

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Illuccix 25 micrograms kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The vial of powder for solution for injection contains 25 micrograms of gozetotide (as trifluoroacetate salt).

The radionuclide is not part of the kit.

Excipient with known effect

The vial of solvent contains 42 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation containing:

- One vial of powder for solution for injection: the vial contains a white lyophilised powder.
- One vial of solvent: the vial contains a clear, colourless solution.
- One empty vial: the vial is sterile, vacuum sealed and used for the radiolabelling of the kit.

For radiolabelling with gallium (^{68}Ga) chloride solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Illuccix, after radiolabelling with gallium-68, is indicated for detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to primary curative therapy.
- Suspected recurrent PCa in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy.
- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated (see section 4.4).

4.2 Posology and method of administration

This medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine imaging agents and only in a designated nuclear medicine facility. PET/CT images should only be interpreted by readers trained in the interpretation of PET/CT images with gallium (^{68}Ga) (see section 4.4).

Posology

Adults

The recommended injected activity is 1.8–2.2 MBq per kilogram of body weight (corresponding to 126 to 154 MBq for an adult weighing 70 kg) with a minimum dose of 111 MBq up to a maximum dose of 259 MBq.

Special populations

Elderly

No dose adjustment is required.

Renal impairment

There are no data with gallium (^{68}Ga) gozetotide in patients with moderate to severe/end-stage renal impairment. No dose adjustment is considered necessary in patients with renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of Illuccix in the paediatric population.

Method of administration

This medicinal product is for intravenous and multidose use. It should be reconstituted and radiolabelled before administration to the patient.

After reconstitution and radiolabelling, gallium (^{68}Ga) gozetotide solution for injection should be administered as a slow single intravenous bolus followed by an intravenous flush of sterile sodium chloride 9 mg/ml (0.9%) solution for injection to ensure full delivery of the dose. Local extravasation resulting in inadvertent radiation exposure to the patient and imaging artefacts should be avoided. The speed of administration depends on the venous tolerability to low pH solution, which is mainly dependent on the blood flow of the vein used for the injection.

The radioactivity of gallium (^{68}Ga) gozetotide solution for injection in the syringe should be measured with a dose calibrator immediately before and after administration to the patient. The dose calibrator must be calibrated and comply with international standards.

For patient preparation, see section 4.4.

For instructions on reconstitution and radiolabelling of the medicinal product before administration, see section 12.

Image acquisition

The patient should be positioned supine with arms above the head whenever possible. A low-dose Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan should be obtained for attenuation correction and anatomic correlation. PET scanning should begin 60 min after the intravenous administration of gallium (^{68}Ga) gozetotide solution for injection, with an acceptable range of 50 to 100 min.

The interval between intravenous administration of gallium (^{68}Ga) gozetotide solution for injection and imaging should be recorded. PET must include a whole-body acquisition from the mid-thigh to the vertex as to exploit the reduced gallium (^{68}Ga) gozetotide ligand activity in the urinary bladder after pre-scan voiding.

Acquisition should proceed from the lower end of the axial field of view cranially, in a three-dimensional (3D) mode with an acquisition time of usually 2-4 min per bed position. Overall, PET coverage should be identical to the anatomical CT scan range. Typically, total scan time is between 20-30 minutes.

Image reconstruction

Image acquisition should be performed in 3D acquisition mode with appropriate data corrections; the CT or MRI scan may be used for attenuation correction. PET reconstruction should be performed with and without attenuation correction to identify potential artefacts caused by the correction algorithm.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

4.4 Special warnings and precautions for usePotential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

To date, no outcome data exist to inform subsequent management of patients with high risk disease when PSMA PET/CT is utilised for primary staging.

Experience of use of gallium (^{68}Ga) gozetotide PET for selection of patients for PSMA based therapy is limited to patients with progressive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy, and for the selection of patients for treatment with lutetium (^{177}Lu) vipivotide tetraxetan. Benefit risk ratio may not be generalisable to other types of PSMA based therapy and patients with mCRPC with different prior treatments.

Radiation risk

Gallium (^{68}Ga) gozetotide contributes to the patient's overall long-term cumulative radiation exposure, which is associated with an increased risk of cancer. Safe handling, reconstitution and radiolabelling procedures should be ensured to protect patients and healthcare professionals from unintentional radiation exposure (see sections 6.6 and 12).

