PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

LOCAMETZ™

Powder for Solution, 25 micrograms per vial, for Intravenous use

Kit for the preparation of gallium (^{68}Ga) gozetotide solution for injection

Diagnostic Radiopharmaceutical Kit

ATC Code: V09IX14

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LOCAMETZ™ [kit for the preparation of gallium (^{68}Ga) gozetotide solution for injection], after radiolabeling with gallium-68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.
- for identification of patients with progressive metastatic castration-resistant prostate cancer (mCRPC), for whom PSMA-targeted therapy is indicated.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Based on the data submitted to Health Canada, gallium (^{68}Ga) gozetotide has been extensively studied in men 65 years or older. No clinically relevant differences in safety and efficacy were observed between these patients and younger patients.

2 CONTRAINDICATIONS

LOCAMETZ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

The co-administration of diuretics could improve image quality by reducing background activity in the urinary bladder and ureters.

4.2 Recommended Dose and Dosage Adjustment

The recommended radioactive 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) as a slow intravenous injection.

Special Populations

Renal impairment

There are no data with gallium (^{68}Ga) gozetotide in patients with severe renal impairment. No dose adjustment is considered necessary in patients with mild and moderate renal impairment (see 10 CLINICAL PHARMACOLOGY).

Hepatic impairment

Gallium (^{68}Ga) gozetotide is metabolized in the liver to a small extent. No dose adjustment is considered necessary in patients with hepatic impairment (see 10 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 10 CLINICAL PHARMACOLOGY).

4.3 Reconstitution

Reconstitute LOCAMETZ with a volume of gallium (^{68}Ga) eluate from a ^{68}Ge/^{68}Ga generator depending on the generator (see 4.7 Instructions for Preparation and Use).

4.4 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 injection of gallium (^{68}Ga) gozetotide solution should be followed by intravenous flush of sterile 0.9% sodium chloride to ensure full delivery of the dose.

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 13 PHARMACEUTICAL INFORMATION).

4.6 Image Acquisition and Interpretation

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. Patients should void immediately prior to image acquisition.

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.

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 in tissues.

Imaging interpretation prior to initial definitive therapy or suspected recurrence

Focal lesions uptake should be considered suspicious if uptake is greater than physiologic uptake in that tissue or greater than adjacent background if no physiologic uptake is expected. Normal physiological uptake can be seen in liver, kidneys, urinary bladder, spleen, colon, small intestine, lacrimal glands, and salivary glands. Increased uptake in tumors is not specific for prostate cancer.

Imaging interpretation for identification of mCRPC for PSMA-targeted therapy

PET images interpretation should be performed along with patients' clinical history and other anatomical imaging modalities (e.g., Computed tomography (CT) or magnetic resonance imaging (MRI)).

4.7 Instructions for Preparation and Use

General

- Use aseptic technique and radiation shielding and wear waterproof gloves throughout the entire preparation procedure.
- Make all transfers of radioactive solutions with a syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.
- The prepared gallium (^{68}Ga) gozetotide injection should be visually inspected behind a lead glass shield for particulate matter and discoloration. Only solutions that are clear, colorless and without undissolved matter should be used.
- Use single-dose syringe fitted with a sterile needle to aseptically withdraw the prepared gallium (^{68}Ga) gozetotide injection.
- The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated dose calibrator prior to and after gallium (^{68}Ga) gozetotide administration.
- Any unused gallium (^{68}Ga) gozetotide injection should be disposed of only by authorized persons in designated clinical settings in accordance with local requirements.

Step 1: Reconstitution

LOCAMETZ allows the direct preparation of gallium (^{68}Ga) gozetotide solution for injection with the eluate from one of the following generators (see below for specific instructions for use with each generator):

- Eckert & Ziegler GalliaPharm germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator
- IRE ELiT Galli Eo 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.

Follow the generator-specific reconstitution procedures as shown in Table 1 and in Figure 1 and Figure 2. Then continue with Step 2.

