swissmedic

Date: 15 June 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Locametz

International non-proprietary name: gozetotide
Pharmaceutical form: kit for radiopharmaceutical preparation
Dosage strength(s): 25 µg
Route(s) of administration: intravenous use
Marketing authorisation holder: ADVANCED ACCELERATOR
Marketing authorisation no.: 68685
Decision and decision date: approved on 3 March 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CT	Computer tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
EANM	European Association of Nuclear Medicine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IR	Infrared spectroscopy
iTLC	Instant thin-layer chromatography
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxin extrusion
Max	Maximum
MBq	Mega-Becquerel
mCi	Millicurie
mCRPC	Metastatic castration-resistant prostate cancer
Min	Minimum
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
OAT	Organic anion transporter

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OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PC	Prostate cancer
PD	Pharmacodynamics
PET	Positron emission tomography
P-gp	P-glycoprotein
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PSMA-11	Gozetotide
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for gozetotide in the above-mentioned medicinal product.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Radiodiagnostic
This medicinal product is intended for diagnostic use only.
Locametz, after radiolabelling with gallium-68, is a radioactive diagnostic agent indicated for the identification of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adult patients with prostate cancer.

2.2.2 Approved indication

Radiodiagnostic
This medicinal product is intended for diagnostic use only.
Locametz, after radiolabelling with gallium-68, is a radioactive diagnostic agent indicated for the identification of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adult patients with prostate cancer.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The standard dosage for adults is 1.8 – 2.2 MBq/kg body weight, with a minimum dose of 111 MBq and a maximum dose of 259 MBq.
The medicinal product has not been tested in children and adolescents.
No dose adjustment is necessary for elderly persons (> 65 years).
A table of radiation exposure for the organs is available.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	23 November 2021
Formal control completed	3 December 2021
List of Questions (LoQ)	8 April 2022
Response to LoQ	7 July 2022
Preliminary decision	4 October 2022
Response to preliminary decision	2 December 2022
Final decision	3 March 2023
Decision	approval

3 Medical context

Prostate cancer (PC) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020, accounting for 14% of all cancers diagnosed. For patients diagnosed with metastatic disease, the overall 5-year survival rate is about 30 to 35%.

Diagnostic tools include prostate-specific antigen (PSA) testing, physical examination, transrectal ultrasound, prostate biopsy, and histopathologic examination. Further imaging procedures at baseline include computer tomography (CT), magnetic resonance imaging (MRI), and bone scan. According to the NCCN guidelines (version 1.2023), 18F piflufolastat PSMA, ^{68}Ga PSMA-11 PET/CT, or PET/MRI can be considered as an alternative to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression.

^{68}Ga-gozetotide is an intravenously administered radioactive diagnostic agent that specifically binds to PSMA, allowing the identification of PSMA-expressing tumours by PET.

The preparation applied for is a kit for a diagnostic radiopharmaceutical, which contains the substance gozetotide (PSMA-11). This is a ligand for gallium-68, which has a half-life of 67.6 minutes (β+-decay). The gallium-68 may be obtained by an Eckert & Ziegler GalliaPharm-Generator (68Ge/68Ga-generator) or an IRE ELiT Galli Ad-Generator (68Ge/68Ga-generator).
The principle of the ligand gozetotide (PSMA-11) is a binding site to the specific tumour antigen, a binding site for the radioactive nuclide, and a linker for these two parts.

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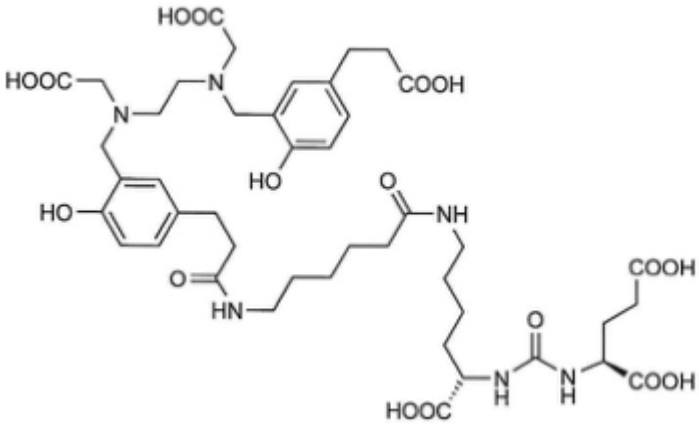
4 Quality aspects