Renal impairment

Careful consideration of the benefit/risk ratio in patients with moderate to severe/end-stage renal impairment is required since there are no data (see section 4.2).

Paediatric population

For information on use in the paediatric population, see section 4.2.

Patient preparation

In order to obtain images of best quality and to reduce the radiation exposure, patients should be encouraged to drink sufficient amounts (with e.g. oral intake of 500 mL of water 2 hours prior to acquisition), and to empty their bladder prior to and after the PET examination.

Interpretation of gallium (^{68}Ga) gozetotide PET images

PET images with gallium (^{68}Ga) gozetotide should be interpreted by visual assessment. Suspicion of malignant lesions is based on gallium (^{68}Ga) gozetotide uptake in comparison with tissue background.

Gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in normal tissues (see section 5.2), other types of cancers and non-malignant processes, potentially leading to false positive findings. Moderate to high physiological PSMA uptake is noted in the kidneys, lacrimal glands, liver, salivary glands and urinary bladder wall. False positive findings include, but are not limited to, renal cell carcinoma, hepatocellular carcinoma, breast cancer, lung cancer, benign bone diseases (e.g. Paget's disease), pulmonary sarcoidosis/granulomatosis, gliomas, meningiomas, paragangliomas and neurofibromas. Ganglia can mimic lymph nodes.

The diagnostic performance of gallium (^{68}Ga) gozetotide may be affected by serum PSA levels, androgen-receptor-targeting treatments, disease stage and size of malignant lymph nodes (see section 5.1).

Gallium (^{68}Ga) gozetotide PET images should be interpreted only by readers appropriately trained in the interpretation of PET images with gallium (^{68}Ga) gozetotide. Findings on gallium (^{68}Ga) gozetotide PET images should always be interpreted in conjunction with and be confirmed by other diagnostic methods (including histopathology) before subsequent change in patient management is initiated.

If acquired, contrast-enhanced CT shall not be used for attenuation correction, since iodine content may induce wrong attenuation correction.

After the procedure

Close contact with infants and pregnant women should be restricted during the initial 2 hours following the injection.

The patient should be encouraged to drink sufficient amounts of water and void as often as possible during the first hours post scan to reduce unnecessary radiation exposure, especially to the bladder.

Specific warnings

Sodium content

This medicinal product contains up to 42 mg sodium per dose, equivalent to 2.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Acidic pH and extravasation

Low pH of gallium (^{68}Ga) gozetotide may lead to injection site reactions after administration. Accidental extravasation may cause local irritation, due to the acidic pH of the solution. Cases of extravasation should be managed as per institutional guidelines.

Precautions with respect to environmental hazard are in section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Given the micro-dose administered, and given that significant hepatic metabolism is unlikely, the risk of clinically significant pharmacokinetic drug interactions is very low. The reduction in signal from the urinary bladder seen with the concomitant administration of furosemide, suggested that the use of furosemide and possibly other diuretics, could reduce the scatter severity in gallium (^{68}Ga) gozetotide PET.

4.6 Fertility, pregnancy and lactation

Pregnancy

Gallium (^{68}Ga) gozetotide is not indicated for use in females. There are no data on the use of gallium (^{68}Ga) gozetotide in females. Reproductive toxicity studies in animals have not been conducted with gallium (^{68}Ga) gozetotide. However, all radiopharmaceuticals, including gallium (^{68}Ga) gozetotide, have the potential to cause foetal harm.

Breast-feeding

Gallium (^{68}Ga) gozetotide is not indicated for use in females. There are no data on the effects of gallium (^{68}Ga) gozetotide on the breast-fed newborn/infant or on milk production. Lactation studies have not been conducted in animals with gallium (^{68}Ga) gozetotide.

Fertility

There are no data on the effect of gallium (^{68}Ga) gozetotide on human fertility.

