PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ILLUCCIX™

Powder for Solution, 25 microgram gozetotide per vial, for Intravenous use
Kit for the preparation of gallium (^{68}Ga) gozetotide solution for injection

Diagnostic Radiopharmaceutical Kit

Manufactured by:

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Imported and Distributed by:

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	09/2024

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

- with suspected metastasis who are suitable 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 and reviewed by Health Canada Illuccix has been extensively studied in men 65 years of age or older. No clinically relevant differences in safety and efficacy were observed between patients ≥65 years and younger patients.

2 CONTRAINDICATIONS

Illuccix 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 the administration of Illuccix and should be encouraged to void immediately before imaging and frequently during the first hours after image acquisition to reduce radiation exposure.

The co-administration of diuretics (*e.g.,* furosemide 20 mg) may improve image quality by reducing background activity in the urinary system. Furosemide should not be administered in patients with contraindications to furosemide including allergies (e.g. sulfa allergies).

4.2 Recommended Dose and Dosage Adjustment

The recommended Illuccix radioactivity dose in adults is 111 to 259 MBq (3 to 7 mCi) as a slow intravenous bolus 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

Reaction vial 1 containing the sterile, non-pyrogenic, lyophilized powder of gozetotide is reconstituted with 2.5 mL or 6.4 mL of sodium acetate in hydrochloric acid (HCl, vial 2). Then the reconstituted powder is added to a volume of gallium (^{68}Ga) chloride (vial 3) depending on the generator type/cyclotron (see 4.7 Instructions for Preparation and Use and 11 STORAGE, STABLITY and DISPOSAL).

4.4 Administration

Gallium (^{68}Ga) gozetotide is to be administered by slow intravenous bolus injection followed by intravenous flush of sterile 0.9% sodium chloride injection to ensure full administration of the dose.

Prior to injection, measure the radioactivity of the vial containing the gallium (^{68}Ga) gozetotide injection with a dose calibrator. Ensure that the injected radioactivity is within ± 10% of the recommended dose.

4.6 Image Acquisition and Interpretation

Image Acquisition

The patient should be positioned with both arms elevated above the head. Begin PET imaging 50 – 100 minutes after intravenous administration of Illuccix injection. Patients should void immediately prior to image acquisition and image acquisition should start from mid-thigh to the base of skull or skull vertex. Adapt imaging technique according to scanner used and patient characteristics to acquire the best image quality possible.

Image Interpretation

Gallium (^{68}Ga) gozetotide binds to prostate-specific membrane antigen (PSMA). The intensity of the PET signal obtained using gallium (^{68}Ga) gozetotide indicates the presence of PSMA in tissues.

Imaging interpretation prior to initial definitive therapy or suspected recurrence

Focal lesion 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, kidney, urinary bladder, spleen, colon, small intestine, lacrimal gland, parotid gland, and submandibular gland. Minimal uptake is normally seen in tissues where prostate cancer metastases are known to occur: retroperitoneal fatty tissue, lymphatic system, and bone. Increased uptake in tumors is not specific for prostate cancer (see 7 WARNINGS AND PRECAUTIONS).

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

The preparation of gallium (^{68}Ga) gozetotide injection may be accomplished by the following procedure.

- Waterproof gloves are to be worn during the preparation and elution processes.

- Aseptic techniques should be employed throughout the preparation and elution processes.
- Make all transfers of radioactive solutions with an adequately shielded 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 to slightly yellow and without visible particles should be used.
- Use a 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.

Kit components

Illuccix is supplied as 3 vials in two different configuration for preparation of gallium (^{68}Ga) gozetotide injection with eluate from one of the following:

- Cyclotron produced $^{68}GaCl_3$ (Configuration A)
- GalliaPharm® Germanium 68/Gallium 68 (^{68}Ge/^{68}Ga) generator (Configuration A)
- Galli Eo® ^{68}Ge/^{68}Ga generator (Configuration B)

The ^{68}Ge/^{68}Ga generators and cyclotron are not supplied with Illuccix.

