

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Isoprotrace 10 micrograms kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains gozetotide trifluoroacetate equivalent to 10 micrograms of gozetotide.

The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

White or almost white powder.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with gallium (^{68}Ga) chloride solution, gallium (^{68}Ga) gozetotide (also known as gallium (^{68}Ga) PSMA-11) is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer in the following clinical settings:

- Primary staging of patients with high-risk prostate cancer prior to primary curative therapy.
- Suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) level, after primary curative therapy.

4.2 Posology and method of administration

The medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine diagnostic agents and only in a designated nuclear medicine facility.

Posology

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

Elderly population

No special dosage regimen for elderly patients is required.

Paediatric population

There is no relevant use of gallium (^{68}Ga) gozetotide in the paediatric population for the identification of PSMA positive lesions in prostate cancer.

The safety and efficacy of gallium (^{68}Ga) gozetotide in children aged 0 to 18 years have not been established.

Hepatic impairment

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been studied in patients with hepatic impairment.

Renal impairment

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been studied in patients with renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients, see section 4.4.

Method of administration

This medicinal product is administered intravenously as a single injection. It should be reconstituted and radiolabelled before administration to the patient.

After reconstitution and radiolabelling, gallium (^{68}Ga) gozetotide solution should be administered by slow intravenous injection. Local extravasation resulting in inadvertent radiation exposure to the patient and imaging artefacts should be avoided. The injection should be followed by an intravenous flush of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose.

The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after administration to the patient. The dose calibrator must be calibrated and comply with international standards. Instructions regarding the dilution of the gallium (^{68}Ga) gozetotide solution should be followed (see section 12).

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

For patient preparation, see section 4.4.

Image acquisition

Gallium (^{68}Ga) gozetotide is suitable for PET medical imaging.

Patients should void immediately prior to image acquisition. The patient should be positioned supine with the arms above the head, as tolerated by the patient. A CT scan should be obtained for attenuation correction and anatomical correlation. The acquisition must include a whole-body acquisition from the base of the skull to mid-thigh.

PET images should be acquired 50 to 100 (ideally 60) minutes after the intravenous administration of gallium (^{68}Ga) gozetotide solution.

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

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 use

Potential 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.

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

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been studied in patients with renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Hepatic impairment

The safety and efficacy of gallium (^{68}Ga) gozetotide have not been studied in patients with hepatic impairment.

Patient preparation

There is no need for fasting. Patients are allowed to take all their medications. PSMA-expression may be increased by androgen-deprivation therapy, but the clinical significance is unclear. The patient should be well-hydrated before the start of the examination and urged to void just prior to the image acquisition. The patient should be urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Concomitant administration of loop diuretics can lower the activity of gallium (^{68}Ga) gozetotide in the bladder and ureter and decrease peri-bladder artefacts.

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

PSMA can be expressed in various cancerous and non-cancerous tissues with a variable intensity. Gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in normal tissues, most notably the kidneys, lacrimal glands, salivary glands, urinary bladder wall, liver as well as in sympathetic ganglia. Furthermore, gallium (^{68}Ga) gozetotide uptake may occur in other types of cancers and non-malignant processes, potentially leading to false positive findings. False positive findings with gallium (^{68}Ga) gozetotide were described in the following cases:

- Inflammatory processes, such as tuberculosis, diverticulosis and post-surgical inflammatory processes, including inflammatory PSMA uptake in the prostatic bed and prostatic urethra after recent (<2 months) radical prostatectomy (RP),
- Bone conditions, such as osteomyelitis, fractures, Paget's disease, fibrous dysplasia, hemangioma, and others,
- Benign neoplasms, for example meningiomas, nerve sheath tumours, thyroid and parathyroid adenomas, thymomas, adrenal adenomas, dermatofibromas and others,
- Other malignant neoplasms, such as tumours of the central nervous system, i.e., gliomas, thyroid cancer, breast, lung, lymphoma, neuroendocrine tumours, colorectal tumours, primary bone tumours, and many others.

False negative results can occur in prostate cancer, not expressing PSMA receptors at a sufficient level to be detected. This is described in approximately 3-10% of cases.

Gallium (^{68}Ga) gozetotide PET images should be interpreted only by readers trained in the interpretation of PET images with gallium (^{68}Ga) gozetotide PET. 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.

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.

After the procedure

The patient should be encouraged to drink sufficiently amounts and void as often as possible during the first hours after the scan in order to reduce radiation exposure of the bladder.

Close contact with infants and pregnant women should be avoided during the first 6 hours after administration of the radiopharmaceutical.