4.7 Effects on ability to drive and use machines

Gallium (^{68}Ga) gozetotide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The radiation dose with gallium (^{68}Ga) gozetotide PET/CT is the combination of the radiation exposure from the radiopharmaceutical and the CT.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 3 mSv when the maximal recommended activity of 2.2 MBq per kilogram of body weight is administered these adverse reactions are expected to occur with a low probability.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials (677 subjects). Adverse reactions are displayed by system organ class and frequency in Table 1 and defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions by system organ class and frequency

MedDRA system organ class	Adverse reactions	Frequency
Metabolism and nutrition disorders	Transient hyperamylasaemia	Rare
Gastrointestinal disorders	Constipation	Rare
General disorders and administration site conditions	Asthenia, injection site reaction*	Rare

*such as injection site haematoma, injection site warmth, injection site pruritus (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

No case of overdose has been reported.

In the event of administration of a radiation overdose with gallium (^{68}Ga) gozetotide solution for injection, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent micturition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX14

Mechanism of action

Gallium (^{68}Ga) gozetotide binds specifically to the prostate-specific membrane antigen (PSMA), i.e., to the cells that express PSMA, including malignant prostate cancer cells, which overexpress PSMA. Gallium-68 is a radionuclide with an emission yield that allows PET imaging. Based on the intensity of the signals, PET images obtained with gallium (^{68}Ga) gozetotide indicate the presence of PSMA protein in tissues.

Pharmacodynamic effects

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

Clinical efficacy and safety

The key evidence of diagnostic efficacy derives from the below mentioned studies for:

Primary staging of patients with high-risk prostate cancer prior to primary curative therapy

A large primary staging prospective, multicentre, single-arm, Phase 3 study (Hope et al., 2021) was performed at 2 institutions: UCLA (NCT03368547) and UCSF (NCT02611882 and NCT02919111) in 764 men (median [interquartile range] age: 69 [63-73] years) with intermediate to high-risk prostate cancer, and 277 of 764 (36%) subsequently underwent prostatectomy with lymph node dissection (efficacy analysis cohort). The study assessed diagnostic accuracy of gallium (^{68}Ga) gozetotide PET/CT imaging for the detection of pelvic nodal metastases compared with histopathology at time of radical prostatectomy and pelvic lymph node dissection (PLND). All patients underwent a single gallium (^{68}Ga) gozetotide injection with target injected activity of 185 MBq (allowed range: 111-259 MBq), and patients received a mean (SD) of 196 (35) MBq. The primary end points of the study were the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of gallium (^{68}Ga) gozetotide PET/CT imaging for the detection of regional nodal metastases compared with pathology at radical prostatectomy on a per-patient basis using nodal regional correlation (left, right, other). A total of 75 of 277 patients (27%) had regional pelvic node metastasis found on pathology (pN1). On a per-patient level, the sensitivity, specificity, PPV, and NPV of gallium (^{68}Ga) gozetotide PET/CT based on the majority reads were 40% (95% CI: 34, 46), 95% (95% CI: 92, 97), 75% (95% CI: 70, 80), and 81% (95% CI: 76, 85), respectively.

On a per-region level, inter-reader agreement was substantial for right-sided nodes ($\kappa = 0.61$; 95% CI, 0.55-0.67) and left-sided nodes ($\kappa = 0.66$; 95% CI, 0.60-0.71). For other nodes, there was moderate inter-reader agreement ($\kappa = 0.52$; 95% CI, 0.46-0.58).

In van Kalmthout et al. (2020), 103 adult male patients with biopsy-proven prostate cancer and intermediate- and high-risk features indicated for extended pelvic lymph node dissection (ePLND) underwent gallium (^{68}Ga) gozetotide PET/CT imaging. PET/CT scans were read by two independent blinded readers and ePLND was the histopathology reference standard for 96 out of 103 (93%) patients. Patient-based sensitivity, specificity, PPV and NPV of gallium (^{68}Ga) gozetotide PET/CT imaging to detect lymph node metastasis (LNM) are summarised in Table 2.

Table 2: Efficacy results in primary staging in patients with biopsy-proven prostate cancer

	Patient-based N=96¹
Sensitivity (95% CI)	42% (27, 58)
Specificity (95% CI)	91% (79, 97)
PPV	77% (54, 91)
NPV	68% (56, 78)

¹ Evaluable population

Inter-reader agreement was $\kappa = 0.67$ for the 2 independent blinded readers. Of the 67 LNM analysed, 26 were detected by gallium (^{68}Ga) gozetotide PET/CT, resulting in 38.8% node-based sensitivity. Median diameter of the metastatic deposit in these detected LNM was 7 mm (range: 0.3-35). The PET reading missed 41 LNM with a median metastatic deposit of 3.0 mm (range: 0.5 to 35.0).