Components of Illuccix include:

- Vial 1 (blue cap, gozetotide) contains a lyophilized powder of 25 mcg of gozetotide and 10 mcg of D-mannose (stabilizer).
- Vial 2 (red-capped "2A" or green-capped "2B" vial, Sterile diluent Vial) contains the diluent of 150 mg of sodium acetate in HCl.
- Vial 3 (white cap, Sterile Evacuated Vial) is a sterile, evacuated vial that serves as the collection of $^{68}GaCl_3$ and radiolabeling reaction.

Vial 2 comes in two configurations: "A" and "B". Both provide a final labelling solution of 7.5 mL at a pH of 4-5, Table 1.

Table 1: Vial 2 Configurations A and B

	Configuration "A"	**Configuration "B"**
For use with	GalliaPharm generator Cyclotron/ASU*	Galli Eo generator
Anhydrous sodium acetate in vial 2 (mg)	150	150
HCl molarity in vial 2 (M)	0.292	0.175
HCl volume in vial 2 (mL)	2.5	6.4

Volume of $^{68}GaCl_3$ to be added to vial 3 (mL)	5.0	1.1
Final labelled solution volume (mL)	7.5	7.5

*ASU: automated synthesis unit

Preparation

- Place a “radioactive” label on Vial 3 (Sterile Evacuated Vial) with product name, lot number and date.
- Remove the vial cap from Vial 1, Vial 2 and Vial 3. Swab the top of each vial with alcohol to disinfect the surface and allow the top of each vial to dry.
- To minimize any potential metallic contamination, the shortest possible needle should be used for the transfer of the ^{68}Ga chloride ($^{68}GaCl_3$) solution. The needle should be clean and dilute acid resistant.
- Use only plastic syringes, resistant to dilute acid; syringes with rubber plungers should not be used.
- Prior to use of any vial, confirm the correct vial is being used by a visual check of the vial label.
- Follow the specific reconstitution procedure below, dependent on ^{68}Ga source. Then continue with the dilution and radiolabeling procedure below.

Step 1: Transfer of $^{68}GaCl_3$ solution from generator or ASU to Vial 3 by piercing Vial 3 (Sterile Evacuated Vial) with a sterile needle connected to 0.2 micron sterile vented filter (not supplied with the kit) to maintain atmospheric pressure within the vial during reconstitution procedure.

Following the $^{68}GaCl_3$ manufacturer's directions, transfer into the evacuated vial (Vial 3):

- 5.0 mL of $^{68}GaCl_3$ eluate from the GalliaPharm generator; or
- 5.0 mL of $^{68}GaCl_3$ solution from the Cyclotron/Automated Synthesis Unit; or
- 1.1 mL of $^{68}GaCl_3$ eluate from the Galli Eo generator.

If ^{68}Ga generator is used, the eluate should be tested for ^{68}Ge breakthrough after completion of conditioning by suitable method according to manufacturer recommendations. ^{68}Ge breakthrough should not be more than 0.001 % of the eluted ^{68}Ga activity.

Step 2: Reconstitution

- Insert a sterile 10 mL syringe with a needle into Vial 2 (Sterile diluent Vial) and draw up 2.5 mL or 6.4 mL (depending on the configuration) of the vial.
- Inject the contents of the 10 mL syringe into Vial 1 (gozetotide Vial).
- Gently swirl Vial 1 to ensure the product is thoroughly dissolved.
- Insert a sterile 10 mL syringe with a needle into Vial 1 containing the dissolved gozetotide and draw up the contents of the vial.

Step 3: Radiolabelling

- Transfer the contents of the 10 mL syringe to Vial 3 (Sterile Evacuated Vial) containing the ^{68}Ga chloride.
- Wait for 5 minutes for radiolabeling to take place at ambient temperature (25 °C; excursions permitted to 15 °C to 30 °C).
- Assay the whole vial containing the gallium (^{68}Ga) gozetotide Injection for total radioactivity using a dose calibrator, calculate the radioactivity concentration and record the result.
- Re-label vial 3 as appropriate with total radioactivity, total volume, the concentration of the radioactive material, and reference time.
- Perform the quality control of gallium (^{68}Ga) gozetotide injection according to the recommended methods below “4.7.4 Quality Control”.
- Prior to use, visually inspect the solution behind a shielded screen. Only use solutions that are clear without visible particles.
- Keep the vial containing the gallium (^{68}Ga) gozetotide injection upright in a radio-protective shield container at ambient temperature until use.
- After reconstitution and addition of ^{68}Ga chloride to the kit components in the reaction vial 3, use gallium (^{68}Ga) gozetotide Injection within 4 hours. The final volume of the gallium (^{68}Ga) gozetotide Injection is 7.5 mL.

