1 Tradename(s)

Locametz® 25 micrograms, kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection.

2 Description and composition

Pharmaceutical form

Locametz® is a multi-dose kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection, containing one vial of white lyophilized powder (powder for solution for injection).

For radiolabeling with gallium-68 chloride solution. The radionuclide is not part of the kit.

Active substance

Locametz vial contains 25 micrograms of gozetotide.

Excipients

Locametz vial contains gentisic acid, sodium acetate trihydrate and sodium chloride.

3 Indications

Locametz, after radiolabelling with gallium-68, is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:
• Primary staging of patients with high-risk PCa prior to primary curative therapy,
• Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,
• Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

4 Dosage regimen and administration

Dosage regimen

General target population

The recommended dose of gallium (^{68}Ga) gozetotide is 1.8 to 2.2 MBq/kg of body weight (0.049 to 0.059 mCi/kg), with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi).

Special populations

Renal/hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 11 Clinical pharmacology).

Pediatric patients (below 18 years)

The safety and efficacy of gallium (^{68}Ga) gozetotide in pediatric patients below 18 years have not been established.

Geriatric patients (65 years of age or above)

No dose adjustment is required in patients 65 years of age or above (see section 11 Clinical pharmacology).

Method of administration

After reconstitution, gallium (^{68}Ga) gozetotide solution should be administered by slow intravenous injection, in order to avoid local extravasation resulting in inadvertent radiation exposure to the patient and imaging artifacts. Accidental extravasation may cause local irritation, due to the acidic pH of the gallium (^{68}Ga) gozetotide solution for injection. Cases of extravasation should be managed as per institutional guidelines.

The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after gallium (^{68}Ga) gozetotide administration to the patient. The dose calibrator must be calibrated and comply with international standards (see section 14 Pharmaceutical information).

Radiation safety

Handling

After reconstitution, gallium (^{68}Ga) gozetotide solution for injection should be handled with appropriate safety measures to minimize radiation exposure. Waterproof gloves, effective radiation shielding and other appropriate safety measures should be used when preparing and handling gallium (^{68}Ga) gozetotide solution in order to avoid unnecessary radiation exposure to the occupational workers, clinical personnel, and other persons (see section 14 Pharmaceutical information).

Appropriate aseptic precautions should be taken when withdrawing and administering gallium (^{68}Ga) gozetotide solution for injection (see section 14 Pharmaceutical information).

Radiopharmaceuticals should be used by or under the control of healthcare providers who are qualified by specific training and experience in the safe use and handling of radionuclides.

Patient preparation

Patients should be well hydrated prior to gallium (^{68}Ga) gozetotide administration and should be advised to void immediately prior to and frequently during the first hours after image acquisition to reduce radiation exposure.

Image acquisition

Gallium (^{68}Ga) gozetotide PET image acquisition should be performed by scanning the whole body starting at mid-thigh and proceeding to skull base. PET images should be acquired 50 to 100 minutes after the intravenous administration of gallium (^{68}Ga) gozetotide solution.

Imaging acquisition start time and duration should be adapted to the equipment used, the patient and the tumor characteristics, in order to obtain the best image quality possible.

Image interpretation

Gallium (^{68}Ga) gozetotide binds to PSMA on the surface of PSMA-expressing cells. Based on the intensity of the signals, PET images obtained with gallium (^{68}Ga) gozetotide indicate the presence of PSMA protein in tissues.

Radiation dosimetry

The mean effective radiation dose of gallium (^{68}Ga) gozetotide is 0.0166 mSv/MBq, resulting in an approximate effective radiation dose of 4.30 mSv for an administered activity of 259 MBq (7 mCi). Radiation absorbed doses for organs and tissues of adult patients, following intravenous injection of gallium (^{68}Ga) gozetotide are shown in Table 4-1.

The highest radiation absorbed dose of gallium (^{68}Ga) gozetotide occurred in the kidneys, salivary glands, bladder wall, lacrimal glands, spleen, and liver. The estimated radiation absorbed doses to these organs for an administered activity of 259 MBq are 64 mGy (kidneys), 25 mGy (salivary glands), 22 mGy (bladder wall), 10 mGy (lacrimal glands), 10 mGy (spleen) and 8 mGy (liver).