Table 1 - Reconstitution with Eckert & Ziegler GalliaPharm and IRE ELiT Galli Eo generators

If Eckert & Ziegler GalliaPharm generator is used	**If IRE ELiT Galli Eo generator is used**
• 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.	Connect the LOCAMETZ vial through the vent needle with 0.2 micron sterile air venting filter to a vacuum vial (25 mL minimum volume) by means of a sterile needle (size 21G-23G) or to a pump to start the elution.
Reconstitute the lyophilized powder with 5 mL of eluate.	Reconstitute the lyophilized powder with 1.1 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.	At the end of the elution, first withdraw the sterile needle from the vacuum vial or disconnect the pump in order to establish atmospheric pressure into the LOCAMETZ vial, then disconnect the vial from the generator by removing both the elution needle and the vent needle with the 0.2 micron sterile air venting filter needle from the rubber septum.

Figure 1 **Reconstitution procedure for Eckert & Ziegler GalliaPharm generator**

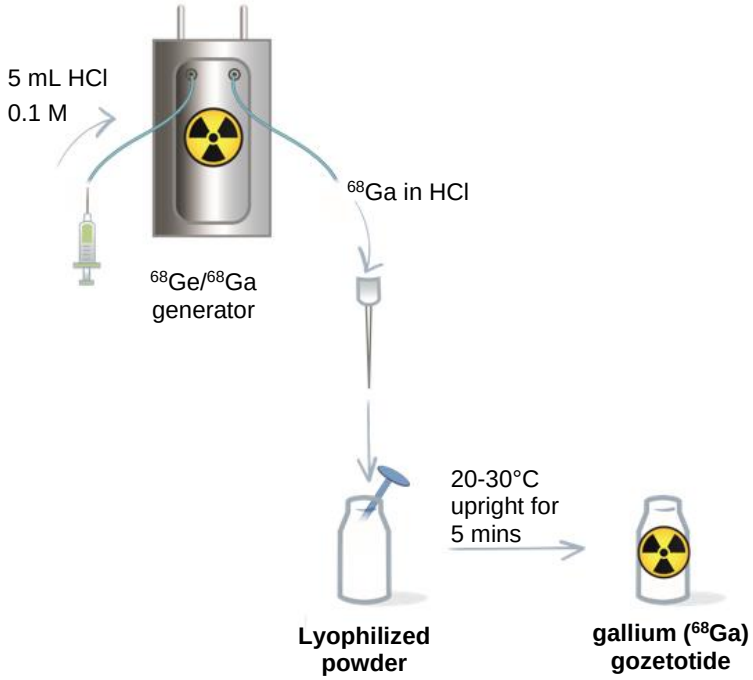
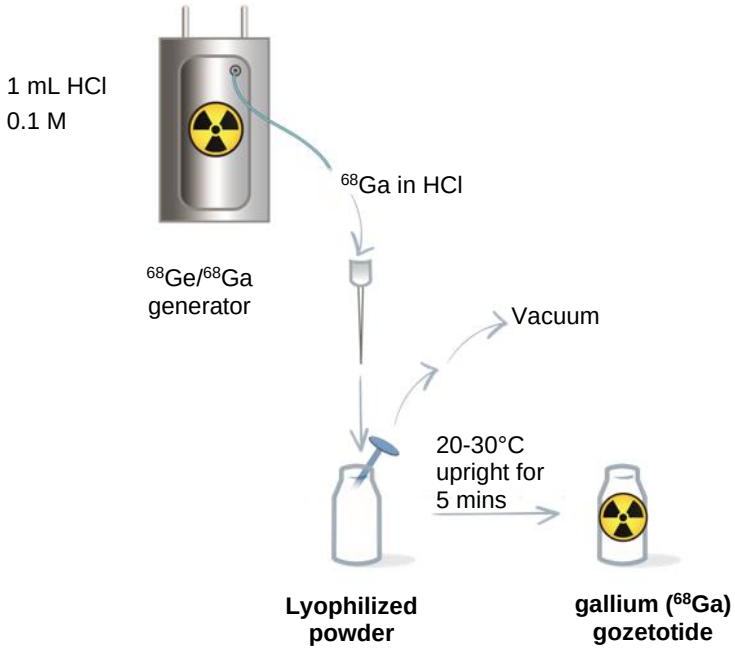


Figure 2 **Reconstitution procedure for IRE ELiT Galli Eo generator**



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 2 behind a lead glass shield for radioprotection purposes.