Quality Control

Prior to use gallium (^{68}Ga) gozetotide must undergo quality control and meet the following specifications. Perform the quality controls in Table 2 behind a shielded screen.

Table 2: Specifications for the Radiolabeled Imaging Product [gallium (^{68}Ga) gozetotide Injection)

Test	Analytical method	Acceptance criteria
Appearance	Visual examination	Colorless to slightly yellow solution Free from visible particles
pH	pH-meter or pH-strips	4.0 to 5.0
Radiochemical purity	Instant thin-layer chromatography, silica gel (iTLC SG); See method below	
• Content of gallium (^{68}Ga) gozetotide		≥ 95%
• Content of free and colloidal ^{68}Ga		≤ 5%

Radiochemical purity test method

- Pour ammonium acetate 1M/methanol (1:1 V/V) solution to a depth of 3 to 4 mm in the developing chamber (e.g. 15 mL centrifuge tube), cover the chamber and allow it to equilibrate.
- Draw a pencil line at 1 cm from the bottom of the iTLC strip (11 cm in length) and place a dot 4 cm from the pencil line. Apply a drop of gallium (^{68}Ga) gozetotide at the center of the pencil line. Place a water-soluble ink dot at 1 cm below the top of iTLC strip to serve as an indicator for the end of the elution.

- Place the iTLC strip in the developing chamber for chromatography and allow it to develop for a distance of 10 cm from the point of application. Note the dotted gallium (^{68}Ga) gozetotide should not be submerged in the chamber solution.
- When the solvent front has climbed to the top of the strip, the smeared ink will serve as an indicator, remove it with forceps and allow it to dry.
- Cut the iTLC strip at the 4.0 cm dot and measure each piece with the radioactivity dose calibrator.
- Calculate the radiochemical purity using the formula:

$$\%\ gallium\ (^{68}Ga)\ PSMA\text{-}11 = \frac{Activity\ top\ piece}{Activity\ bottom\ piece + Activity\ top\ piece} \times 100$$

Radiochemical purity should be not less than 95%.

4.8 Radiation Dosimetry

Estimated radiation absorbed doses per injected activity for organs and tissues of adult male patients following an intravenous bolus of gallium (^{68}Ga) gozetotide Injection are shown in Table 3.

The effective radiation dose resulting from the administration of 259 MBq (7 mCi) is about 4.4 mSv. The radiation doses for this administered dose to the critical organs, which are the kidneys, urinary bladder, and spleen, are 96.2 mGy, 25.4 mGy, and 16.8 mGy, respectively.

These radiation doses are for gallium (^{68}Ga) gozetotide Injection alone. If CT or a transmission source are used for attenuation correction, the radiation dose will increase by an amount that varies by technique.

Table 3: Estimated Radiation Absorbed Dose per Injected Activity in Selected Organs and Tissues of Adults after Intravenous Administration of gallium (^{68}Ga) gozetotide Injection

	Mean radiation absorbed dose (mGy/MBq)	
Organ	**Mean**	**SD**
Adrenals	0.0156	0.0014
Brain	0.0104	0.0011
Breasts	0.0103	0.0011
Gallbladder	0.0157	0.0012
Lower Colon	0.0134	0.0009
Small Intestine	0.0140	0.0020
Stomach	0.0129	0.0008
Heart	0.0120	0.0009
Kidneys	0.3714	0.0922
Liver	0.0409	0.0076
Lungs	0.0111	0.0007
Muscle	0.0103	0.0003
Pancreas	0.0147	0.0009

Red Marrow	0.0114	0.0016
Skin	0.0091	0.0003
Spleen	0.0650	0.0180
Testes	0.0111	0.0006
Thymus	0.0105	0.0006
Thyroid	0.0104	0.0006
Urinary Bladder	0.0982	0.0286
Total Body	0.0143	0.0013
Effective Dose (mSv/MBq)	**0.0169**	**0.0015**

5 OVERDOSAGE

In case of overdose with Illuccix, the patient should be monitored and managed as clinically indicated. Reduce the radiation dose to the patient by increasing the elimination of the drug from the body by hydration and frequent bladder voiding. A diuretic may also be considered.