Table 4-1 Estimated mean radiation absorbed doses of gallium (^{68}Ga) gozetotide

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
	Mean	**SEM**
Adrenals	0.0080	0.0004
Brain	0.0032	0.0004
Breasts	0.0034	0.0004
Gallbladder wall	0.0073	0.0004
Lower colon/LLI wall	0.0051	0.0004
Small intestine	0.0054	0.0003
Stomach wall	0.0053	0.0003
Upper colon/ULI wall	0.0054	0.0003
Heart wall	0.0045	0.0004
Kidneys	0.2460	0.0406
Lacrimal glands[2]	0.0402	0.0081
Liver	0.0294	0.0057
Lungs	0.0042	0.0004
Muscle	0.0043	0.0003
Pancreas	0.0072	0.0003
Red marrow	0.0120	0.0015
Osteogenic cells	0.0102	0.0010
Salivary glands[2]	0.0957	0.0247
Skin	0.0034	0.0003
Spleen	0.0388	0.0067
Testes	0.0040	0.0004
Thymus	0.0037	0.0004

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
	Mean	**SEM**
Thyroid	0.0035	0.0004
Urinary bladder wall	0.0840	0.0213
Total body	0.0062	0.0005
Effective dose (mSv/MBq)	**0.0166**	**0.0018**

SEM: standard error of mean; LLI: lower large intestine; ULI: upper large intestine.
[1]Calculated by Olinda EXM.
[2]Calculated using the unit density sphere model.

Gallium-68 decays with a half-life of 68 min to stable zinc-68. The principal radiation emission data, radiation attenuation by lead shielding, and physical decay of gallium-68 are shown in Tables 4-2, 4-3 and 4-4.

Table 4-2 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 4-3 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 4-4 Physical decay chart for gallium-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

5 Contraindications

Hypersensitivity to the active substance, to any of the excipients or to any of the components of the labelled radiopharmaceutical.

6 Warnings and precautions

Risk for misinterpretation

While the uptake of gallium (^{68}Ga) gozetotide reflects the levels of PSMA expression in prostate cancer, gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues.

Interpretation of gallium (^{68}Ga) gozetotide PET imaging findings in the context of histopathology and/or other diagnostic procedures is recommended.

Radiation risk

Gallium (^{68}Ga) gozetotide contributes to the patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Safe handling and reconstitution procedures should be ensured to protect patients and healthcare workers from unintentional radiation exposure (see section 4 Dosage regimen and administration and section 14 Pharmaceutical information).

Patients should be well hydrated prior to gallium (^{68}Ga) gozetotide administration and should be advised to void immediately prior to and frequently during the first hours after image acquisition to reduce radiation exposure (see section 4 Dosage and Administration).

7 Adverse drug reactions

The safety profile of gallium (^{68}Ga) gozetotide was evaluated in 1003 patients receiving gallium (^{68}Ga) gozetotide at median dose per body weight of 1.9 Mbq/kg (range: 0.9-3.7 MBq/kg). Patients underwent PET/CT imaging to establish their eligibility for the VISION clinical study, based on the PSMA expression of their prostate cancer lesions. Gallium (^{68}Ga) gozetotide was concomitantly administered with physician's discretion for best standard of care.

Mild to moderate adverse drug reactions occurred in patients receiving gallium (^{68}Ga) gozetotide, with the exception of a Grade 3 fatigue event (0.1%). No serious adverse drug reactions occurred in patients receiving gallium (^{68}Ga) gozetotide.

The most common adverse drug reactions of any grade (incidence ≥ 0.5%) are fatigue (1.2%), nausea (0.8%), constipation (0.5%) and vomiting (0.5%).