Table 2 - 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 gallium-68 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 4 DOSAGE 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 4 DOSAGE AND ADMINISTRATION).

c. After reconstitution, gallium (^{68}Ga) gozetotide solution for injection can be diluted with water for injection 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 4 DOSAGE 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 4 DOSAGE AND ADMINISTRATION).

4.8 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 3.

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 (7 mCi) are 64 mGy (kidneys), 25 mGy (salivary glands), 22 mGy (bladder wall), 10 mGy (lacrimal glands), 10 mGy (spleen) and 8 mGy (liver).

Table 3 - Estimated mean radiation absorbed doses of gallium (^{68}Ga) gozetotide

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
ORGAN	**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
Thyroid	0.0035	0.0004

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
ORGAN	**Mean**	**SEM**
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.
Reference: Demirci et al (2018)

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Kit for the preparation of gallium (^{68}Ga) gozetotide Vial contains: 25 mcg gozetotide	Vial contains: gentisic acid, sodium acetate trihydrate and sodium chloride

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 gallium (^{68}Ga) is not part of the kit and is obtained from one of the following generators:

- Eckert & Ziegler GalliaPharm germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator
- IRE ELiT Galli Eo germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator.

After radiolabelling with gallium-68, each vial contains a sterile, clear, colorless solution without undissolved matter of gallium Ga 68 gozetotide at an activity of up to 1369 MBq (37 mCi) in up to 10 mL at calibration date and time.

6.1 Physical Characteristics

Gallium-68 decays with a half-life of 68 minutes to stable zinc-68 (^{68}Zn).

The principal radiation emission data, radiation attenuation by lead shielding, and physical decay of

gallium-68 are shown in Table 5, Table 6 and Table 7.

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.

Table 5 – Principal Radiation Emission Properties (>1%) of Gallium (^{68}Ga)

Radiation/Emission	% Disintegration	Mean Energy (keV)
beta+	88%	836
beta+	1.1%	353
Gamma	178%	511
Gamma	3%	1077
X-ray	2.8%	8.6
X-ray	1.4%	8.6

6.2 External Radiation

Shielding lead [Pb]:

Half value layer [HVL]: 6 mm (0.24 in).

Tenth value layer [TVL]: 17 mm (0.67 in).

Table 6 – 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 7 – Physical Decay Chart for Gallium-68

Minutes	Fraction Remaining
0	1.000
15	0.858
30	0.736
60	0.541

Minutes	Fraction Remaining
90	0.398
120	0.293
180	0.158
360	0.025

7 WARNINGS AND PRECAUTIONS

General

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

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

Contamination

Proper radiopharmaceutical practices should be used to minimize radioactive contamination. Following administration, a toilet should be used instead of a urinal and the toilet should be flushed several times after use.

Special precautions such as bladder catheterisation should be taken following administration to incontinent patients to minimise the risk of radioactive contamination of clothing, bed linen and the patient's environment.

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 4 DOSAGE AND ADMINISTRATION and 4.7 Instructions for Preparation and Use).

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 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

- **Fertility**

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

Risk for Image 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 (such as breast cancer, hepatocellular carcinoma, renal cell carcinoma, lung cancer, brain tumors), non-malignant processes (such as Paget's disease, fibrous dysplasia, and osteophytosis) and normal tissues (see 10.3 Pharmacokinetics).