Specific warnings

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

For precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the extremely low mass dose of not more than 10 mcg single dose, gallium (^{68}Ga) gozetotide is not expected to have any clinically significant interaction with other medicinal products (see section 5.2). No interaction studies have been performed.

Patients subjected to diagnostic examinations with the use of gallium (^{68}Ga) gozetotide, it is recommended on an empirical basis not to withdraw treatment.

Androgen deprivation therapy and other therapies targeting the androgen receptor pathway

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

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. Dedicated 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

In an extended single-dose toxicity study in rats intravenously administered 710 $\mu\text{g}/\text{kg}$ of gozetotide, male reproductive organs were not found to be target organs of toxicity.

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 safety profile

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose, resulting from the administration of an average activity of 2 MBq/kg to an 80 kg man is 3.5 mSv, these adverse reactions are expected to occur with a low probability.

Mild to moderate adverse reactions occurred in patients receiving gallium (^{68}Ga) gozetotide. The most commonly reported reactions were fatigue, headache, injection site reactions, nausea and rash.

Tabulated list of adverse reactions

Adverse reactions (Table 1) are listed by MedDRA system organ class and according to the MedDRA convention frequencies: 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 ($< 1/10\ 000$).

Table 1: List of adverse reactions

MedDRA system organ class	Adverse reactions	Frequency
Nervous system disorders	Headache, dizziness, paraesthesia, insomnia	Uncommon
Gastrointestinal disorders	Nausea, diarrhoea, dysphagia	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
General disorders and administration site conditions	Fatigue, injection site reactions*	Uncommon

* Injection site reactions include injection site burning, pruritus and injection site pain.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No cases of overdose have been reported.

Gallium (^{68}Ga) gozetotide is administered as a single dose for diagnostic use. Overdose due to repeated drug administrations is not likely.

In the event of an overdose of gallium (^{68}Ga) gozetotide, reduce the radiation adsorbed dose to the patient where possible by increasing the elimination of the drug from the body using hydration and frequent bladder voiding. A diuretic might also be considered. If possible, an estimate of the radiation effective dose given to the patient should be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Gallium (^{68}Ga) gozetotide binds to prostate-specific membrane antigen (PSMA). It binds to cells that express PSMA, including malignant prostate cancer cells, which usually overexpress PSMA. Gallium (^{68}Ga) is a β^+ emitting radionuclide that allows positron emission tomography (PET).

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

PSMA-pre-radical prostatectomy

In a prospective study by Hope et al. (2021), a total of 764 men with intermediate- to high-risk prostate cancer according to D'Amico criteria, who underwent a gallium (^{68}Ga) gozetotide PET imaging scan, the sensitivity and specificity of (^{68}Ga) gozetotide PET imaging was assessed using histopathology as the reference standard. Overall, 166 patients were assessed as intermediate-risk and 590 had a high-risk prostate cancer. In the surgery cohort, 49 patients had intermediate-risk, while 225 patients had high-risk prostate cancer.

Based on pathology reports, 75 of 277 patients (27%) had pelvic nodal metastasis. Results of gallium (^{68}Ga) gozetotide PET were positive in 40 of 277 (14%), 2 of 277 (1%), and 7 of 277 (3%) of patients for pelvic nodal, extrapelvic nodal, and bone metastatic disease. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for pelvic nodal metastases (summarised in Table 2) were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85), respectively. Of the 764 patients, 487 (64%) did not undergo prostatectomy, of which 108 were lost to follow-up. Patients with follow-up instead underwent radiotherapy (262 of 379 [69%]), systemic therapy (82 of 379 [22%]), surveillance (16 of 379 [4%]), or other treatments (19 of 379 [5%]).

Table 2: Patient-level performance of gallium (^{68}Ga) gozetotide PET for detection of pelvic lymph node metastasis (n=277)

Per-patient values	Majority reads Mean value in % (95% CI)
Sensitivity	40 (34-46)
Specificity	95 (92-97)
PPV	75 (70-80)
NPV	81 (76-85)

PSMA-biochemical recurrence (BCR)

In the study by Fendler et al, 2019, 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: 0.1-1 154 ng/mL). A composite reference standard, including histopathology, serial serum PSA levels and imaging (CT, MRI, and/or bone scan) findings was available for 223 of 635 (35.1%) patients, while histopathology reference standard alone was available for 93 (14.6%) patients. PET/CT scans were read by 3 independent readers blinded to clinical information other than the type of primary therapy and most recent serum PSA level.