The adverse drug reactions of any grade in patients receiving gallium (^{68}Ga) gozetotide are shown in Table 7-1.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions observed with gallium (^{68}Ga) gozetotide in the VISION clinical study

Adverse drug reactions	Gallium (^{68}Ga) gozetotide 0.9-3.7 MBq/kg N=1003 n (%) All grades	Frequency category N=1003 All grades
Gastrointestinal disorders		
Nausea	8 (0.8)	Uncommon
Constipation	5 (0.5)	Uncommon
Vomiting	5 (0.5)	Uncommon
Diarrhoea	4 (0.4)	Uncommon
Dry mouth	4 (0.4)	Uncommon
General disorders and administration site conditions		
Fatigue	12 (1.2)	Common
Injection site reactions[1]	2 (0.2)	Uncommon
Chills	1 (0.1)	Uncommon

[1]Injection site reactions includes: Injection site haematoma, injection site warmth

8 Interactions

No clinical drug interaction studies were required. Based on *in vitro* interaction studies, gallium (^{68}Ga) gozetotide is not expected to have any clinically significant interaction with other medications (see section 11 Clinical pharmacology).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been established in females, as Locametz is not indicated for use in females.

There are no adequate and well-controlled studies with gallium (^{68}Ga) gozetotide in pregnant women to inform any product-associated risk. Animal reproduction studies have not been conducted with gallium (^{68}Ga) gozetotide. However, all radiopharmaceuticals, including gallium (^{68}Ga) gozetotide, have the potential to cause fetal harm..

9.2 Lactation

Risk summary

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been established in females, as Locametz is not indicated for use in females.

There are no data on the presence of gallium (^{68}Ga) gozetotide in human milk, the effect on the breastfed child, or the effect on milk production.

Lactation studies have not been conducted in animals with gallium (^{68}Ga) gozetotide.

9.3 Females and males of reproductive potential

Infertility

Fertility studies have not been conducted in animals with gallium (^{68}Ga) gozetotide.

10 Overdosage

In the event of administration of a radiation overdose with gallium (^{68}Ga) gozetotide, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by hydration and frequent bladder voiding. It might be helpful to estimate the effective radiation dose that was applied.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: not yet assigned. ATC code: V09IX14.

Mechanism of action (MOA)

Gallium (^{68}Ga) gozetotide binds to cells that express PSMA, including malignant prostate cancer cells, which overexpress PSMA. Gallium-68 is a radionuclide with an emission yield that allows PET imaging.

Pharmacodynamics (PD)

At the chemical concentrations used for diagnostic examinations, gallium (^{68}Ga) gozetotide does not have any pharmacodynamic activity.

Pharmacokinetics (PK)

Distribution

Based on *in vitro* data, gozetotide mainly distributes to plasma with a mean blood-to-plasma ratio of 0.71. Gozetotide is 33% bound to human plasma proteins.

Gallium (^{68}Ga) gozetotide has bi-exponential behavior in blood, with biological half-life of 6.5 minutes for the fast component and 4.4 hours for the slower component.

Biotransformation/metabolism

Based on *in vitro* data, gozetotide undergoes negligible hepatic and renal metabolism

Elimination

Gallium (^{68}Ga) gozetotide is mainly eliminated via the renal route. Approximately 14% of the gallium (^{68}Ga) gozetotide dose administered is excreted in the urine after 2 hours post-injection.

Half-life

Based on the gallium (^{68}Ga) gozetotide biological half-life of 4.4 hours and on the gallium-68 (^{68}Ga) physical half-life of 68 minutes, the resulting gallium (^{68}Ga) gozetotide effective half-life is 54 minutes.

In Vitro evaluation of drug interaction potential

CYP450 enzymes

Gozetotide is not a substrate, inhibitor or inducer of cytochrome P450 (CYP450) enzymes. Gallium (^{68}Ga) gozetotide is not expected to have any drug interactions with CYP450 substrates, inhibitors or inducers

Transporters

Gozetotide is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2. Gozetotide is not an inhibitor of BCRP, BSEP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2. Gallium (^{68}Ga) gozetotide is not expected to have any drug interactions with the substrates of these transporters.

Special populations

Geriatric patients (65 years of age or above)

In the VISION clinical study, 752 of 1003 (75%) patients were aged 65 years or older. No overall differences in safety and efficacy were observed between these patients and younger patients.

Race/Body weight

The effect of race or body weight on gallium (^{68}Ga) gozetotide pharmacokinetics and biodistribution has not been established.