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 (68Ga) gozetotide Vial contains: 25 ± 2.5 mcg gozetotide	Powder for solution for injection: D-mannose Reconstitution solutions: hydrochloric acid, sodium acetate anhydrous, water for injections

Illuccix is supplied as a multi-dose kit for the preparation of gallium (^{68}Ga) gozetotide. The kit consists of:

- Vial 1 (gozetotide Vial): 25 ± 2.5 mcg gozetotide and 10 ± 1.0 mcg D-mannose (stabilizer) as lyophilized powder.
- Vial 2 (Sterile diluent): Diluent with two configurations (red-capped "2A" or green-capped "2B" vial):
    - Vial 2A in Configuration A contains 150 ± 1 mg anhydrous sodium acetate in 0.292 M HCl, total volume is 2.5 ± 0.05 mL.
    - Vial 2B in Configuration B contains 150 ± 1 mg anhydrous sodium acetate in 0.175 M HCl, total volume is 6.4 ± 0.05 mL.

- Vial 3 (Sterile Evacuated Vial): An evacuated vial (white-capped) for the collection of gallium (^{68}Ga) gozetotide and radiolabelling reaction.

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:

- Cyclotron produced $^{68}GaCl_3$
- Eckert & Ziegler GalliaPharm® Germanium 68/Gallium 68 (^{68}Ge/^{68}Ga) generator
- IRE ELiT Galli Eo® ^{68}Ge/^{68}Ga generator

After reconstitution, pH adjustment with acetate buffer, and radiolabelling with ^{68}Ga, Vial 3 is a multiple-dose vial containing up to 1850 MBq (50 mCi) in 7.5 mL of a sterile solution at a strength of up to 247 MBq (6.7 mCi) per mL.

6.1 Physical Characteristics

Illuccix is a 3-vial kit which contains non-radioactive ingredients required to produce radiolabeled gallium (^{68}Ga) gozetotide. The prepared gallium (^{68}Ga) gozetotide injection for intravenous use is a sterile, pyrogen free, clear, colorless to slightly yellow, buffered solution with a pH between 4.0-5.0.

6.2 External Radiation

^{68}Ga decays by positron (ß+) emission to stable ^{68}Zn with a half-life of 67.7 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons resulting from the interaction of the emitted positron with an electron (Table 5).

Table 5: Principal Radiation Emission for ^{68}Ga

Radiation	Mean Energy Level (keV)	% Disintegration
Positron	836	87.7
Gamma	511	177.8

To correct for physical decay of ^{68}Ga radionuclide, the percent that remain at selected intervals after calibration are shown in Table 6.

Table 6: Physical Decay Chart for ^{68}Ga

Minutes	Percent remaining	Minutes	Percent remaining
30	73.6	210	11.6
60	54.1	240	8.6
90	39.8	270	6.3
120	29.3	300	4.6
150	21.5	330	3.4
180	15.8	360	2.5

The first half-value thickness of lead for ^{68}Ga gamma rays is approximately 6 mm. The relative reduction of radiation emitted by ^{68}Ga that results from various thicknesses of lead shielding is shown in Table 7.

Table 7: Radiation Attenuation of 511 keV by Lead (Pb) Shielding

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

7 WARNINGS AND PRECAUTIONS

General

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.

The contents of the kit are intended ONLY for use in the preparation of gallium (^{68}Ga) gozetotide injection and is NOT to be administered directly to the patient.

The contents of the reaction vial before preparation are not radioactive. However, after the ^{68}Ga chloride is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

The components of the kit are sterile and non-pyrogenic. Aseptic procedures employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the ^{68}Ga chloride and the withdrawal of doses for patient administration.

After radiolabelling with ^{68}Ga chloride, the solution may be stored at ambient room temperature in a suitable lead shield.