Detection of PSMA-positive lesions occurred in 475 of 635 (75%) patients receiving (^{68}Ga) gozetotide and the detection rate was significantly increased with PSA levels. The detection rate of gallium (^{68}Ga) gozetotide positive lesions increased with increasing serum PSA levels. Sensitivity, specificity, positive predictive value, and negative predictive value of gallium (^{68}Ga) gozetotide PET/CT imaging are summarised in Table 3. Inter-reader Fleiss κ for gallium (^{68}Ga) gozetotide PET/CT imaging ranged from 0.65 (95% CI: 0.61, 0.70) to 0.78 (95% CI: 0.73, 0.82) across the assessed regions (prostate bed, pelvic nodes, extrapelvic soft tissues and bones).

Table 3: Diagnostic performance of gallium (^{68}Ga) gozetotide PET/CT in patients with biochemically recurrent prostate cancer

	Composite reference standard	Histopathology reference standard
Number of patients	233	93
Sensitivity (%; 95% CI) per-patient	Not available	92 (84-96)
Specificity (%; 95% CI) per-patient	Not available	90 (82-95)
PPV (%; 95% CI) per-patient	92 (88-95)	84 (75-90)
NPV (%; 95% CI) per-patient	92 (88-85)	84 (76-91)

5.2 Pharmacokinetic properties

Distribution

After intravenous administration, gallium (^{68}Ga) gozetotide is rapidly eliminated from the blood. Already after 5 to 10 minutes, accumulation of the gallium (^{68}Ga) gozetotide is seen in the kidneys, as well as in tumours expressing PSMA receptors.

Organ uptake

The highest radiation absorbed dose of gallium (^{68}Ga) gozetotide occurred in the kidneys, lacrimal glands, salivary glands, urinary bladder wall and liver (see section 11).

Maximal values of the tumour/background ratio are observed between 1 and 2 hours after injection. Cancer lesions are still visible after 3 hours. However, it is critical that the patient has voided just prior to imaging.

Biotransformation

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

In vitro evaluation of drug interaction potential

CYP450 enzymes

No studies have been performed to evaluate the interaction with CYP450 enzymes. Based on the low systemic exposure of not more than 10 mcg/dose resulting in a peak plasma level of not more than 2 ng/mL, no clinically relevant interaction with these enzymes is expected.

Transporters

No studies have been performed to evaluate the interaction with drug transporters. Based on the low systemic exposure of not more than 10 mcg/dose resulting in a peak plasma level of not more than 2 ng/mL, no clinically relevant interaction with these transporters is expected.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies on single-dose toxicity and genotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrolysed gelatine
Sodium acetate anhydrous
Sodium chloride

After radiolabelling, the solution obtained also contains, as excipient, hydrochloric acid.

6.2 Incompatibilities

Radiolabelling of carrier molecules with gallium (^{68}Ga) chloride is very sensitive to the presence of trace metal impurities. Only syringe and syringe needles able to minimise trace metal impurity levels (for example, non-metallic or coated with silicone needles – not supplied) should be used. Generator instructions should be followed.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution and radiolabelling: Store upright below 25 °C and use within 4 hours.

From a microbiological point of view, the medicinal 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

Store in a refrigerator (2 °C – 8 °C).

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

10 mL multidose colourless vial (type I glass) closed with a rubber stopper (bromobutyl) and sealed with a flip-off cap (aluminium) bearing a protective disk (polypropylene).

Pack size: 5 vials.

6.6 Special precautions for disposal

General warning

After radiolabelling of Isoprotrace, the common protective measures for radioactive medicinal product must be applied.

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 licenses 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.

Contents of the vial are intended only for use in the preparation of gallium (^{68}Ga) gozetotide and are not to be administered directly to a patient without first undergoing the preparative procedure.

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

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

The content of the kit before extemporary preparation is not radioactive. However, after gallium (^{68}Ga) solution is added, adequate shielding of the final preparation must be maintained.

After reconstitution and radiolabelling, Isoprotrace contains a sterile solution for injection of gallium (^{68}Ga) gozetotide at an activity of up to 1 369 MBq. The gallium (^{68}Ga) gozetotide solution for injection also contains hydrochloric acid derived from the gallium (^{68}Ga) chloride solution.

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.

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

7 MARKETING AUTHORISATION HOLDER

Billev Pharma ApS
Slotsmarken 10
2970 Hørsholm
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/02/2025

10 DATE OF REVISION OF THE TEXT

14/02/2025

11 DOSIMETRY

Gallium (^{68}Ga) solution is obtained from a $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator and decays by positron emission (energy 511 keV) with a physical half-life of 67.71 minutes to the stable zinc-68 isotope.