Renal/hepatic impairment

Gallium (^{68}Ga) gozetotide pharmacokinetics and biodistribution are not affected by renal/hepatic impairment to any clinically relevant extent.

12 Clinical studies

The safety and efficacy of gallium (^{68}Ga) gozetotide as a patient identification method for PSMA-targeted therapy were established in the multi-center, randomized, open-label, Phase III study VISION and in the VISION reviewer variability sub-study.

Gallium (^{68}Ga) gozetotide PET/CT imaging was used to identify adult patients with metastatic prostate cancer and establish their eligibility for the VISION clinical study, based on the PSMA expression of their prostate cancer lesions.

A total of 1,003 adult male patients received gallium (^{68}Ga) gozetotide at median dose per body weight of 1.9 Mbq/kg (range: 0.9 to 3.7 MBq/kg) and underwent PET/CT image acquisition at approximately 60 minutes (range: 50 to 100 minutes) after injection. Gallium (^{68}Ga) gozetotide

PET/CT scans were assessed in conjunction with contrast-enhanced CT and/or MRI images and were read by independent central readers blinded to clinical information.

Eight hundred and thirty-one of 1,003 patients were identified as eligible for the VISION clinical study. Patients were then randomized in a 2:1 ratio to receive either PSMA-targeted therapy (Pluvicto) 7,400 MBq (200 mCi) every 6 weeks for up to a total of 6 doses plus best standard of care (BSoC, N=551) or BSoC alone (N=280). BSoC was administered at the physician's discretion. Patients were males of median age 71 years (range: 40 to 94 years), White (86.8%), Black or African American (6.6%) and Asian (2.4%) and had median baseline PSA levels of 76 ng/mL (range: 0 to 8,995 ng/mL).

The alternate primary efficacy endpoints of the VISION clinical study were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review per PCWG3 criteria.

Patients identified by gallium (^{68}Ga) gozetotide PET/CT imaging had median OS of 15.3 months (95% CI: 14.2, 16.9) when receiving PSMA-targeted therapy (Pluvicto) plus BSoC and 11.3 months (95% CI: 9.8, 13.5) when receiving BSoC alone, with a hazard ratio of 0.62 (95% CI: 0.52, 0.74). The median rPFS was 8.7 months (99.2% CI: 7.9, 10.8) in patients receiving PSMA-targeted therapy (Pluvicto) plus BSoC, and 3.4 months (99.2% CI: 2.4, 4.0) in patients receiving BSoC alone, with a hazard ratio of 0.40 (99.2% CI: 0.29, 0.57). OS and rPFS outcomes support gallium (^{68}Ga) gozetotide PET/CT imaging as a patient identification method for PSMA-targeted therapy in metastatic prostate cancer.

A total of 125 gallium (^{68}Ga) gozetotide PET/CT baseline scans were evaluated in conjunction with contrast-enhanced CT and/or MRI images by three independent readers blinded to clinical information to assess inter-reader variability. Twenty of the 125 PET/CT scans were used to assess intra-reader reproducibility. Inter-reader Fleiss κ was 0.60 (95% CI: 0.50, 0.70) across the three independent readers, while intra-reader Cohen κ was 0.78 (95% CI: 0.49, 0.99), 0.76 (95% CI: 0.46, 0.99) and 0.89 (95% CI: 0.67, 0.99) for each reader.

The efficacy of Locametz was further established in the two following prospective studies:

In Study 1, 300 adult male patients with untreated, biopsy-proven prostate cancer and high-risk features were randomized 1:1 and underwent gallium (^{68}Ga) gozetotide PET/CT (N=148) or CT and bone scanning imaging (N=152). A composite reference standard, including histopathology, imaging, clinical and biochemical findings was available for 295 of 300 (98%) patients and the PET/CT scans were read by two independent readers. Gallium (^{68}Ga) gozetotide PET/CT had improved sensitivity and specificity compared to CT and bone scanning imaging, as summarized in Table 12-1. Radiation exposure from gallium (^{68}Ga) gozetotide was lower (8.4 mSv, 95% CI: 8.1, 8.7) than CT and bone scanning imaging radiation exposure (19.2 mSv, 95% CI: 18.2, 20.3)..