Carcinogenesis and Mutagenesis

No long-term animal studies were performed to evaluate the carcinogenicity potential of gallium (^{68}Ga) gozetotide. Mutagenesis studies have not been conducted.

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 exposure

Gallium (^{68}Ga) gozetotide contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Encourage patients to drink fluids and bladder void as frequently as possible after intravenous administration.

Reproductive Health: Female and Male Potential

Studies have not been performed to evaluate whether gallium (^{68}Ga) gozetotide injection has an effect on fertility in males or females.

Risk for Image Misinterpretation

Image interpretation errors can occur with gallium (^{68}Ga) gozetotide PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of gallium (^{68}Ga) gozetotide for imaging of biochemically recurrent prostate cancer seems to be affected by serum PSA levels and by site of disease (see 14 CLINICAL TRIALS). The performance of gallium (^{68}Ga) gozetotide for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by node size (see 14 CLINICAL TRIALS).

Due to high background activity in the liver, liver metastases can be obscured. In advanced disease, especially liver metastases, tumors may lose PSMA-expression due to de-differentiation. In these cases, the diagnostic CT scan should be the mainstay for detection of metastases. As gallium (^{68}Ga) gozetotide undergoes renal excretion and accumulates in the urinary bladder, small local recurrences might be missed. It is therefore especially important to evaluate PET images in axial as well as coronal and sagittal planes and to change the SUV-threshold to judge the gallium (^{68}Ga) gozetotide uptake in soft-tissue structures near the urinary bladder.

PSMA is expressed in neovasculature endothelial cells (NECs) of various solid tumors (*e.g.,* breast, lung, and urothelial cancer). Gallium (^{68}Ga) gozetotide uptake has been reported in glioblastoma, hepatocellular carcinoma, renal cell carcinoma and thyroid cancer. Gallium (^{68}Ga) gozetotide uptake has also been reported in benign lesions such as thyroid adenoma, Paget's disease, schwannoma, tuberculosis, adrenal adenoma, or splenic sarcoidosis. Coeliac ganglia show gallium (^{68}Ga) gozetotide uptake which may mimic lymph node metastases in this area.

7.1 Special Populations

7.1.1 Pregnant Women

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

Illuccix is not indicated for use in females. There are no available data on gallium (^{68}Ga) gozetotide injection use in pregnant women to assess drug-associated risks of birth defect, miscarriage, or adverse maternal or fetal outcomes. All radiopharmaceuticals, including Illuccix, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose.

7.1.2 Breast-feeding

Illuccix 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.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Based on the data submitted and reviewed by Health Canada Illuccix has been extensively studied in men 65 years of age or older. In the VISION clinical study, 752 of 1003 (75%) patients were 65 years of age and older. No clinically relevant differences in efficacy and safety were observed between patients ≥65 years and those younger than 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of gallium (^{68}Ga) gozetotide was assessed in published literature. Patients were monitored up to 2 hours after injection, and 1 to 3 days by phone call to evaluate for delayed adverse events. No serious adverse reactions were identified in these studies.

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

The safety of gallium (^{68}Ga) gozetotide was evaluated in 960 patients, each receiving one dose of gallium (^{68}Ga) gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium (^{68}Ga) gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

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

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, can result in changes in uptake of gallium (^{68}Ga) gozetotide in prostate cancer. The impact of these therapies on performance of gallium (^{68}Ga) gozetotide PET has not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Gallium (^{68}Ga) gozetotide binds to the prostate specific membrane antigen (PSMA), including malignant prostate cancer with increased expression in poorly differentiated, metastatic, and hormone-refractory carcinomas. ^{68}Ga is a β+ emitting radionuclide that allows imaging via positron emission tomography (PET).

10.2 Pharmacodynamics

No pharmacodynamic studies in humans were identified. This product is administered at microdose levels and is not intended to elicit any pharmacological effects. 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

Intravenously injected gallium (^{68}Ga) gozetotide is cleared from the blood and is accumulated preferentially in the liver (15%), kidneys (7%), spleen (2%), and salivary glands (0.5%). Gallium (^{68}Ga) gozetotide uptake is also seen in the adrenals and prostate. There is no uptake in the cerebral cortex or in the heart, and usually lung uptake is low.