4.1 Drug substance

Drug substance precursor Gozetotide

Molecular structure of the drug substance precursor:



INN:	Gozetotide (sequence: OH-Glu-CO-Lys(Ahx-CC-HBED)-OH)
Chemical name (IUPAC):	(2S)-2-[[(1S)-1-carboxy-5-[6-[3-[3-[[2-[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl-(carboxymethyl)amino]ethyl-(carboxymethyl)amino]methyl]-4-hydroxyphenyl]propanoylamino] hexanoylamino]pentyl]carbamoylamino]pentanedioic acid
Chemical name (CAS):	4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22- [3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl] methyl] (carboxymethyl)amino] ethyl] (carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)-, 2,2,2-trifluoroacetate (1:x)
Molecular formula:	$C_{44}H_{62}N_6O_{17}$
Molecular mass:	Exact mass (m.i.): 946.4 g/mol; molecular weight (av.): 947.0 g/mol

Gozetotide is a white to slightly coloured powder. The lyophilisate is soluble in acetonitrile / water.

Synthesis:
The synthesis of the drug substance precursor gozetotide has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates. The quality of starting materials, reagents, solvents, and auxiliary materials used in the manufacturing process of gozetotide is adequately controlled. The development of the commercial manufacturing process for the drug substance followed a systematic approach which has been addressed in suitable detail. A clear overview of batches used in development, validation, and stability has been presented. Full batch analytical data are provided. Changes introduced have been presented in sufficient detail and have been justified. Based on the outcome of development studies, critical process parameters, in-process controls, and specifications on raw materials, intermediates, and the drug substance precursor have been defined.

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Structure elucidation:
The structure of gozetotide is supported by the synthetic route and has been fully elucidated using adequate analytical techniques. Enantiomeric purity and risk of isomerisations are sufficiently controlled. Potential impurities have been adequately discussed. Based on a detailed evaluation and risk assessment the presence of nitrosamines can be excluded.

Specification:
Gozetotide is used as chemical precursor for radiopharmaceutical preparations. Specification is set according to the general Ph. Eur. monograph 2902 for chemical precursors. The specification also includes the parameters generally required for the control of the quality of the drug substance in line with the general monographs of the Ph. Eur. and with ICH guideline Q6A *Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*. Test parameters are appearance, identification (MS and IR), assay/peptide content, enantiomeric impurity, impurities, residual organic solvents, trifluoroacetic acid (TFA) content, water content, bacterial endotoxins, and bioburden.

Analytical methods:
The test methods are mass spectrometry (MS), infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), chiral GC-MS acc. for enantiomeric purity of amino acids, and gas chromatography (GC) or ion chromatography (IC) for determination of counter ion content TFA. All analytical methods are scientifically based, commonly used, and suitable for general peptide analysis, and are performed in accordance with the respective Ph. Eur. general monographs (e.g. Ph. Eur. 2.2.24, 2.2.28, 2.2.29, 2.2.43, 2.6.12, and 2.6.14). Analytical procedures are validated in a substance-specifical manner with respect to the critical parameters and include considerations of characteristics according to the ICH Q2 guideline on validation of analytical procedures and under consideration of the recommendations of the Guidance for Industry *Analytical procedures and methods validation for drugs and biologicals*. Batch analysis data are provided for several batches used in validation and stability studies. The analytical results are in full compliance with the specified limits and show only little variability with respect to the individual parameters tested, thus demonstrating reliable and reproducible manufacturing with consistent results from batch to batch.

Container closure system:
The container closure system for the lyophilised drug substance precursor gozetotide (10 ml glass vial) is adequately described and its suitability is assured.

Stability:
Appropriate stability data have been generated resulting in a suitable shelf life when packaged in the packaging type as described above.

Quality conclusions
Satisfactory and consistent quality of the drug substance precursor gozetotide is demonstrated.

