minutes heating) without agitation or stirring.
m. After 7 minutes, remove the vial from the dry bath, place it in an appropriate lead shield and let it cool down to room temperature for approximately 10 minutes.
n. Assay the whole vial containing the Ga 68 dotatate injection for total radioactivity concentration using a dose calibrator and record the result.

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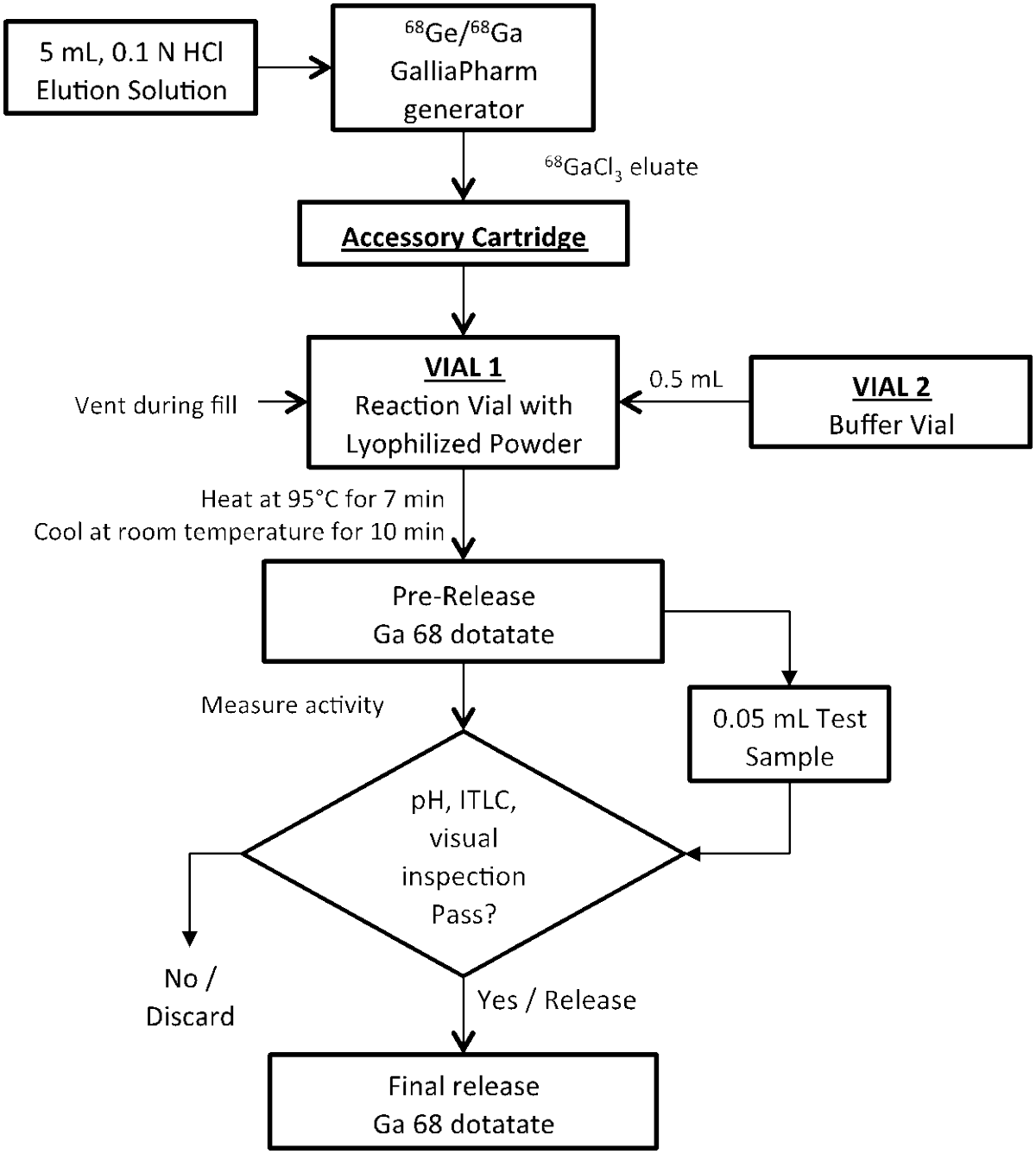
o. Perform the quality controls according to the recommended methods in order to check the compliance with the specifications *[see Dosage and Administration (2.5)]*.
p. Prior to use, visually inspect the solution behind a shielded screen for radioprotection purposes. Only use solutions that are clear without visible particles.
q. Keep the vial containing the Ga 68 dotatate injection upright in a lead glass shield container at a temperature below 77 °F (25 °C) until use.
r. After addition of Ga 68 chloride to the reaction vial, use Ga 68 dotatate injection within 4 hours.