A change in patient management intent occurred in 28% (95% CI: 21, 36) of patients undergoing gallium (^{68}Ga) gozetotide PET/CT and in 15% (95% CI: 10, 22) of patients undergoing CT and bone scanning imaging. The change in patient management upon gallium (^{68}Ga) gozetotide PET/CT imaging included either a transition from curative to palliative treatment intent or a change in treatment approach (14% patients each).

Table 12-1 Efficacy results in patients with untreated, biopsy-proven prostate cancer

	Gallium (^{68}Ga) gozetotide PET/CT N=145[1]	CT and bone scanning N=150[1]
Sensitivity (95% CI)	85% (74, 96)	38% (24, 52)
Specificity (95% CI)	98% (95, 100)	91% (85, 97)

[1]*Evaluable population*

In Study 2, 635 adult male patients with histopathology-proven and biochemical recurrence (BCR) prostate cancer after prostatectomy (N=262), radiation therapy (N=169) or both (N=204) underwent gallium (^{68}Ga) gozetotide PET/CT or PET/MRI imaging. BCR was defined by serum PSA of ≥0.2 ng/mL more than 6 weeks after prostatectomy or by an increase in serum PSA of at least 2 ng/mL above nadir after definitive radiotherapy. Patients had median PSA level of 2.1 ng/mL above nadir after radiation therapy (range: 0.1 to 1,154 ng/mL). A composite reference standard, including histopathology, serial serum PSA levels and imaging (CT, MRI, and/or bone scan) findings was available for 223 of 635 (35.1%) patients, while histopathology reference standard alone was available for 93 (14.6%) patients. PET/CT scans were read by 3 independent readers blinded to clinical information other than the type of primary therapy and most recent serum PSA level.

Detection of PSMA-positive lesions occurred in 475 of 635 (75%) patients receiving gallium (^{68}Ga) gozetotide and the detection rate was significantly increased with PSA levels. Sensitivity and positive predictive value (PPV) of gallium (^{68}Ga) gozetotide PET/CT imaging are summarized in Table 12-2. Inter-reader Fleiss κ for gallium (^{68}Ga) gozetotide PET/CT imaging ranged from 0.65 (95% CI: 0.61, 0.70) to 0.78 (95% CI: 0.73, 0.82) across the assessed regions (prostate bed, pelvic nodes, extrapelvic soft tissues and bones).

Table 12-2 Efficacy results in patients with histopathology-proven and BCR prostate cancer

	Composite reference standard N=223[1]	Histopathology reference standard N=93[1]
Sensitivity per-patient (95% CI)	NA	92% (84, 96)
Sensitivity per-region (95% CI)	NA	90% (82, 95)
PPV per-patient (95% CI)	92% (88, 95)	84% (75, 90)
PPV per-region (95% CI)	92% (88, 95)	84% (76, 91)

[1]*Evaluable population*

13 Non-clinical safety data

Gozetotide was evaluated in safety pharmacology and extended single-dose toxicity studies.

Non-clinical data reveal no hazard for humans based on conventional studies of safety pharmacology and single-dose toxicity.

Safety pharmacology

Based on safety pharmacology studies, gozetotide did not have any effect on the central nervous and respiratory systems in rats at doses up to 0.75 mg/kg, which is equivalent to an estimated safety margin of approximately 300-fold based on body surface area scaling at the gallium (^{68}Ga) gozetotide maximum mass dose of 25 micrograms. Gozetotide did not have any effect

on the cardiovascular system in minipigs at doses up to 0.29 mg/kg, which is equivalent to an estimated safety margin of approximately 690-fold based on body surface area scaling at the gallium (^{68}Ga) gozetotide maximum mass dose of 25 micrograms.

In an *in vitro* study, gozetotide did not inhibit the human Ether-à-go-go-Related Gene (hERG) channels up to 100 micromolar, which is equivalent to 10,000-fold the highest theoretical Cmax in patients receiving gallium (^{68}Ga) gozetotide at the maximum mass dose of 25 micrograms.