Suspected recurrent prostate cancer in patients with increasing levels of serum PSA after primary curative therapy

PSMA-BCR study (Fendler et al., 2019) was a single-arm, prospective study that enrolled 635 adult male patients with a median age of 69 years (44-95 years) with biochemical recurrence (BCR) after radical prostatectomy (n=262; 41%), radiation therapy (n=169; 27%), or both (n=204; 32%). 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: 0.1-1154 ng/mL).

In the efficacy cohort, 223 patients (35.1%) had information on composite reference standard (CRS), i.e., a combination of follow-up data from histopathologic analysis (primary endpoint), imaging (CT, MRI and/or bone scan), and serial serum PSA at a median duration of 9 months. Histopathology alone as a reference standard (SOT) was available for 93 patients (14.6%). PET/CT scans were read by 3 independent readers blinded to clinical information other than the type of primary therapy and most recent serum PSA level.

Detection of PSMA-positive lesions occurred in 475 of 635 (75%) patients receiving gallium (^{68}Ga) gozetotide and higher detection rate (DR) were observed in the patients with higher initial PSA levels ranging from 38% (n=136) in patients with PSA<0.5 ng/mL to 97% (n=173) in patients with PSA \geq 5.0 ng/mL.

Diagnostic performance on patient basis (at any location) and by reference standard are presented in Table 3.

Table 3: Diagnostic performance of gallium (^{68}Ga) gozetotide in BCR patients

	Composite reference standard N=223¹	Histopathology reference standard N=93¹
Sensitivity per-patient (95% CI)	NA	92% (84, 96)

Sensitivity per-region (95% CI)	NA	90% (82, 95)
PPV per-patient (95% CI)	92% (88, 95)	84% (75, 90)
PPV per-region (95% CI)	92% (88, 95)	84% (76, 91)
¹ Evaluable population		

Gallium (⁶⁸Ga) gozetotide PET resulted in a relevant impact on patient management in more than half of patients undergoing PET scan for localisation of biochemically recurrent prostate cancer (Fendler et al., 2020).

Identification of patients with PSMA-positive progressive mCRPC for whom PSMA-targeted therapy is indicated

VISION study (NCT03511664) was a prospective, randomised, multicentre, open-label Phase III study using gallium (⁶⁸Ga) gozetotide PET scan at screening to evaluate PSMA positivity of 1003 adult male patients with prostate cancer lesions and select patients to therapy with lutetium (¹⁷⁷Lu) vipivotide tetraxetan. Imaging criteria was that it allowed patients with PSMA-positive mCRPC to receive life-extending therapy on the basis of only one PET scan plus conventional imaging with a central reader defining PSMA positivity on the basis of this single PET scan. Improved overall survival and radiographic progression-free survival were reported in the PSMA-targeted therapy arm.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Illuccix in all subsets of the paediatric population in the visualisation of prostate specific membrane antigen in prostate cancer.

5.2 Pharmacokinetic properties

Pharmacokinetic properties are derived from blood/plasma and urinary clearance of gallium (⁶⁸Ga) gozetotide from a single clinical study (Jamar, et al., 2016) in 3 subjects.

Distribution

Gallium (⁶⁸Ga) gozetotide biodistribution in normal organs is relatively rapid, which accounts for the recommended 60 min interval (acceptable range 50 to 100 min) for uptake time between injection of the tracer and PET imaging.

Organ uptake

Gallium (⁶⁸Ga) gozetotide is preferentially taken up into prostate cancer cells with overexpressed PSMA. Significant off-target tissue uptake was highest for the kidneys, urinary bladder wall, lacrimal glands, salivary glands, small bowel, spleen and liver with mean absorbed doses between 0.456 and 0.022 mGy/MBq in decreasing order, with the first 2 organs indicating that the primary route of excretion is via the urinary tract.

Biotransformation

Based on *in vitro* data, gallium (⁶⁸Ga) gozetotide undergoes negligible hepatic and renal metabolism.