Figure 1 Reconstitution procedure



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2.4 Administration

Prior to use, visually inspect the prepared Ga 68 dotatate injection behind a lead glass shield for radioprotection purposes. Only use solutions that are clear without visible particles. Using a single-dose syringe fitted with a sterile needle and protective shielding, aseptically withdraw the prepared Ga 68 dotatate injection prior to administration. Measure the total radioactivity in the syringe by a dose calibrator immediately prior to administration. The dose calibrator must be calibrated with National Institute of Standards and Technology (NIST) traceable standards.

Handle and dispose radioactive material in accordance with applicable regulations.

2.5 Specifications and Quality Control

Perform the quality controls in Table 1 behind a lead glass shield for radioprotection purposes.

Table 1. Specifications of the Radiolabeled Imaging Product (Ga 68 dotatate)

Test	Acceptance Criteria	Method
Appearance	**Colorless and particulate free**	**Visual Inspection**
pH	**3.2 – 3.8**	**pH-indicator strips**
Labeling Efficiency	**Ga 68 dotatate ≥ 92% and Other Ga 68 species ≤ 5%**	**Thin layer chromatography (ITLC, see details below)**

Determine labeling efficiency of Ga 68 dotatate:

Obtain the following materials:

- ITLC SA pre-cut to1 cm x 12 cm strips and marked with a pencil 1 cm from each end of the strip.
- Ammonium acetate 1M: Methanol(1:1 V/V)
- Developing tank
- Radiometric ITLC scanner

Perform the following:

a. Pour ammonium acetate 1M: Methanol (1:1 V/V) solution to a depth of 3 to 4 mm in the developing tank, cover the tank, and allow it to equilibrate.
b. Apply a drop of the Ga 68 dotatate injection on a pencil line 1 cm from the bottom of the ITLC strip.
c. Place the ITLC strip in the developing tank and allow it to develop for a distance of 10 cm from the point of application (i.e. to the top pencil mark).
d. Scan the ITLC with a radiometric ITLC scanner
e. Calculate radiochemical purity (RCP) by integration of the peaks on the chromatogram. Do not use the reconstituted product if the RCP is less than 92%.
f. The retention factor (Rf) specifications are as follows:
   Non-complexed Ga 68 species, Rf = 0 to 0.1; Ga 68 dotatate, Rf = 0.6 to 0.8

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2.6 Image Acquisition

For Ga 68 dotatate PET imaging, the acquisition must include a whole body acquisition from skull to mid-thigh. Images can be acquired 40 to 90 minutes after the intravenous administration of the Ga 68 dotatate. Adapt imaging acquisition delay and duration according to the equipment used, and the patient and tumor characteristics, in order to obtain the best image quality possible.

2.7 Image Interpretation

Ga 68 dotatate binds to somatostatin receptors. Based upon the intensity of the signals, PET images obtained using Ga 68 dotatate indicate the presence and density of somatostatin receptors in tissues. Tumors that do not bear somatostatin receptors will not be visualized. Increased uptake in tumors is not specific for NET *[see Warnings and Precautions (5.2)]*.

2.8 Radiation Dosimetry

Estimated radiation absorbed doses per injection activity for organs and tissues of adult patients following an intravenous bolus of Ga 68 dotatate are shown in Table 2. Estimated radiation effective doses per injection activity for adult and pediatric patients following an intravenous bolus of Ga 68 dotatate are shown in Table 3.