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

7.1 Special Populations

7.1.1 Pregnant Women

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 available data with gallium (^{68}Ga) gozetotide in pregnant women to inform about a drug-related risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with gallium (^{68}Ga) gozetotide. All radiopharmaceuticals, including gallium (^{68}Ga) gozetotide, have the potential to cause fetal harm.

7.1.2 Breast-feeding

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 infant, or the effect on milk production.

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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. Similar data were observed between patients who were 65 years or older and those younger than 65 years in the ProPSMA and PSMA-BCR studies.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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). 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 common adverse drug reaction of any grade (incidence ≥ 1%) is fatigue (1.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of LOCAMETZ has been established based on studies of another formulation of gallium (^{68}Ga) gozetotide in patients with prostate cancer (see 14 CLINICAL TRIALS).

The adverse drug reactions of any grade in patients receiving gallium (^{68}Ga) gozetotide are shown in Table 8.

Table 8 - Adverse drug reactions (≥ 1.0%) observed with gallium (^{68}Ga) gozetotide in the VISION clinical study

Adverse drug reaction	**Gallium (^{68}Ga) gozetotide 0.9-3.7 MBq/kg N=1003 n (%)** **All grades**
General disorders and administration site conditions	
Fatigue	12 (1.2)

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions (< 1.0%) were observed with gallium (^{68}Ga) gozetotide in the VISION clinical study:

Gastrointestinal disorders: nausea, constipation, vomiting, diarrhea, dry mouth

General disorders and administration site conditions: injection site reactions[1], chills

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

8.5 Post-Market Adverse Reactions

No post-marketing adverse drug reactions have been identified to date.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

***In vitro* evaluation of drug interaction potential**

CYP450 enzymes

Gozetotide is not a substrate of cytochrome P450 (CYP450) enzymes, and not an inhibitor of CYP450 isoforms (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) nor an inducer of CYP 1A2, 2B6 and 3A4.

Transporters

Gozetotide is not a substrate of MATE1, MATE2-K, OAT1, OAT3 or OCT2. Gozetotide is not an inhibitor of BCRP, BSEP, MDR1/P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted. Based on *in vitro* interaction studies, gallium (^{68}Ga) gozetotide is not expected to have any clinically significant interaction with other medications (see 10 CLINICAL PHARMACOLOGY).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

At the chemical concentrations used for diagnostic examinations, gallium (^{68}Ga) gozetotide does not have any pharmacodynamic activity. The relationship between gallium (^{68}Ga) gozetotide plasma concentrations and successful imaging was not explored in clinical trials.

10.3 Pharmacokinetics

Absorption

Gallium (^{68}Ga) gozetotide is administered intravenously; thus it is immediately and completely bioavailable.

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. The organs with the highest radiation absorbed doses are kidneys, salivary glands, bladder wall, lacrimal glands, spleen, and liver.

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.

Special Populations and Conditions

- **Hepatic Insufficiency:** The effect of hepatic impairment on gallium (^{68}Ga) gozetotide pharmacokinetics has not been established. Hepatic impairment is not expected to affect gallium (^{68}Ga) gozetotide pharmacokinetics to any clinically relevant extent.
- **Renal Insufficiency:** The effect of renal impairment on gallium (^{68}Ga) gozetotide pharmacokinetics has not been established. Renal impairment is not expected to affect Gallium (^{68}Ga) gozetotide pharmacokinetics to any clinically relevant extent.

11 STORAGE, STABILITY AND DISPOSAL

Do not use the kit beyond the expiration date stamped on the box.

Special precautions for storage

Before reconstitution, store below 25°C.

After reconstitution, store upright below 30°C.

After reconstitution, use within 6 hours.

The storage of the radiolabeled product must comply with regulatory requirements for radioactive materials.

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.

Incompatibilities

This product must not be mixed with medicinal products other than those mentioned in the Instructions for use and handling (see 4.7 Instructions for Preparation and Use).