4.2 Drug product

Description and composition
The drug product gozetotide 25 µg kit for radiopharmaceutical preparation contains gozetotide as the drug substance and sodium acetate trihydrate, sodium chloride, and gentisic acid as excipients. The kit is a multidose product to be labelled with Ga-68 in HCl. To be used with a GalliaPharm or Galli Ad generator. The labelled product can be diluted with NaCl up to a max. volume of 10 ml. Specific activity (GBq/total peptide) is ≤ 42.05/µmol. Different elution volumes are applied depending on the generator type (5 ml vs. 1.1 ml).

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Pharmaceutical development
The development of the product has been described in detail. Activities in an appropriate MBq range were tested during pharmaceutical development. A study on the robustness of the radiolabelling was performed. All necessary information is provided and complete.

Manufacture
All development steps in the manufacturing process of the kit have been described.

Specification
The drug product consists of a clear, colourless solution without undissolved matter. Specifications of the radiolabelled product include tests for appearance, pH range, and radiochemical purity (HPLC, UV, and TLC). Specific end-user specifications have been proposed and include visual appearance, pH, and iTLC for radiochemical purity. All analytical methods for batch specifications have been described and validated. Batch analysis of a suitable number of independent batches has been provided, including all necessary microbiological and impurity testing. All results met the suggested product specifications.

Container closure system
The primary packaging consists of a glass vial closed with a rubber stopper. The rubber stopper is sealed with an aluminium cap with a flip-off polypropylene component.
Material certificates of all materials used are provided.

Stability
Data were provided for a suitable number of batches and met all specifications. Additionally, a stability study plan has been proposed.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

5.1 Pharmacology

The applicant determined the binding affinity of ^{68}Ga-gozetotide in PSMA-positive cells to be 12.0 ± 2.8 nM using competitive cell binding assays. *In vitro* uptake of ^{68}Ga-gozetotide was approximately 55-70%, whereas the internalised fraction was approximately 10% to 15% of the total added radioactivity. The uptake of ^{68}Ga-gozetotide dropped to <0.5% when the investigators used PSMA-negative cells, which demonstrates PSMA-specific uptake/internalisation.
Gozetotide did not exert any interactions in a panel of 87 receptors, ion channels, enzymes, and transporters.
In vitro studies showed that gozetotide was not cytotoxic in PSMA-positive and PSMA-negative cell lines.
In the *in vivo* safety pharmacology studies, gozetotide did not cause any significant effects on either the central nervous system or respiratory function in rats (safety margin approx. 300-fold based on body surface scaling) or on cardiac electrophysiological function or haemodynamics in conscious minipigs (safety margin approx. 690-fold based on body surface scaling).
No pharmacodynamic drug interaction studies have been conducted.

5.2 Pharmacokinetics

Concentrations of radioactivity in blood, urine, and tissues from the biodistribution studies were measured by an automated gamma counter. The applicant quantified gozetotide by liquid chromatography coupled with UV detector. As ^{68}Ga-gozetotide is administered intravenously, no absorption or bioavailability studies were conducted. Umbricht *et al* (2017) investigated the biodistribution of ^{68}Ga- gozetotide in mice showing the kinetics of its uptake and retention in organs and tumours. Gozetotide was metabolically stable against enzymatic degradation when evaluated during 1-hour incubation. The renal system was the major route of elimination. This is consistent with clinical data.

5.3 Toxicology

As outlined in the EMA/CHMP *Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018)* and the FDA Guideline for Industry *Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (2018*), the applicant investigated the toxicity and toxicokinetic profile of gozetotide in a GLP extended single-dose toxicity study in rats with intravenous administration of 0.67 or 1.33 mg/kg gozetotide. Treatment was well tolerated and no toxicological effects were observed. The dose level of 1.33 mg/kg (NOAEL) corresponds to approximately 530-fold the maximum recommended human dose of 25 µg, based on body surface area scaling.
Since ^{68}Ga-gozetotide is a microdose radiodiagnostic, no repeat-dose toxicity studies have been conducted.
In line with the above-mentioned guidelines, the applicant did not conduct genotoxicity, carcinogenicity, or reproductive toxicity studies.
The environmental risk assessment did not raise any concerns.
On the grounds that the disease or condition for which this medicinal product is intended does not occur in the specified paediatric subset(s), a product-specific waiver was granted.