Metabolism

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

Elimination

A total of 43% of the injected dose is excreted in the urine in the first 3 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

Studies on the pharmacokinetics of gallium (^{68}Ga) gozetotide in special populations have not been conducted.

- **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

Store Illuccix refrigerated at 5 ± 3 °C. Do not freeze.

After radiolabeling, keep gallium (^{68}Ga) gozetotide injection upright with appropriate shielding to protect from radiation at ambient temperature 25 °C; excursions permitted to 15 °C to 30 °C.

Illuccix is meant to be radiolabelled immediately after reconstitution. Do not store the reconstituted solution prior to labelling.

Reconstituted and radiolabelled Illuccix should be injected within 4 hours of preparation.

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.

12 SPECIAL HANDLING INSTRUCTIONS

Radiopharmaceuticals should be used only by healthcare professionals who are qualified by specific training and experience in the safe use and handling of radionuclide, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radionuclides. The receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent organization.

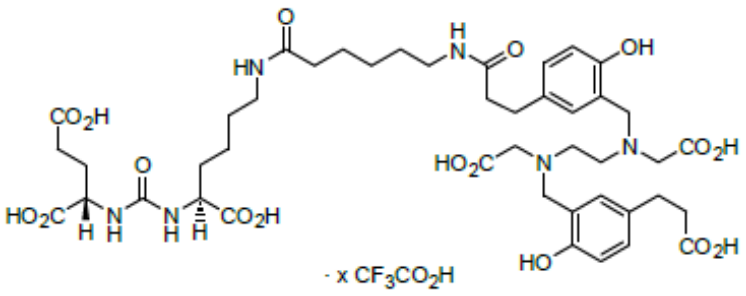
As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug substance

Proper name:	Gozetotide
Chemical name:	4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxy-ethyl)-2-hydroxyphenyl]-methyl]-(carboxymethyl) amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- Gozetotide peptide sequence is Glu-NH-CO-NH-Lys(Ahx), (Ahx = 6-aminohexanoic acid)
Molecular formula:	$C_{44}H_{62}N_6O_{17} \bullet CF_3CO_2H$
Molecular mass:	947.0 g/mol (net peptide)
Structural formula:	



Physicochemical properties: ILLUCCIX™ is a white to off-white amorphous freeze-dried powder, free of any visible contamination.

Product Characteristics

Illuccix, a radioactive diagnostic agent, is supplied as a sterile, multiple-dose kit for the preparation of gallium (^{68}Ga) gozetotide injection for intravenous use. Gallium (^{68}Ga) gozetotide is a radioconjugate composed of a human prostate specific membrane antigen (PSMA)-targeting ligand peptide conjugated via the acyclic radiometal chelator, N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC) to the radioisotope gallium (^{68}Ga).

Illuccix is supplied as a 3-vial kit which contains the non-radioactive ingredients needed to produce gallium (^{68}Ga) gozetotide solution for injection. There are two configurations available to allow preparation of gallium (^{68}Ga) gozetotide solution for injection using ^{68}Ga from different generator or cyclotron sources. The prepared gallium (^{68}Ga) gozetotide solution for injection for intravenous use is a sterile, pyrogen free, clear, colorless to slightly yellow, buffered solution with a pH between 4.0 to 5.0.

14 CLINICAL TRIALS

The safety and efficacy of Illuccix is based on two published studies containing the same amount of gallium (^{68}Ga) gozetotide in patients with prostate cancer. Below is a summary of the results of these two prospective, open-label studies published in peer-reviewed journals: PSMA-PreP and PSMA-BCR.

Imaging Prior to Initial Definitive Therapy

PSMA-PreP

This two-center study enrolled 764 patients with intermediate- to high-risk prostate cancer who were considered candidates for prostatectomy and pelvic lymph node dissection. All enrolled patients met at least one of the following criteria: serum prostate-specific antigen (PSA) of at least 10 ng/mL, tumor stage cT2b or greater, or Gleason score greater than 6. Each patient received a single gallium (^{68}Ga) gozetotide PET/CT or PET/MR from mid-thigh to skull base.