Elimination

Renal uptake of gallium (⁶⁸Ga) gozetotide indicated the route of excretion of the radiotracer via the renal pathway. About 43% of the activity of gallium (⁶⁸Ga) gozetotide is eliminated from the body by urine within 3 hours post-injection.

Half-life

Based on the gallium (⁶⁸Ga) gozetotide biological and terminal half-life in blood of 4.4 h and on the gallium-68 physical half-life of 68 minutes, the resulting gallium (⁶⁸Ga) gozetotide effective half-life is 54 minutes.

Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment have not been characterised. However, gallium (⁶⁸Ga) gozetotide pharmacokinetics are not expected to be affected by renal or hepatic impairment to any clinically relevant extent (see section 4.2).

5.3 Preclinical safety data

A toxicological study in rats has demonstrated that with a single intravenous injection of 86 µg gozetotide per kg body weight no adverse effects were observed. Based on the highest anticipated clinical dose of 25 µg gozetotide (0.5 µg/kg; based on 50 kg adult) and the NOAEL of gozetotide in the rat of 86 µg/kg, a safety margin of 28-fold was obtained based on body surface area.

Mutagenicity and long-term carcinogenicity studies have not been carried out.

No reproductive or developmental toxicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection

D-Mannose

Solvent

Water for injections

Sodium acetate anhydrous

Hydrochloric acid

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

Kit: 2 years.

After radiolabelling: 2 hours. Do not store above 25°C nor freeze the solution after radiolabelling.

From a microbiological point of view, once reconstituted and radiolabelled, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Before reconstitution, store in a refrigerator (2°C – 8°C).

Store in the original package in order to protect from light.

For storage conditions after reconstitution and radiolabelling of the medicinal product, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Illuccix is supplied as a kit for radiopharmaceutical preparation of gallium (⁶⁸Ga) gozetotide solution for injection.

For use with Eckert & Ziegler GalliaPharm germanium-68/gallium-68 (⁶⁸Ge/⁶⁸Ga) generator, the box contains:

- One vial of powder for solution for injection: the vial contains 25 micrograms of gozetotide.
- One vial of solvent containing 2.5 mL of acetate buffer.
- One empty vial, sterile, vacuum-sealed.
- Label for radiolabelled product shielding.

For use with IRE ELiT Galli Ad germanium-68/gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generator, the box contains:

- One vial of powder for solution for injection: the vial contains 25 micrograms of gozetotide.
- One vial of solvent containing 6.4 mL of acetate buffer.
- One empty vial, sterile, vacuum-sealed.
- Label for radiolabelled product shielding.

Each vial is a 10 mL capacity glass vial made of type I closed with a rubber stopper and sealed with a coloured cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

The contents of the vials are intended only for use in the preparation of gallium (^{68}Ga) gozetotide solution for injection and are not to be administered directly to the patient without first undergoing the preparative procedure (see section 12).

Precautions to be taken before handling or administration of the medicinal product

The content of the kit before reconstitution and radiolabelling is not radioactive. However, after gallium (^{68}Ga) chloride Ph. Eur. is added, adequate shielding of the final preparation must be maintained.

After reconstitution and radiolabelling, Illuccix contains a sterile solution for injection of gallium (^{68}Ga) gozetotide at an activity of up to 1 315 MBq. The gallium (^{68}Ga) gozetotide solution for injection also contains hydrochloric acid derived from the gallium-68 chloride solution.

Gallium (^{68}Ga) gozetotide is a sterile, clear, colourless solution for intravenous administration, practically free from visible particles and with pH between 4.0 to 5.0.

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

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

If at any time in the preparation of this medicinal product the integrity of the vials is compromised, it should not be used.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

For instructions on reconstitution and radiolabelling of the medicinal product before administration, see section 12.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Telix Innovations
Rue De Hermee 255
Herstal
4040

8 MARKETING AUTHORISATION NUMBER

PA23504/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATIONDate of first authorisation: 4th April 2025**10 DATE OF REVISION OF THE TEXT****11 DOSIMETRY**

Gallium-68 is produced by means of a germanium-68/gallium-68 (⁶⁸Ge/⁶⁸Ga) generator and decays with a half-life of 68 min to stable zinc-68. Gallium-68 decays as follows:

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

Estimated radiation absorbed doses per injection activity for organs and tissues of adult patients following an intravenous bolus of gallium (⁶⁸Ga) gozetotide solution for injection, studied in Phase I study, are shown in Table 4. The software OLINDA-EXM was used to calculate absorbed organ doses according to the Committee on Medical Internal Radiation Dose (MIRD) methodology, and effective dose according to ICRP (International Commission on Radiological Protection) Publication 103.