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

- 89% through positron emission with a mean energy of 836 keV followed by photonic annihilation radiations of 511 keV (178%),
- 10% through orbital electron capture (X-ray or Auger emissions), and
- 3% through 13 gamma transitions from 5 exited levels.

The effective radiation dose resulting from the administration of 150 MBq (4.05 mCi) [within the range of the recommended Ga 68 dotatate injection dose] to an adult weighing 75 kg, is about 3.15 mSv. For an administered activity of 150 MBq (4.05 mCi) the typical radiation dose to the critical organs, which are the urinary bladder wall, the spleen and the kidneys/adrenals, are about 18, 16 and 12 mGy, 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.

1. Physical data
   Gamma constant: 0.67 mrem/hr per mCi at 1 meter [1.8E-4 mSv/hr per MBq at 1 meter]
   Specific Activity: 4.1E7 Ci/g [1.51E18 Bq/g] max
2. Shielding
   Lead [Pb] Half Value Layer [HVL]: 6 mm (0.24 in)
   Tenth Value Layer [TVL]: 17 mm (0.67 in)

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Table 2 Estimated Radiation Absorbed Dose per Injection Activity in Selected Organs and Tissues of Adults after a Ga 68 Dotatate Injection Dose

Absorbed Dose per Injection Activity in Selected Organs and Tissues of Adults	mGy/MBq		mGy/150 MBq
	Mean	SD	
Adrenals	0.086	0.052	12.90
Brain	0.010	0.002	1.50
Breasts	0.010	0.002	1.50
Gallbladder wall	0.016	0.002	2.40
Lower large intestine wall	0.015	0.002	2.25
Small intestine	0.025	0.004	3.75
Stomach wall	0.013	0.002	1.95
Upper large intestine wall	0.021	0.003	3.15
Heart wall	0.018	0.003	2.70
Kidneys	0.093	0.016	13.95
Liver	0.050	0.015	7.50
Lungs	0.006	0.001	0.90
Muscle	0.012	0.002	1.80
Ovaries	0.016	0.001	2.40
Pancreas	0.015	0.002	2.25
Red marrow	0.015	0.003	2.25
Osteogenic cells	0.021	0.005	3.15
Skin	0.010	0.002	1.50
Spleen	0.109	0.058	16.35
Testes	0.010	0.001	1.50
Thymus	0.012	0.002	1.80
Thyroid	0.011	0.002	1.65
Urinary bladder wall	0.098	0.048	14.70
Uterus	0.015	0.002	2.25
Total body	0.014	0.002	2.10
Effective dose per injection activity	**mSv/MBq**		**mSv/150 MBq**
	0.021	0.003	3.15

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Table 3 Estimated Radiation Effective Dose per Injection Activity after a Ga 68 Dotatate Injection Dose

Age	Effective Dose per Injection Activity (mSv/MBq)
Adult	0.021
15 years	0.025
10 years	0.040
5 years	0.064
1 year	0.13
Newborn	0.35

Table 3 indicates how effective dose per injection activity scales with body habitus in computational models of adult and pediatric patients.

3 DOSAGE FORMS AND STRENGTHS

NETSPOT is supplied as a single-dose kit, containing two vials and an accessory cartridge for preparation of Ga 68 dotatate injection:

- **Vial 1 (**reaction vial with lyophilized powder**)**: 40 mcg of dotatate, 5 mcg of 1,10-phenanthroline, 6 mcg gentisic acid and 20 mg D-mannitol for injection as a white lyophilized powder in a 10 mL glass vial with light-blue flip-off cap
- **Vial 2** (buffer vial): clear, and colorless reaction buffer solution (60 mg formic acid, 56.5 mg sodium hydroxide in approximately 1 mL volume) in a 10 mL olefin polymer vial with a yellow flip-off cap
- Accessory cartridge: plastic column filled with silica to reduce the amount of Germanium 68 (Ge 68) potentially present in generator eluate [*see Dosage and Administration (2.3)*].

Gallium 68 is obtained from an Eckert & Ziegler GalliaPharm Ge 68/Ga 68 generator and is not part of the kit.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risk

Ga 68 dotatate 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 reconstitution procedures to protect patients and health care workers from unintentional radiation exposure [*see Dosage and Administration (2.1)*].