A total of 277 patients subsequently underwent prostatectomy and pelvic lymph node dissection and had sufficient histopathology data for evaluation. The remaining 487 patients either underwent other treatments (n=379) or were lost to follow up (n=108). Three members of a pool of six central readers independently interpreted each PET scan for the presence of gallium (^{68}Ga) gozetotide uptake in pelvic lymph nodes located in the common iliac, external iliac, internal iliac, and obturator subregions bilaterally as well as in any other pelvic location. The readers were blinded to all clinical information except for the history of prostate cancer prior to definitive treatment. Extrapelvic sites and the prostate gland itself were not analyzed in this study. For each patient, gallium (^{68}Ga) gozetotide PET results and reference standard histopathology obtained from dissected pelvic lymph nodes were compared by region (left hemipelvis, right hemipelvis, and other). For the 277 evaluable patients, the median age was 67 years (range 61 to 71 years), and 89% were white. The median serum PSA was 11.1 ng/mL. The summed Gleason score was 6-7 for 42%, and 8-10 for 58%.

Table 9 shows patient-level diagnostic performance of gallium (^{68}Ga) gozetotide for pelvic nodal metastases. Disease prevalence was 27% (75/277).

Table 9: Diagnostic performance of gallium (^{68}Ga) gozetotide PET for detection of pelvic lymph node metastasis in the PSMA-PreP Study (n=277) per patient-level

Parameter*	Result
True positive (n)	30
False positive (n)	10
True negative (n)	192
False negative (n)	45
Sensitivity (mean [$CI_{95\%}$])	40% [34, 46]
Specificity (mean [$CI_{95\%}$])	95% [92, 97]
PPV (mean [$CI_{95\%}$])	75% [70, 80]
NPV (mean [$CI_{95\%}$])	82% [76, 86]

*PPV: positive predictive value, NPV: negative predictive value, $CI_{95\%}$: 95 % confidence interval

Sensitivity (59%, [41, 75], N=27) was higher in detecting the larger-than-10-mm pelvic lymph node metastasis than in detecting the smaller-than-10-mm pelvic lymph node metastasis (29%, [18, 43], N=48). True-positive and false negative pelvic lymph node metastasis measured an average of 11 mm and 6 mm, respectively.

Imaging Prior to Suspected Recurrence Therapy

PSMA-BCR

This two-center study enrolled 635 patients with biochemically recurrent (BCR) prostate cancer after definitive therapy, 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 received a single dose of 185 MBq of gallium (^{68}Ga) gozetotide followed by PET/CT or PET/MRI from mid-thigh to skull base. Three members of a pool of nine independent central readers evaluated each scan for the presence and regional location of gallium (^{68}Ga) gozetotide uptake suggestive of recurrent prostate cancer. The readers were blinded to all clinical information other than type of primary therapy and most recent serum PSA level.

Of 635 patients, 269 (42%) were followed for a median duration of 9 months. Of the 635 patients, 114 (18%) had histopathologic follow-up. Forty-six of 269 patients (17%) were excluded from efficacy analysis based on PET vs follow-up location mismatch or absence of prostate cancer both on PET and histopathologic analysis. Thus, efficacy cohorts were 223 patients with composite validation and 93 patients with histopathologic validation.

In the 223 evaluable patients, the mean age was 70 years (range 49 to 88 years). The median serum PSA was 3.7 ng/mL. Prior treatment included radical prostatectomy in 26% and radiotherapy in 41% or both in 33% of patients.

The primary endpoint was positive predictive value (PPV) on a per-patient and per-region basis for detection of tumor confirmed by histopathologic analysis. Secondary endpoints included PPV using a composite reference standard of follow-up imaging and PSA response to treatment (Table 10). The overall detection rate was 75%. Detection rate increased significantly as PSA level increased.