12 SPECIAL HANDLING INSTRUCTIONS

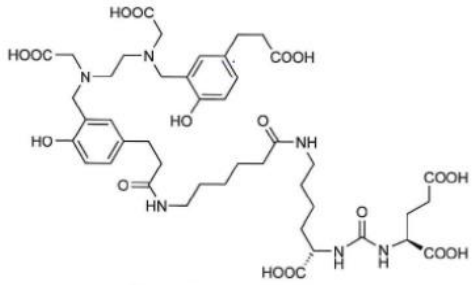
After reconstitution and radiolabeling, gallium (^{68}Ga) gozetotide solution for injection should be handled with appropriate safety measures to minimize radiation exposure. Waterproof gloves, effective radiation shielding and other appropriate safety measures should be used when preparing and handling gallium (^{68}Ga) gozetotide solution in order to avoid unnecessary radiation exposure to the occupational workers, clinical personnel, and other persons (see 4.7 Instructions for Preparation and Use).

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, and whose experience and training have been approved by the governmental agency authorized to license the use of radionuclides.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	gozetotide
Chemical name:	OH-Glu-CO-Lys(Ahx-CC-HBED)-OH
Molecular formula and molecular mass:	$C_{44}H_{62}N_6O_{17}$ x CF_3CO_2H, 947.0 g/mol
Structural formula:	
Physicochemical properties:	White to slightly colored powder. 1 mg lyophilisate soluble in 1 mL 10% CH_3CN/ 90% water. (-20 ± 5)°C.

Product Characteristics:

LOCAMETZ is supplied as a multi-dose kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). After reconstitution, effective radiation shielding of the gallium (^{68}Ga) gozetotide solution for injection should be maintained (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The efficacy of LOCAMETZ is based on two published studies and a prospective VISION trial to identify PSMA-positive lesions in mCRPC patients. These studies used another gallium(^{68}Ga) gozetotide formulation containing comparable amount of gallium (^{68}Ga) gozetotide in patients with prostate cancer. Below is a summary of the results of two prospective, open-label studies published in peer-reviewed journals (ProPSMA and PSMA-BCR), and VISION trial.

Imaging Prior to Initial Definitive Therapy

ProPSMA

A total of 302 men were randomly assigned, 152 (50%) men were assigned to conventional imaging and 150 (50%) to gallium (^{68}Ga) gozetotide PET/CT. Of 295 (98%) men with follow-up, 87 (30%) had pelvic nodal or distant metastatic disease. Participants were adult male with untreated, biopsy-proven high-risk prostate cancer who were considered for prostatectomy or radiotherapy. All enrolled patients must have met one of the following inclusion criteria: PSA ≥ 20.0 ng/ml within 12 weeks prior to randomisation, Gleason grade group ≥ 3, or clinical stage ≥ T3. Patients underwent upper thighs to base-of-skull gallium (^{68}Ga) gozetotide PET/CT (N=148) or whole-body bone scan and abdomen and pelvis CT imaging (N=152). Patients were males of median age 70 years (interquartile range: 64 to 74 years). 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 central blinded readers. Gallium (^{68}Ga) gozetotide PET/CT had a 27% (95% CI 23–31) greater accuracy than that of conventional imaging (92% [88–95] vs 65% [60–69]; p<0·0001). Gallium (^{68}Ga) gozetotide PET/CT had improved sensitivity and specificity compared to CT and bone scan imaging, as summarized in Table 9.

Table 9 - Efficacy results in patients with untreated, biopsy-proven prostate cancer

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

CI: Confidence interval

[1]Evaluable population

The observed radiation exposure from gallium (^{68}Ga) gozetotide PET/CT was 8.4 mSv and was 19.2 mSv for CT and bone scan imaging.

Imaging Prior to Suspected Recurrence Therapy

PSMA-BCR

A total of 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. Three members of a pool of nine independent central readers evaluated each PET/CT scan for the presence of abnormal gallium (^{68}Ga) gozetotide uptake suggestive of recurrent prostate cancer. The readers were 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. The efficacy cohorts were 223 patients with composite reference standard and 93 patients with histopathologic reference standard. Composite reference standard information collected in a PET positive region (evaluable patients), consisting of at least one of the following: histopathology, imaging (bone scintigraphy, CT, or MRI) acquired at baseline or within 12 months after gallium (^{68}Ga) gozetotide PET, or serum PSA levels. Composite reference standard information for gallium (^{68}Ga) gozetotide PET negative regions was not systematically collected in this study.