5.2 Risk for Image Misinterpretation

The uptake of Ga 68 dotatate reflects the level of somatostatin receptor density in NETs. However, uptake can also be seen in a variety of other tumor types (e.g. those derived from neural crest tissue). Increased uptake might also be seen in other pathologic conditions (e.g. thyroid disease or subacute inflammation) or might occur as a normal physiologic variant (e.g. uncinate process of the pancreas).

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The uptake may need to be confirmed by histopathology or other assessments *[see Dosage and Administration (2.7)]*.

6 ADVERSE REACTIONS

The safety of Ga 68 dotatate was evaluated in three single center studies *[see Clinical Studies (14)]* and in a survey of the scientific literature. No serious adverse reactions were identified.

7 DRUG INTERACTIONS

Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors as Ga 68 dotatate. Image patients with Ga 68 dotatate PET 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 dotatate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with Ga 68 dotatate in pregnant women to inform any drug-associated risks; however, all radiopharmaceuticals, including Ga 68 dotatate have the potential to cause fetal harm. Animal reproduction studies have not been conducted with Ga 68 dotatate.

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 dotatate 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 dotatate injection and any potential adverse effects on the breastfed child from Ga 68 dotatate injection or from the underlying maternal condition.

Clinical Considerations

Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for 12 hours after Ga 68 dotatate administration in order to minimize radiation exposure to a breastfed infant.

8.4 Pediatric Use

The efficacy of Ga 68 dotatate PET imaging in pediatric patients with neuroendocrine tumors is based on extrapolation from adult studies, from studies demonstrating the ability of Ga 68 dotatate to bind to somatostatin receptors *[see Clinical Pharmacology (12.1)]*, and from a published study of Ga 68 dotatate PET imaging in pediatric patients with somatostatin receptor positive tumors. The safety profile of Ga 68 dotatate is similar in adult and pediatric patients with somatostatin receptor positive tumors. The recommended Ga 68 dotatate injection dose in pediatric patients is weight based as in adults *[see Dosage and Administration (2.2)]*.

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8.5 Geriatric Use

Clinical studies of Ga 68 dotatate injection 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.

10 OVERDOSAGE

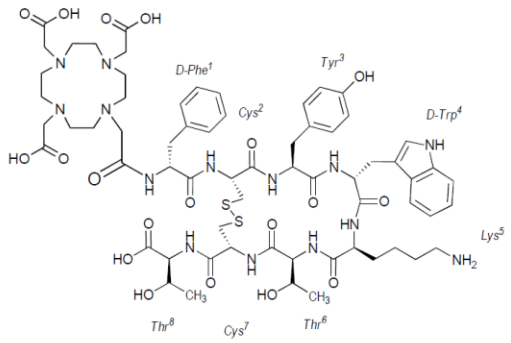
In the event of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by reinforced hydration and frequent bladder voiding. A diuretic might also be considered. If possible, an estimate of the radioactive dose given to the patient should be performed.

11 DESCRIPTION

NETSPOT is supplied as a sterile, single-dose kit for preparation of Ga 68 dotatate injection for intravenous use.

Dotatate, also known as **DOTA-0-Tyr3-Octreotate**, 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. Dotatate has a molecular weight of 1435.6 Daltons and its chemical structure is shown in Figure 2 .

Figure 2 Chemical Structure of dotatate



[(4,7,10-Tricarboxymethyl-1,4,7,10-tetrazacyclododec-1-yl)acetyl]-(D)-Phenylalanyl-(L)Cysteinyl-(L)-Tyrosyl-(D)-Tryptophanyl-(L)-Lysyl-(L)-Threoninyl-(L)-Cysteinyl-(L)-Threonine-cyclic(2-7)disulfide

NETSPOT is a Kit with the following components:

- **Vial 1** (reaction vial with lyophilized powder) contains: 40 mcg dotatate, 5 mcg 1,10-phenanthroline; 6 mcg gentisic acid; 20 mg mannitol.
- **Vial 2** (buffer vial) contains: 60 mg formic acid; 56.5 mg sodium hydroxide and water for injection.
- Accessory cartridge contains: 660 mg porous silica.