Table 10: Positive predictive value of gallium (^{68}Ga) gozetotide PET in the PSMA-BCR Study (n=316) per patient-level and per region-level

Parameter*	Histology		Composite	
	Patient-basis	Region-basis	Patient-basis	Region-basis
True Positive	73	76	200	229
False Positive	14	14	17	20
PPV (mean [$CI_{95\%}$])	84% [75, 90]	84% [76, 91]	92% [88, 95]	92% [88, 95]
Sensitivity (mean [$CI_{95\%}$])	92% [84, 96]	90% [82, 95]		

* PPV: positive predictive value; $CI_{95\%}$: 95 % confidence interval

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

Fifteen male and fifteen female rats were given an intravenous dose of 86 µg/kg of gozetotide. Animals were sacrificed at 24 hours and 14 days after injection. There were no signs of acute intoxication.

Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicology
No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether Illuccix 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

ILLUCCIX™

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

Read this carefully before you start taking Illuccix. 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 Illuccix.

Serious warnings and precautions

Because Illuccix is a 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 Illuccix used for?

Illuccix is a kit used to prepare the radiopharmaceutical product gallium (^{68}Ga) gozetotide injection, which is used with positron emission tomography (PET) for the detection of prostate-specific membrane antigen (PSMA) positive prostate cancer.

How does it work?

After attaching a radioactive atom to Illuccix, the product travels in the blood and accumulates in prostate lesions that have increased expression of PSMA. The radioactive atom is called gallium-68 which allows the visualization of PSMA-positive prostate tumors via an imaging procedure called positron emission tomography (PET).

The use of Illuccix involves exposure to small amount of radioactivity. Your doctor and the nuclear medicine doctor will determine whether the benefits outweigh the potential risks due to radiation exposure.

Ask your nuclear medicine doctor if you have any questions about how Illuccix works or why this medicine has been prescribed for you.

What are the ingredients?

Medicinal ingredients: gozetotide combined with the radioactive substance gallium-68.

Non-medicinal ingredients: D-mannose, hydrochloric acid, sodium acetate and water for injection.

Illuccix comes in the following dosage forms:

Powder (25 microgram) in a vial as kit for intravenous injection.

Do not use Illuccix 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 Illuccix. Talk about any health conditions or problems you may have, including if you:

- Have other type of cancer or other non-malignant condition or other medical condition as image interpretation could be affected by other conditions;
- Are under 18 years of age;
- Have signs of dehydration before and after examination.

Other warnings you should know about:

The use of Illuccix involves exposure to small amount of radioactivity. Long-term cumulative radiation exposure is associated with an increased risk of cancer.

Before administration of Illuccix, you should:

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

Children and adolescents

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

Older people (65 years or above)

You can use Illuccix if you are aged 65 years or older at the same dose as other adults.

Pregnancy and breast feeding

Illuccix is not indicated for use in females. All radiopharmaceuticals, including Illuccix, 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 Illuccix:

- Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway.

How to take Illuccix:

- There are strict laws on the use, handling and disposal of radiopharmaceutical products. Illuccix 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 experienced in the use of radiopharmaceuticals safely.
- You will receive only one injection intravenously (directly into vein) which is sufficient to conduct the imaging procedure.

- Your nuclear medicine doctor will inform you about the duration of the imaging procedure.
- After injection, drink plenty of fluids and urinate as often as possible. This helps remove the radioactivity from your body.
- Your doctor will inform you if you need to take any special precautions after receiving Illuccix.
- Avoid close contact with young children and pregnant women for 6 hours after the injection.

Usual dose

The doctor or specialist supervising the procedure will decide on the dose of Illuccix to be used depending on your clinical situation, the type of PET camera being used, and other factors. The dose will be the smallest amount needed to get the desired information. The recommended dose for an adult is 111 MBq to 259 MBq (MBq = megabecquerel, which is the unit used to express radioactivity).

Overdose

An overdose is unlikely because you will only receive a single dose in a controlled clinical setting. However, in the case of an overdose, you will receive the appropriate treatment. Drinking water and emptying your bladder frequently will help remove the medicine from your body more quickly.

What are possible side effects from using Illuccix?

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

Illuccix 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 you 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 your healthcare specialist. Storage of radiopharmaceuticals are in accordance with national regulations on radioactive material.

Keep out of reach and sight of children.

If you want more information about Illuccix:

- 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/drugproducts/drug-product-database.html); the manufacturer's website (https://www.illuccix.com) or by calling 1-844-455-8638.

This leaflet was prepared by Telix Pharmaceuticals (US) Inc.

Last Revised