The kidneys were the organs receiving the highest absorbed dose. Additional organs with higher dose were urinary bladder, small intestines, and salivary glands.

Table 4: Estimated mean radiation absorbed dose per injection activity in selected organs and tissues of adults after a gallium (⁶⁸Ga) gozetotide dose

Adults Organ/Tissue	Estimated Mean Radiation Absorbed Dose per Injection Activity (mGy/MBq)
Adrenals	0.012
Brain	0.001
Breasts	0.006
Gallbladder	0.012
Heart	0.013
Kidneys	0.456
Liver	0.022
Lower colon	0.010
Lungs	0.008
Muscle	0.008
Osteogenic cells	0.013
Pancreas	0.011
Red marrow	0.012
Salivary glands	0.096
Skin	0.006
Small intestine	0.057
Spleen	0.037
Stomach	0.009
Testes	0.007
Thymus	0.007
Thyroid	0.007

Total body	0.011
Upper Colon	0.013
Urinary bladder	0.112
Effective dose (mSv/MBq)	0.0162

The effective dose resulting from the administration of a 2.2 MBq per kilogram of body weight is about 3 mSv (Fendler et al., 2017).

For an administered activity of 185 MBq, the typical radiation dose to the target organs is 84, 21, 18 and 11 mGy for the kidneys, urinary bladder, salivary glands and small intestine, respectively.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

Step 1: Reconstitution and radiolabelling

Ilucix 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 ($^{68}\text{Ge}/^{68}\text{Ga}$) generator
- IRE-ELiT Galli Ad germanium-68/gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generator

Gallium (^{68}Ga) chloride solution eluate from generator complies with the requirements of the Ph. Eur. monograph 2464, gallium (^{68}Ga) chloride solution for radiolabelling. The instructions for use provided by the germanium-68/gallium-68 generator manufacturer should also be followed.

The preparation of gallium (^{68}Ga) gozetotide solution for injection should be done according to the following aseptic procedure:

- Use suitable shielding to reduce radiation exposure.
- Wear waterproof gloves all the time during preparation and quality control of gallium (^{68}Ga) gozetotide.
- Put the label for radiolabelled product on the shielding.
- Remove the flip-off disc from powder vial (gozetotide), solvent vial (acetate buffer) and empty vial, swab the top of each vial with alcohol to disinfect the surface and allow the stoppers to dry.
- Use only plastic syringes for preparation and administration. Do not use syringes with rubber plungers.

Reconstitution and radiolabelling with Eckert & Ziegler GalliaPharm generator

Reconstitution of powder vial

1. Insert a sterile 10 mL syringe with a needle into the solvent vial and draw up the 2.5 mL of acetate buffer contained in the vial.
2. Inject the content of the 10 mL syringe into the powder vial.
3. Gently swirl powder vial to ensure the product is thoroughly dissolved.

Elution of generator and collection of gallium (^{68}Ga) chloride

1. Prepare a syringe containing 5 mL of sterile ultrapure 0.1M HCl provided with the GalliaPharm generator for elution.
2. Pierce the empty vial with a sterile needle connected to a 0.2 micron sterile vented filter to maintain atmospheric pressure within the vial during the reconstitution process.
3. Connect the male luer of the outlet line of the GalliaPharm generator to a sterile needle.
4. Connect the empty vial directly to the outlet line of the GalliaPharm generator by pushing the needle through the rubber septum and place the vial in a radiation shielded container.
5. Elute the generator directly into the empty vial according to the instructions for use of the GalliaPharm generator. Perform the elution manually or by means of a pump. Collect 5 mL of eluate.

6. At the end of the elution, disconnect the generator from the empty vial by removing the needle from the rubber septum.

Radiolabelling

1. Insert a sterile 10 mL syringe with a needle into the powder vial containing the dissolved gozetotide and draw up the content of the vial.
2. Transfer the content of the 10 mL syringe to the empty vial containing the gallium (^{68}Ga) chloride.
3. Wait for 5 minutes for radiolabelling to take place at room temperature.