After reconstitution and radiolabeling, *[see Dosage and Administration (2.3)]*, Ga 68 dotatate injection also contains hydrochloric acid as an excipient derived from the generator eluate. The prepared Ga 68 dotatate injection for intravenous use, is a sterile, pyrogen free, clear, colorless, buffered solution, with a pH -between 3.2 - 3.8. Table 4, Table 5, and Table 6 display the principle radiation emission data, radiation attenuation by lead shielding, and physical decay of Ga 68.

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Table 4 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 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

Table 6 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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ga 68 dotatate binds to somatostatin receptors, with highest affinity for subtype 2 receptors (sstr2). It binds to cells that express somatostatin receptors including malignant cells, which overexpress sstr2 receptors. Gallium 68 (^{68}Ga) is a β+ emitting radionuclide with an emission yield that allows positron emission tomography (PET) imaging.

12.2 Pharmacodynamics

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

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12.3 Pharmacokinetics

Distribution

Ga 68 dotatate distributes to all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There is no uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low.

Elimination

A total of 12% of the injected dose is excreted in urine in the first four hours post-injection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies on fertility, embryology, mutagenic potential, or carcinogenic potential have been conducted with Ga 68 dotatate. However, genotoxicity studies conducted with a very similar molecule (mixture Lu 175 dotatate/dotatate) shows that these non-radioactive compounds do not induce mutation at the TK locus of L5178Y mouse lymphoma cells in vitro, nor reverse mutation in *Salmonella typhimurium*, or *Escherichia coli* (both in the absence or presence of S9 metabolic activation).

14 CLINICAL STUDIES

The efficacy of NETSPOT was established in three open label single center studies (Study A-C).

In Study A, 97 adult patients (mean age 54; 41men and 56 women) with known or suspected neuroendocrine tumors (NETs) were evaluated with Ga 68 dotatate PET. The Ga 68 dotatate images were read by two independent readers blinded to clinical information. The reads were compared to CT and/or MR images and to indium In 111 pentetreotide images obtained with Single Photon Emission Computed Tomography (SPECT) within previous 3 years. Among 78 patients in whom CT and/or MR images and In 111 pentetreotide images were available, Ga 68 dotatate PET was in agreement with the CT and/or MR images in 74 patients. Out of 50 patients with NETs localized by CT and/or MR imaging, Ga 68 dotatate was positive in 48 patients including 13 patients in whom In 111 pentetreotide was negative. Ga 68 dotatate was negative in 26 out of 28 patients in whom CT and/or MR imaging was negative.

Study B was a published study which involved 104 patients (mean age 58; 52 men and 52 women) with suspected NETs due to clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET. Diagnostic performance of Ga 68 dotatate PET in localizing tumor sites was retrospectively assessed using a reference standard: histopathology (n=49) or clinical follow up of up to 5 month duration (n=55). Images were interpreted by consensus between two on-site readers who were not blinded to clinical information. NET sites were localized by reference standard in 36 patients (all by histopathology). Out of these, Ga 68 dotatate was positive, correctly identifying an NET site, in 29 patients and was falsely negative in seven. In 68 patients with no NET identified by a reference standard, the images were negative in 61 and falsely positive in seven patients.

Study C was a published study which involved 63 patients (mean age 58; 34 men and 29 women) evaluated for NET recurrence using a reference standard as described for Study B.
Ga 68 dotatate images were interpreted independently by two central readers blinded to clinical information. Reader 1 correctly localized NETs in 23 out of 29 reference standard-positive patients and reader 2 correctly localized NETs in 22 such patients. In 34 patients with no NET identified by a reference standard, reader 1 was correct in 29 patients and reader 2 in 32.

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16 HOW SUPPLIED/STORAGE AND HANDLING

NETSPOT is supplied as a single-dose kit (NDC# 69488-001-40) for preparing a single-dose of gallium 68 (Ga 68) radiolabeled dotatate injection.