Single-dose toxicity

Based on an extended single-dose acute toxicity study in rats, a single intravenous administration of gozetotide at doses up to 1.33 mg/kg No-Observed-Adverse-Effect Level (NOAEL) was equivalent to an estimated safety margin of 530-fold based on body surface area scaling in patients receiving gallium (^{68}Ga) gozetotide at the maximum mass dose of 25 micrograms.

Carcinogenicity and mutagenicity

No studies on mutagenic or carcinogenic potential have been conducted with gallium (^{68}Ga) gozetotide.

Reproductive toxicity

No animal studies on fertility have been conducted with gallium (^{68}Ga) gozetotide.

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Instructions for preparation and administration

Nature and contents of container

Locametz is supplied as a multi-dose kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection (see section 2 Description and composition**).** Locametz contains one 10 mL type I Plus glass vial closed with a rubber stopper and sealed with a flip-off cap.

Before reconstitution, the content of Locametz is not radioactive (see section 2 Description and composition). After reconstitution, effective radiation shielding of the gallium (^{68}Ga) gozetotide solution for injection should be maintained (see section 2 Description and composition).

After reconstitution, Locametz contains a sterile solution for injection of gallium (^{68}Ga) gozetotide at an activity of up to 1369 MBq (37 mCi). The gallium (^{68}Ga) gozetotide solution for injection also contains hydrochloric acid derived from the gallium-68 chloride solution.

Gallium (^{68}Ga) gozetotide solution for injection is a sterile, clear, colorless solution for intravenous administration, without undissolved matter and with pH between 3.2 to 6.5.

Instructions for use and handling

Preparation

Step 1: Reconstitution

Locametz allows the direct preparation of gallium (^{68}Ga) gozetotide solution for injection with the eluate from Eckert & Ziegler GalliaPharm germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator.

The instructions for use provided by the germanium-68/gallium-68 generator manufacturer should also be followed.

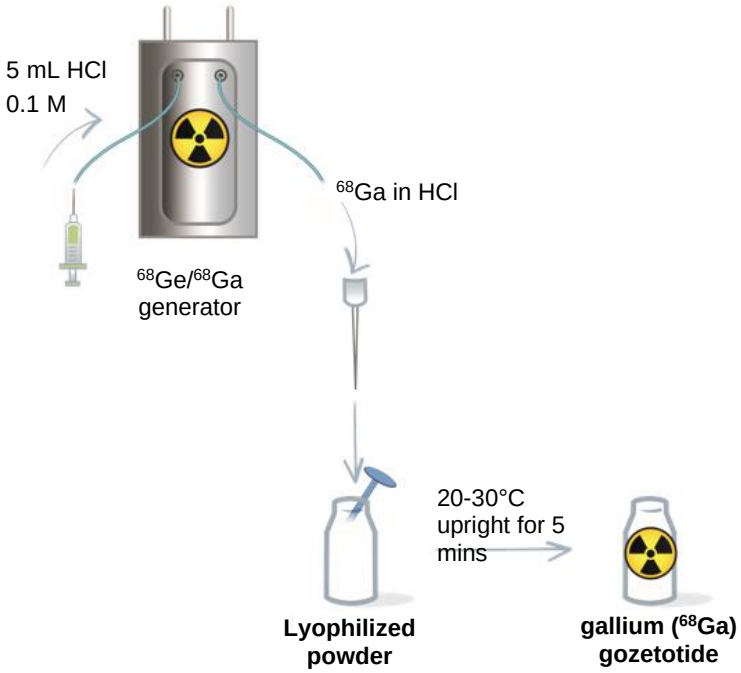
Gallium (^{68}Ga) gozetotide solution for injection should be prepared according to the following aseptic procedure:

a. Flip the cap off the Locametz vial and swab the septum with an appropriate antiseptic, then allow the septum to dry.
b. Pierce the Locametz vial septum with a sterile needle connected to a 0.2 micron sterile air venting filter to maintain atmospheric pressure within the vial during the reconstitution process. Place the Locametz vial in a lead shield container.