Dosimetry data have been studied in several trials with consistent findings. In a study from Sandgren et al. (2019) four adult prostate-cancer patients with BCR underwent 3-dimensional, image-based dosimetry of gallium (^{68}Ga) gozetotide assessed with the OLINDA/EXM software with time-integrated activity coefficients estimated from sequential PET/CT scans over 5 hours post-administration. The average organ absorbed doses and effective dose of gallium (^{68}Ga) gozetotide are given in the table below:

Table 4: Estimated median radiation absorbed doses of gallium (^{68}Ga) gozetotide (mGy/MBq). All values are for adult males, except where indicated differently.

Organ	Median (mGy/MBq)	Min (mGy/MBq)	Max (mGy/MBq)
Adrenals	0.05185	0.0431	0.098
Brain	0.00791	0.00628	0.00891
Breast	0.00853	0.00763	0.00898
Colon wall	0.01365	0.0129	0.0147
Endosteum (bone surface)	0.0109	0.00927	0.011
Endothoracic region	0.00537	0.0047	0.0546
Eye lenses	0.00502	0.00407	0.04091
Gallbladder wall	0.02935	0.0234	0.0373
Heart wall	0.02685	0.0239	0.0324
Kidneys	0.2075	0.0248	0.288
Liver	0.0588	0.043	0.077
Lung	0.01635	0.0151	0.0191
Lymph nodes	0.01685	0.0157	0.0215
Muscle	0.00862	0.00709	0.00881
Oesophagus	0.01375	0.0132	0.016
Oral mucosa	0.00836	0.00723	0.0128
Ovaries*	0.01585	0.0146	0.0189
Pancreas	0.0199	0.0184	0.0218
Prostate	0.01385	0.0112	0.0203

Red (active) bone marrow	0.01495	0.0146	0.0167
Salivary glands	0.10885	0.0748	0.891
Skin	0.00632	0.00536	0.0066
Small intestine wall	0.014	0.0131	0.0152
Spleen	0.0528	0.0372	0.108
Stomach wall	0.0156	0.0143	0.0166
Testes	0.008175	0.00678	0.0085
Thymus	0.008435	0.00702	0.0853
Thyroid	0.00984	0.00912	0.0119
Urinary bladder wall	0.04585	0.0267	0.0814
Uterus/cervix*	0.0153	0.0127	0.0222
Effective dose (mSv/MBq)	0.02305	0.0209	0.0333

*value for adult female

The estimates were calculated based on the time-integrated activity coefficients reported in the publication by Sandgren et al. (2019) using the IDAC Dose 2.1. software.

The effective dose is derived according to ICRP Publication 103.

The effective dose resulting from the administration of an average activity of 2 MBq/kg to an 80 kg weighing man is 3.5 mSv.

For an administered activity of maximal 259 MBq the typical radiation dose to the critical organs kidneys, liver and urinary bladder are 62.2, 13.73 and 14.77 mGy, respectively.

These radiation doses are for (⁶⁸Ga) 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.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. Usual safety precautions for the handling of radioactive materials should be followed.

The vial must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

Isoprotrace should only be used with a gallium (⁶⁸Ga) chloride solution from the approved generators listed below (see preparation description).

Materials used in the process of preparation (not supplied):

- 0.2 µm filter (to be used as vent when needed, depending on the generator being used)
- Needle 20G x 2¾" (*non-metallic/coated needle or plastic spike is mandatory*)
- Needle 23Gx 1" (*non-metallic/coated needle or plastic spike is mandatory*)
- Sterile alcohol pads

Preparation for multidose application

Isoprotrace is supplied as a single-vial kit.

Preparation of gallium (^{68}Ga) gozetotide solution is to be done according to the following aseptic procedure:

For reconstitution and radiolabelling with Eckert & Ziegler GalliaPharm Generator:

- a. Before use, bring the Isoprotrace vial to room temperature for a minimum of 10 minutes.
- b. Remove the cap from the top of the vial and sanitize the closure of the vial with an appropriate alcohol pad to disinfect the surface and allow to air dry.
- c. Place the vial in a suitable shielding.
- d. Connect a 0.2 μm vent filter to a short sterile needle (e.g., 1") and inject the vial. Alternatively, sterile vented plastic spike can be used to connect the $^{68}\text{Ge}/^{68}\text{Ga}$ generator's outlet line in the next step.
- e. Connect the male luer of the generator's outlet line to longer sterile elution needle (e.g., 2 $\frac{3}{4}$ ") or use a sterile vented plastic spike.
- f. Insert the sterile elution needle (or sterile vented plastic spike) into the vial through the rubber stopper.
- g. Elute the generator directly into the vial according to the instructions for use of the GalliaPharm generator to get a net volume of 5 mL of eluate into the vial. Perform the elution manually or by means of a pump.
- h. Disconnect the vial from the generator by removing the elution needle and vent needle with the 0.2 μm vent filter from the rubber stopper and swirl and invert the vial for 15-30 seconds to dissolve its contents.
- i. Let the vial stand upright for 5 minutes at room temperature.
- j. After 5 minutes, assay the vial containing the gallium (^{68}Ga) gozetotide for total radioactivity using a dose calibrator, calculate the radioactivity concentration and record the result.
- k. The solution is ready to use after successful quality control.
- l. Prior to use, visually inspect the solution behind a shielded screen for radioprotection purposes. Only use solutions that are clear without visible particles.
- m. Store the vial containing the gallium (^{68}Ga) gozetotide solution upright in a lead shield below 25 °C until use. At the time of administration, the product must be aseptically withdrawn, and the radioprotection standards must be followed. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Product administration data should also be recorded.
- n. After reconstitution and radiolabelling and successful quality control, gallium (^{68}Ga) gozetotide solution for injection can be diluted with water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection up to a final volume of 10 mL.

For reconstitution and radiolabelling with IRE ELiT GalliAd Generator:

- a. Before use, bring the Isoprotrace vial to room temperature for a minimum of 10 minutes.
- b. Remove the cap from the top of the vial and sanitize the closure of the vial with an appropriate alcohol pad to disinfect the surface and allow to air dry.
- c. Place the vial in a suitable shielding.
- d. Using a syringe coupled with a very fine needle (max. 29G, e.g. insulin syringe), inject 0.5 mL of sterile water for injections into the vial through the surrounding of the stopper. The use of a very fine needle is essential to maintain the negative pressure inside the vial.

- e. Use a new container of water for injections to prevent introduction of metal impurities.
- f. Remove the syringe and reconstitute the vial's contents.
- g. Connect the male luer of the generator's outlet line to a non-metallic or coated sterile elution needle (e.g., 20G).
- h. Turn the generator button to the loading position and wait for at least 10 seconds. Then, turn back the button to its initial position.
- i. Insert the elution needle into the vial through the rubber stopper.
- j. Elute the generator directly into the vial according to the instructions for use of the GalliAd generator to get a net volume of 1.1 mL of eluate into the reconstituted vial.
- k. Disconnect the vial from the generator by removing the elution needle. Swirl and invert the vial for 15-30 seconds to dissolve its contents.
- l. Let the vial stand upright for at least 5 minutes at room temperature.
- m. After 5 minutes, assay the vial containing the gallium (^{68}Ga) gozetotide for total radioactivity using a dose calibrator, calculate the radioactivity concentration and record the result.
- n. The solution is ready to use after successful quality control.
- o. Prior to use, visually inspect the solution behind a shielded screen for radioprotection purposes. Only use solutions that are clear without visible particles.
- p. Store the vial containing the gallium (^{68}Ga) gozetotide solution upright in a lead shield below 25 °C until use. At the time of administration, the product must be aseptically withdrawn, and the radioprotection standards must be followed. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Product administration data should also be recorded.
- q. After reconstitution and radiolabelling and successful quality control, gallium (^{68}Ga) gozetotide solution for injection can be diluted with water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection up to a final volume of 10 mL. Dilution to a minimum volume of 4 mL is required in order to reduce osmolality.

Gallium (^{68}Ga) gozetotide solution is stable up to 4 hours after preparation. Therefore, the radiolabelled solution can be used within 4 hours after preparation according to the radioactivity required for the administration.

Radioactive waste must be disposed of in accordance with relevant national regulations.

Quality Control

a. Materials and equipment:

- Mobile phase – 77 g/L solution of ammonium acetate in water: Methanol (50:50 V/V).
- Glass-fiber iTLC-SG strips (e.g., Agilent SGI001)
- Dose calibrator/ionization chamber or radioTLC scanner.

b. QC process

Using radioTLC scanner

- Transfer the mobile phase into a TLC developing chamber, to a depth of 3 to 4 mm. Cover the chamber and allow the vapour to equilibrate for minimum 5 minutes. The use of freshly prepared solvents is highly recommended.
- Prepare a TLC strip with 10 cm length and 1 cm width.