At the end of radiolabelling step, the vial contains 7.5 mL of gallium (^{68}Ga) gozetotide.

Then continue with Step 2.

Reconstitution and radiolabelling with IRE ELiT Galli Ad generator

Reconstitution of powder vial

1. Insert a sterile 10 mL syringe with a needle into the solvent vial and draw up the 6.4 mL of acetate buffer contained in the vial.
2. Inject the content of the 10 mL syringe into the powder vial.
3. Gently swirl powder vial to ensure the product is thoroughly dissolved.

Elution of generator and collection of gallium (^{68}Ga) chloride

1. Connect the male luer of the outlet line of the Galli Ad generator to a sterile needle.
2. Elute the generator directly into the empty vial according to the instructions for use of the Galli Ad generator. Collect 1.1 mL of eluate.
3. At the end of the elution, disconnect the generator from the empty vial by removing the needle from the rubber septum.

Radiolabelling

1. Insert a sterile 10 mL syringe with a needle into the powder vial containing the dissolved gozetotide and draw up the content of the vial.
2. Transfer the content of the 10 mL syringe to the empty vial containing the gallium (^{68}Ga) chloride.
3. Wait for 5 minutes for radiolabelling to take place at room temperature.

At the end of radiolabelling step, the vial contains 7.5 mL of gallium (^{68}Ga) gozetotide.

Then continue with Step 2.

Step 2: After radiolabelling

1. After 5 minutes of radiolabelling, assay the vial containing the gallium (^{68}Ga) gozetotide solution for injection for total radioactivity concentration using a dose calibrator and record the result.
2. Perform quality controls according to the recommended methods in order to check compliance with the specifications (see Step 3).
3. Store the Illuccix vial containing the gallium (^{68}Ga) gozetotide solution for injection upright in a lead shield container at room temperature until use.

Step 3: Specifications and Quality control

Perform the quality controls behind a lead glass shield for radioprotection purposes. The gallium (^{68}Ga) gozetotide solution for injection should only be used if the acceptance criteria presented in Table 5 are met.

Table 5: Specifications of Gallium (^{68}Ga) gozetotide solution for injection

Test	Analytical method	Acceptance criteria
Appearance	Visual inspection	Clear, colourless solution, practically free from visible particles
pH	pH-strips or pH-meter	4.0 to 5.0
Radiochemical purity Free and colloidal gallium-68 species	Instant Thin layer chromatography (iTLC, see details below)	$\leq 3\%$

Determine labelling efficiency of gallium (^{68}Ga) gozetotide solution for injection by performing 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:

1. Develop immediately the iTLC SG strip over 2/3 of the plate.
2. Measurement:

a) Cutting technique:

Measure each piece with the radioactivity dose calibrator.

Calculate the quantity (in percent) of free and colloidal gallium-68 species in the solution using the formula:

$$\% \text{ Free and colloidal gallium (68Ga) species} = \frac{\text{Activity bottom piece}}{\text{Activity bottom piece} + \text{Activity top piece}} \times 100$$

b) Scanning technique:

Scan the iTLC SG strip with a radiometric iTLC scanner.

Calculate labelling efficiency by integration of the peaks on the chromatogram.

The retention factor (Rf) specifications are:

- Free and colloidal gallium-68 species, Rf = 0 to 0.2
- Gallium (^{68}Ga) gozetotide, Rf = 0.8 to 1.0

Step 4: Administration

- Aseptic technique and radiation shielding should be used when withdrawing and administering gallium (^{68}Ga) gozetotide solution for injection.
- Prior to use, visually inspect the prepared gallium (^{68}Ga) gozetotide solution for injection behind a lead glass shield for radioprotection purposes. Only solutions that are clear, colourless and practically free from visible particles should be used.
- Using a single-dose syringe fitted with a sterile needle and protective shielding, aseptically withdraw the prepared gallium (^{68}Ga) gozetotide solution for injection prior to administration.
- The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after gallium (^{68}Ga) gozetotide solution for injection administration to the patient. The dose calibrator must be calibrated and comply with international standards.
- Radioactive waste must be disposed of in accordance with relevant national regulations.