5.4 Nonclinical conclusions

In conclusion, the toxicological profile of ^{68}Ga-gozetotide is considered to be sufficiently characterised. The submitted nonclinical data support the use as a radiodiagnostic. The relevant information has been included in the information for healthcare professionals.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

The PK characteristics of ^{68}Ga-gozetotide have been described based on *in vitro* data and limited clinical data from literature.

ADME

Distribution and excretion
Based on *in vitro* assays, unlabelled gozetotide is moderately (33%) bound to human plasma protein and does not distribute to red blood cells.

Distribution of radioactivity in humans following IV administration of ^{68}Ga-gozetotide was assessed by whole body dosimetry. These data indicated that ^{68}Ga-gozetotide is rapidly distributed throughout the body and that ^{68}Ga-gozetotide has a high renal excretion.

Metabolism
No *in vivo* data on the potential metabolism of ^{68}Ga-gozetotide in humans are available. In *in vitro* assays, unlabelled gozetotide was metabolised to a low extent in human plasma and in human liver and kidney S9 fractions.

Special populations

The PK of gozetotide or ^{68}Ga-gozetotide has not been studied in patients with impaired renal or hepatic function.
The liver is anticipated not to be the major eliminating organ and therefore no impact of hepatic impairment on the exposure of ^{68}Ga-gozetotide is expected.
As renal elimination is anticipated to be the main elimination pathway, clearance of ^{68}Ga-gozetotide is expected to be reduced in patients with impaired renal function.
Potential effects of other demographic factors (e.g. age, ethnic background) have not been studied.

Interactions

Effects of other drugs on Ga-gozetotide
Gozetotide was only minimally metabolised *in vitro* in human plasma and liver and kidney S9 fractions, and urinary excretion is considered to be the major elimination pathway. Therefore, the interaction potential with inhibitors of drug metabolising enzymes is considered to be low.
Based on *in vitro* assays, Ga-gozetotide is not a substrate of MATE1, MATE2-K, OAT1, OAT3, and OCT2. The substrate characteristics of Ga-gozetotide for BCRP and P-gp could not be assessed due to methodological limitations.

Effects of Ga-gozetotide on other drugs
The interaction potential of Ga-gozetotide with CYPs and drug transporters was assessed *in vitro* and the results indicated that gozetotide is not a reversible or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Gozetotide is not an inducer of CYP1A2, CYP2B6, and CYP3A4.
Furthermore, gozetotide did not inhibit BCRP, BSEP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

6.2 Dose finding and dose recommendation

No specific dose-finding studies were performed. The recommended dose of ^{68}Ga-gozetotide is 1.8-2.2 MBq/kg body weight with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 256 MBq (7 mCi). This dose range is in line with the recommendations of the joint European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI)

procedure guideline for prostate cancer (Fendler et al. 2017, updated 2023). In study PSMA-617-01, a dose range of 93 MBq to 288 MBq was applied.

6.3 Efficacy

The sources for the evaluation of efficacy were mainly literature-based. The following two literature studies were found to provide sufficient evidence for efficacy, and data were integrated into the information for health care professionals.

The prospective, randomised, two-arm, open-label study proPSMA (named study 1[1]) investigated the use of ^{68}Ga-gozetotide PET/CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy. Both sensitivity and specificity were higher in patients assigned to ^{68}Ga-gozetotide PET/CT compared to conventional imaging (for details please refer to the "Properties/Effects" section of the attached information for healthcare professionals).

The efficacy of ^{68}Ga-gozetotide for PET of PSMA-positive lesions in men with prostate cancer with suspected recurrence based on an elevated serum PSA level has been established in a prospective single-arm study (named study 2[2]). In 635 patients, presence of prostate cancer was recorded by 3 blinded readers and lesions were validated by histopathologic analysis. Of the evaluable patients, 92% were found to be true positive in one or more regions against the composite reference standard (95% CI: 88%, 95%).
Two meta-analyses in patients receiving ^{68}Ga-gozetotide PET/CT for either initial staging or in the relapse setting confirmed these results[3, 4].