The primary endpoint was positive predictive value (PPV) on a per-patient and per-region basis for detection of tumor confirmed by histopathologic reference standard. A secondary endpoint included PPV on a per-patient and per-region basis using a composite reference standard. Results are summarized in Table 10.

Table 10 - 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)	ND	92% (84, 96)
Sensitivity per-region (95% CI)	ND	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

ND: Not Determined

Imaging for Identification of mCRPC for PSMA-targeted Therapy

VISION

Gallium (^{68}Ga) gozetotide was used to identify patients with progressive PSMA-positive metastatic castration resistant prostate cancer (mCRPC) for the randomized, multicentre, open-label, phase III study, VISION, which established the efficacy of PSMA-targeted therapy (lutetium (^{177}Lu) vipivotide tetraxetan) plus best standard of care (N = 551) or best standard of care (N = 280). Only patients with PSMA-positive lesions were eligible for randomization and receipt of lutetium (^{177}Lu) vipivotide tetraxetan. A total of 1003 adult male patients with mCRPC received gallium (^{68}Ga) gozetotide by intravenous administration and underwent PET imaging at approximately 60 minutes (range, 50 to 100 minutes) after injection. Gallium (^{68}Ga) gozetotide PET imaging was interpreted in conjunction with contrast-enhanced CT and/or MRI of the chest, abdomen, and pelvis for all patients. Patients were

males of median age 71 years (range, 40 to 94 years), White (87%), Black or African American (7%) and Asian (2.4%), and had median baseline PSA levels of 76 ng/mL (range, 0 to 8995 ng/mL). Gallium (^{68}Ga) gozetotide PET and anatomical imaging was interpreted by one central reader who was blinded to clinical information and other PET and bone imaging. Of the patients evaluated by the central reader, 869 (86.6%) were found to be PSMA-positive (eligible) and 126 (12.6%) were found to be PSMA-negative (ineligible) for PSMA-targeted therapy.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Single-dose toxicity

In a two-week single-dose toxicity study, gozetotide was administered to male and female rats at the doses of 0.67 and 1.33 mg/kg by intravenous injection. Gozetotide was well tolerated and the 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, Genotoxicity, and Reproductive and Developmental Toxicology

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether LOCAMETZ affects fertility in males or females.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

For information on reproductive toxicity, see 7.1 SPECIAL POPULATIONS.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

LOCAMETZ™

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

Read this carefully before you start taking **LOCAMETZ™**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LOCAMETZ**.

Serious Warnings and Precautions

- Because gallium (^{68}Ga) gozetotide solution for injection is a radiopharmaceutical (radioactive substance), it can only be given by doctors and other health professionals who are specially trained and experienced in the safe use and handling of these substances.

What is LOCAMETZ used for?

This medicine is a radiopharmaceutical product for diagnostic use only.

LOCAMETZ contains gozetotide. Before use, the powder in the vial is mixed with a radioactive substance called gallium-68 to make gallium (^{68}Ga) gozetotide solution (this procedure is called radiolabeling).

- After radiolabeling, gallium (^{68}Ga) gozetotide is used in adult patients to identify prostate cancer lesions expressing a protein called prostate-specific membrane antigen (PSMA).

How does LOCAMETZ work?

By binding to cells that express PSMA, gallium (^{68}Ga) gozetotide makes these parts of the body visible to doctors during a medical imaging procedure called positron emission tomography (PET). PET allows your doctor to obtain images of your organs to help locate abnormal cells or tumors giving valuable information about your disease.