The kit contains:

- **Vial 1** (10-mL Ultra inert Type I Plus glass vial, light-blue flip-off cap): 40 mcg of dotatate, 5 mcg 1,10-phenanthroline, 6 mcg gentisic acid, 20 mg mannitol as lyophilized powder (NDC# 69488-001-04)
- **Vial 2** (10-mL cyclic olefin polymer vial, with a yellow flip-off cap): reaction buffer solution (approximately 1 mL volume), 60 mg formic acid, 56.5 mg sodium hydroxide and water for injection (NDC# 69488-001-01)
- One accessory cartridge (plastic column filled with 660 mg porous silica).

The radionuclide is not part of the kit. Before reconstitution and radiolabelling with Ga 68, the contents of this kit are not radioactive.

Expiry date is indicated on the original outer packaging, and on the vials. This medicinal product must not be used beyond the date indicated on the packaging.

For prolonged storage, store NETSPOT in its original packaging at room temperature below 25°C (do not freeze). After reconstitution and radiolabeling *[see Dosage and Administration (2.3)]* with activities of up to 1110 MBq (30 mCi), keep Ga 68 dotatate injection upright with an appropriate shielding to protect from radiation, at a temperature below 25 °C (do not freeze), and for a maximum of 4 hours. The storage of the radiolabelled product must comply with regulatory requirements for radioactive materials.

17 PATIENT COUNSELING INFORMATION

Adequate Hydration

Advise patients to drink a sufficient amount of water to ensure adequate hydration before their PET study and urge them to drink and urinate as often as possible during the first hours following the administration of Ga 68 dotatate injection, in order to reduce radiation exposure *[see Dosage and Administration (2.3)]*.