In addition, the applicant conducted the phase 3 study PSMA-617-01 (VISION study) including a reviewer variability study using ^{68}Ga-gozetotide PET/CT scans from study PSMA-617-01. In the VISION study, n=1003 patients with metastatic castration-resistant prostate cancer (mCRPC) received ^{68}Ga-gozetotide PET/CT in combination with contrast-enhanced CT or MRI. Overall, n=831 patients were identified as PSMA-positive and were randomised 2:1 to either PSMA-directed ^{177}Lu-Vipivotid-Tetraxetan in combination with best standard of care or best standard of care only. This study was used to identify patients by ^{68}Ga-gozetotide PET/CT scans for subsequent PSMA-directed radioligand therapy.

6.4 Safety

The safety evaluation was based primarily on the patients of study PSMA-617-01 exposed to ^{68}Ga-gozetotide PET/CT.

The most common treatment-emergent adverse events (TEAE) were fatigue, nausea, constipation, and vomiting. In addition, dry mouth and injection site reactions were observed. There were no serious adverse events or grade 5 TEAEs.

[1] Hofman MS et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet; 395(10231):1208-16
[2] Fendler WP et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. JAMA Oncol; 5(6):856-63.
[3] Hope TA et al. Metaanalysis of 68Ga-PSMA-11 PET Accuracy for the Detection of Prostate Cancer Validated by Histopathology. J Nucl Med. 2019 Jun;60(6):786-793.
[4] Perera M et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020 Apr;77(4):403-417.

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6.5 Final clinical and clinical pharmacology benefit risk assessment

Prostate cancer is the second most commonly diagnosed cancer in men and is associated with high mortality in the metastatic setting. Despite advances in imaging, challenges persist in the correct diagnosis and staging of patients with prostate cancer with the aim of determining the optimal treatment approach.
^{68}Ga-gozetotide is an intravenously administered radioactive diagnostic agent that specifically binds to PSMA, thereby allowing the identification of PSMA-expressing prostate cancer tumours by PET in either the primary staging prior to curative therapy or in the biochemical recurrence setting. The identification of PSMA-positive lesions in patients with prostate cancer also enables the identification of eligibility for PSMA-directed therapy.

Based on the efficacy and safety data provided by the applicant, the overall benefit-risk assessment is positive for the authorised indication.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Locametz was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Locametz® 25 micrograms kit for radiopharmaceutical preparation

Composition

Active substances

25 µg gozetotide

Excipients

1 mg gentisic acid, 78 mg sodium acetate trihydrate, 40 mg sodium chloride
Sodium content per vial: 28.97 mg

Radiolabelled product

The gallium (^{68}Ga) gozetotide solution for injection also contains hydrochloric acid from the gallium-68 chloride solution. The radionuclide is not part of the kit.

Specifications of the radiolabelled product

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

Test	Acceptance criteria
Appearance	Clear, colourless and without undissolved matter
pH	3.2-6.5
Labelling efficiency	Non-complexed gallium-68 species ≤3%

Pharmaceutical form and quantity of active substance per unit

Locametz is a multidose kit for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection containing one vial of 25 µg gozetotide, a white lyophilised powder (powder for solution for injection).
After reconstitution Locametz contains a sterile solution for injection of gallium (^{68}Ga) gozetotide at an activity of up to 1,369 MBq. Gallium (^{68}Ga) gozetotide solution for injection is a sterile, clear, colourless solution for intravenous administration without undissolved matter and with a pH of between 3.2 and 6.5.

Indications/Potential uses

Radiodiagnostic
This medicinal product is intended for diagnostic use only.

Locametz, after radiolabelling with gallium-68, is a radioactive diagnostic agent indicated for the identification of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adult patients with prostate cancer.

Dosage/Administration

The medicinal product is intended exclusively for use in institutions authorised to use radionuclides. Radiopharmaceuticals must only be used by or under the control of qualified healthcare professionals who have completed relevant training and know how to use and handle radionuclides safely, and whose experience and training have been recognised by governmental agencies authorised to issue approvals for the use of radionuclides.

Usual dosage

The recommended dose of gallium (^{68}Ga) gozetotide is 1.8-2.2 MBq/kg of body weight. The minimum dose is 111 MBq and the maximum dose is 259 MBq.