The use of LOCAMETZ involves exposure to a small amount of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

If you have any questions about how LOCAMETZ works or why this medicine has been prescribed for you, ask your nuclear medicine doctor.

What are the ingredients in LOCAMETZ?

Medicinal ingredient: gozetotide. One vial contains 25 micrograms of gozetotide.

Non-medicinal ingredients: gentisic acid, sodium acetate trihydrate and sodium chloride.

LOCAMETZ comes in the following dosage forms:

Kit for radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection, 25 micrograms.

Do not use LOCAMETZ if:

- If you are allergic to gallium (^{68}Ga) gozetotide or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LOCAMETZ. Talk about any health conditions or problems you may have, including if you:

- If you have any other type of cancer or any other non-malignant condition as these could affect the interpretation of the image;
- Have signs of dehydration (feeling very thirsty) before or after the examination;
- Have any other medical condition as these could affect the interpretation of the image.

Other warnings you should know about:

The use of LOCAMETZ involves exposure to a small amount of radioactivity. Long-term cumulative radiation exposure contributes to an increased risk of cancer. Your nuclear medicine doctor will explain the necessary radioprotection measures to you (see How to take LOCAMETZ).

Before administration of LOCAMETZ you should:

Drink plenty of water in order to urinate immediately before and as often as possible during the first hours after the examination, in order to eliminate the product from your body.

Children and adolescents (below 18 years)

The safety and efficacy of this medicine have not been established in children and adolescents under 18 years of age.

Older people (65 years of age or above)

You can use LOCAMETZ if you are aged 65 years or over at the same dose as for other adults.

Pregnancy and breast-feeding

LOCAMETZ is not indicated for use in women. All radiopharmaceuticals, including LOCAMETZ, have the potential to cause harm to an unborn baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LOCAMETZ:

- There is no information available about the use of LOCAMETZ in combination with other medicines.

How to take LOCAMETZ:

- There are strict laws on the use, handling and disposal of radiopharmaceutical products. LOCAMETZ will only be used in special controlled areas. This medicine will only be handled and given to you by healthcare professionals who are trained and qualified to use it safely. They will take special care for the safe use of this medicine and will keep you informed of their actions.

Usual dose:

The nuclear medicine doctor supervising the procedure will decide on the quantity of LOCAMETZ to be used in your case. It will be the smallest quantity necessary to get the desired information.

The recommended dose for an adult is 1.8 to 2.2 MBq/kg of body weight, ranging from a minimum quantity of 111 MBq up to a maximum quantity of 259 MBq (MBq, megabecquerel, the unit used to express radioactivity).

Administration of LOCAMETZ and conduct of procedure

After radiolabeling, LOCAMETZ is administered by slow intravenous injection. One injection is sufficient to conduct the test that your nuclear medicine doctor needs.

Duration of the procedure

Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of LOCAMETZ

Drink plenty of water to urinate frequently during the first hours after the examination in order to eliminate the product from your body.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

Overdose:

An overdose is unlikely because you will only receive a single dose of LOCAMETZ precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. You may be asked to drink and urinate frequently, in order to eliminate the product from your body.

If you have any further questions on the use of LOCAMETZ, ask the nuclear medicine doctor who supervises the procedure.

What are possible side effects from using LOCAMETZ?

These are not all the possible side effects you may have when taking LOCAMETZ. If you experience any side effects not listed here, tell your healthcare professional.

LOCAMETZ will deliver low amounts of ionizing radiation associated with the least risk of cancer and hereditary abnormalities.

Common: *may affect up to 1 in every 10 people*

- tiredness (fatigue)

Uncommon: *may affect up to 1 in every 100 people*

- nausea
- constipation
- vomiting
- diarrhea
- dry mouth
- a reaction at the site where an injection was given, which may cause some redness, swelling and warmth (injection site reactions)
- chills

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in the hospital. Storage of radiopharmaceuticals are in accordance with national regulations on radioactive materials.

If you want more information about LOCAMETZ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.novartis.ca) or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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LOCAMETZ is a trademark.