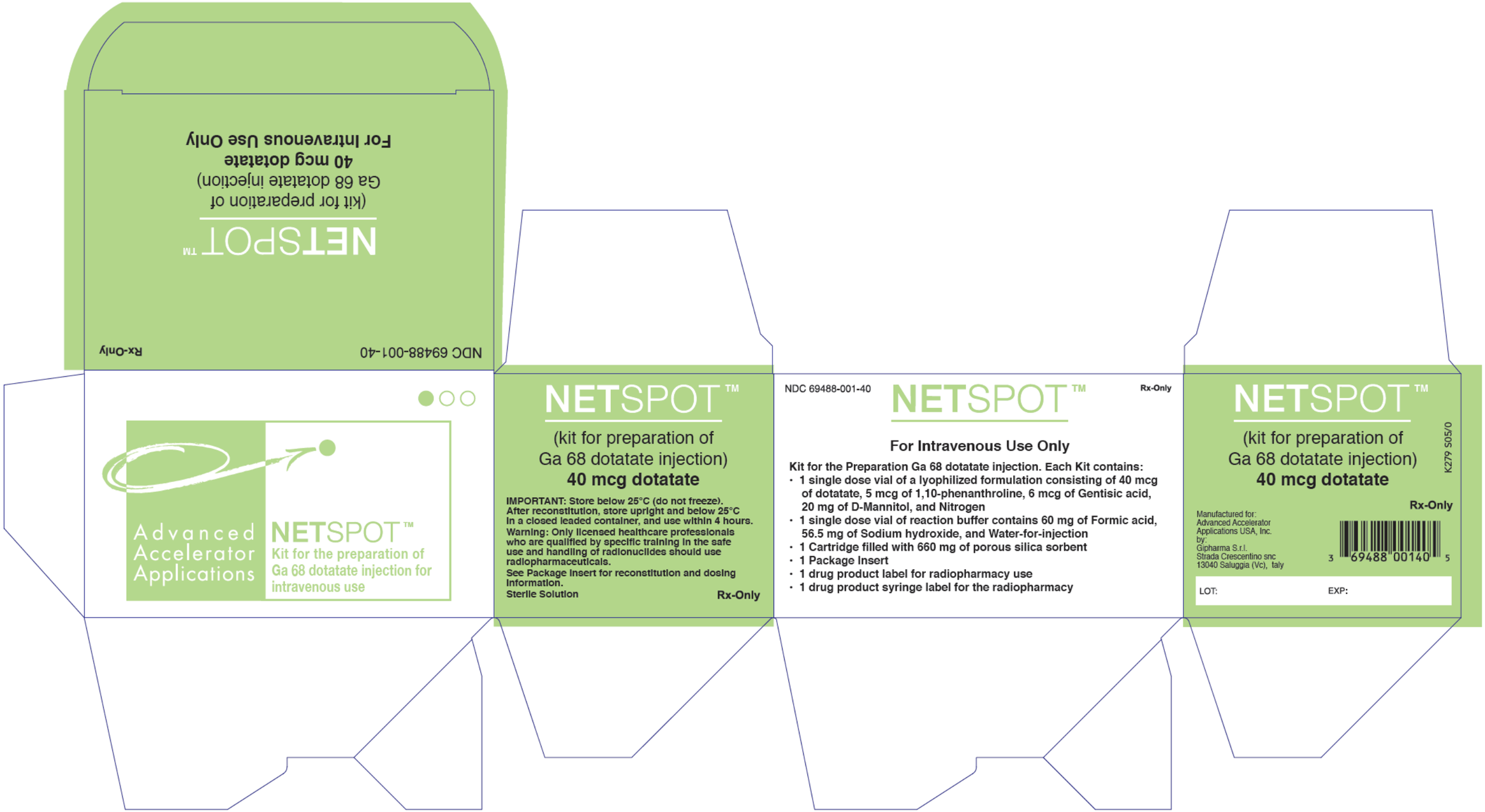
Lactation

Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for 12 hours after Ga 68 dotatate injection administration in order to minimize radiation exposure to a breastfed infant *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Gipharma S.r.l.
Strada Crescentino snc-1
3040 Saluggia (Vc), Italy

Distributed by:
Advanced Accelerator Applications USA, Inc., NY 10118

Reference ID: 3945407



Reference ID: 3945407

NETSPOT™

NDC# 69488-001-04

40 mcg dotatate per vial
dotatate, 40 mcg
Vial 1 (Reaction vial with lyophilized powder) - For intravenous Use Only
After reconstitution with Ga 68 chloride and pH adjustment with Reaction Buffer prior to use. Sterile
Usual dosage: See package Insert before use.
Store below 25°C (do not freeze).
After reconstitution, store upright and below 25°C in a closed leaded container, and use within 4 hours.

Rx-Only Single dose vial
Lot (number) EXP: {MM/DD/YYYY}

Advanced Accelerator Applications

E334 R06/01

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NDC# 69488-001-01

For Adjusting pH of Ga 68 dotatate injection
For pH adjustment of radiolabeled Netspot only
1 mL in 10 mL Vial.
Vial 2 (Buffer). Reaction buffer for preparation of Ga 68 dotatate injection
Sterile
Not for direct administration
See package Insert for preparation and administration instructions.
Store below 25°C (do not freeze).

Rx-Only Single dose vial. Discard unused portion
Lot (number) EXP: {MM/DD/YYYY}

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E336 R06/01

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Cartridge for preparation of Ga 68 dotatate injection

Cartridge

Store below 25°C (do not freeze).
See package Insert before use.

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E339 R06/01

Rx-Only
Lot (number)

Single use cartridge. Discard after use.
EXP: {MM/DD/YYYY}

NETSPOT

(kit for preparation of Ga 68 dotatate injection) syringe

APPLY TO SYRINGE

Ga 68 dotatate injection
See Package Insert before use.

Lot: (number)

Reconstitution: (MMMDDYYYY)

E331 R06/01

Ga 68 dotatate Injection
Diagnostic

FOR INTRAVENOUS USE

For information of dosage, administration and indications, see package insert.

Store upright and below 25°C in a closed leaded container, and use within 4 hours.

Warning: Only licensed healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides should use radiopharmaceuticals.

E343 R06/0

Total Activity

Lot.....

.....MBq.....(mCi)

Volume.....mL

Concentration

.....MBq/mL.....mCi/mL

EOS .....

Expiry.....

Manufactured for:
Advanced Accelerator Applications USA, Inc.
By Gipharma S.r.l.

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/s/

CHARLES J GANLEY
06/01/2016