Reconstitution with Eckert & Ziegler GalliaPharm generators

- Connect the male luer of the outlet line of the generator to a sterile elution needle (size 21G-23G).
- Connect the Locametz vial directly to the outlet line of the generator by pushing the elution needle through the rubber septum
- Elute directly from the generator into the Locametz vial.
- Perform the elution manually or by means of a pump according to the generator instructions for use.
- Reconstitute the lyophilized powder with 5 mL of eluate.
- At the end of the elution, disconnect the Locametz vial from the generator by removing the elution needle and the vent needle with the 0.2 micron sterile air venting filter from the rubber septum. Then, invert Locametz vial once and place it upright.

Figure 14-1 Reconstitution procedure for Eckert & Ziegler GalliaPharm generator



Step 2: Incubation

a. Incubate the Locametz vial upright at room temperature (20 to 30°C) for at least 5 minutes without agitation or stirring.
b. After 5 minutes, assay the vial containing the gallium (^{68}Ga) gozetotide solution for injection for total radioactivity concentration using a dose calibrator and record the result.
c. Perform quality controls according to the recommended methods in order to check compliance with the specifications (see step 3)
d. Store the Locametz vial containing the gallium (^{68}Ga) gozetotide solution for injection upright in a lead shield container below 30°C until use.
e. After addition of gallium-68 chloride to the Locametz vial, use gallium (^{68}Ga) gozetotide solution for injection within 6 hours.

Step 3: Specifications and quality control

Perform the quality controls in Table 14-1 behind a lead glass shield for radioprotection purposes.

Table 14-1 Specifications of the gallium (^{68}Ga) gozetotide solution for injection

Test	Acceptance criteria	Method
Appearance	Clear, colorless and without undissolved matter	Visual inspection
pH	3.2 to 6.5	pH-indicator strips
Labeling efficiency	Non-complexed gallium-68 species ≤ 3%	Instant thin layer chromatography (ITLC, see details below)

Determine labeling efficiency of gallium (^{68}Ga) gozetotide solution for injection by performing instant thin layer chromatography (ITLC).

Perform ITLC using ITLC SG strips and using ammonium acetate 1M: Methanol (1:1 V/V) as mobile phase.

ITLC method

a. Develop the ITLC SG strip for a distance of 6 cm from the point of application (i.e. to 7 cm from the bottom of the ITLC strip).
b. Scan the ITLC SG strip with a radiometric ITLC scanner.
c. Calculate labeling efficiency by integration of the peaks on the chromatogram.
   Do not use the reconstituted product if the percentage (%) of non-complexed ^{68}Ga species is higher than 3%

The retention factor (Rf) specifications are as follows:

- Non-complexed gallium-68 species, Rf = 0 to 0.2;
- Gallium (^{68}Ga) gozetotide, Rf = 0.8 to 1

Step 4: Administration

a. Aseptic technique and radiation shielding should be used when withdrawing and administering gallium (^{68}Ga) gozetotide solution for injection (see section 4 Dosage regimen and administration).
b. Prior to use, the prepared gallium (^{68}Ga) gozetotide solution for injection should be visually inspected behind a lead glass shield for radioprotection purposes. Only solutions that are clear, colorless and without undissolved matter should be used (see section 4 Dosage regimen and administration).
c. After reconstitution, gallium (^{68}Ga) gozetotide solution for injection can be diluted with water for injections or sodium chloride 9 mg/mL (0.9%) solution for infusion up to a final volume of 10 mL.
d. Using a single-dose syringe fitted with a sterile needle (size 21G to 23G) and protective shielding, aseptically withdraw the prepared gallium (^{68}Ga) gozetotide solution for injection prior to administration (see section 4 Dosage regimen and administration).
e. The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after gallium (^{68}Ga) gozetotide administration to the patient. The dose calibrator must be calibrated and comply with international standards (see section 4 Dosage regimen and administration).

Incompatibilities

This product must not be mixed with medicinal products other than those mentioned in the Instructions for use and handling.

Special precautions for storage

Before reconstitution, store below 25°C.

After reconstitution, store upright below 30°C.

After reconstitution, use within 6 hours.

Special precautions for disposal

Any unused product or waste material should be disposed of only by authorized persons in designated clinical settings in accordance with local requirements.

Manufacturer:
See folding box.

® = registered trademark

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