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Patients with renal impairment

No dose adjustment is required in patients with renal impairment.
No data are available on use in patients with severe renal impairment.

Elderly patients

No dose adjustment is required in patients aged 65 years or above (see “Clinical efficacy”).

Children and adolescents

The safety and efficacy of gallium (^{68}Ga) gozetotide in children and adolescents aged under 18 years have not been investigated.

Method of administration

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

Patient preparation

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

Image acquisition

During gallium (^{68}Ga) gozetotide PET image acquisition, the whole body, from the mid-thigh to the skull base, should be scanned. PET images should be acquired 50 to 100 minutes after the intravenous administration of gallium (^{68}Ga) gozetotide solution.
Imaging acquisition start time and duration should be adapted to the equipment used, the individual patient and the tumour characteristics in order to obtain the best image quality possible.

Image interpretation

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

Radiation exposure

The mean effective radiation dose of gallium (^{68}Ga) gozetotide is 0.0166 mSv/MBq, resulting in an approximate effective radiation dose of 4.30 mSv for an administered activity of 259 MBq. Radiation absorbed doses for organs and tissues of adult patients following intravenous injection of gallium (^{68}Ga) gozetotide are shown in **Table 2**.
The highest radiation absorbed dose of gallium (^{68}Ga) gozetotide occurred in the kidneys, salivary glands, bladder wall, lacrimal glands, spleen and liver. The estimated radiation absorbed doses to these organs for an administered activity of 259 MBq are 64 mGy (kidneys), 25 mGy (salivary glands), 22 mGy (bladder wall), 10 mGy (lacrimal glands), 10 mGy (spleen) and 8 mGy (liver).The estimated mean radiation absorbed doses relate to the dose of gallium (^{68}Ga) gozetotide as presented in Table 2. These radiation doses only apply to the injection of gallium (^{68}Ga) gozetotide. Use of CT or a radiation source for attenuation correction increases the radiation dose by an amount that is dependent on the technique used.

Table 2: Estimated mean radiation absorbed doses of gallium (^{68}Ga) gozetotide

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
	Mean	**SEM**
Adrenals	0.0080	0.0004
Brain	0.0032	0.0004
Breasts	0.0034	0.0004
Gallbladder wall	0.0073	0.0004
Lower colon/lower colon wall	0.0051	0.0004
Small intestine	0.0054	0.0003
Stomach wall	0.0053	0.0003
Upper colon/upper colon wall	0.0054	0.0003
Heart wall	0.0045	0.0004
Kidneys	0.2460	0.0406
Lacrimal glands[2]	0.0402	0.0081
Liver	0.0294	0.0057
Lungs	0.0042	0.0004

	Mean radiation absorbed dose (mGy/MBq)[1] N=7	
	Mean	**SEM**
Muscle	0.0043	0.0003
Pancreas	0.0072	0.0003
Red marrow	0.0120	0.0015
Osteogenic cells	0.0102	0.0010
Salivary glands[2]	0.0957	0.0247
Skin	0.0034	0.0003
Spleen	0.0388	0.0067
Testes	0.0040	0.0004
Thymus	0.0037	0.0004
Thyroid	0.0035	0.0004
Urinary bladder wall	0.0840	0.0213
Total body	0.0062	0.0005
Effective dose (mSv/MBq)	**0.0166**	**0.0018**

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

Contraindications

Hypersensitivity to the active substance or any of the excipients listed in the “Composition” section.

Warnings and precautions

Risk of misinterpretation

While the uptake of gallium (^{68}Ga) gozetotide reflects PSMA expression in prostate cancer, gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues.
Interpretation of gallium (^{68}Ga) gozetotide PET imaging findings in the context of histopathology and/or other diagnostic procedures is recommended. The diagnostic performance of gallium (^{68}Ga) gozetotide may be affected by serum PSA levels (see “Clinical efficacy”).

Radiation risk

Gallium (^{68}Ga) gozetotide contributes to the patient’s overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Safe handling and reconstitution procedures must be ensured to protect patients and healthcare workers from unintentional radiation exposure (see “Dosage/Administration” and “Instructions for use and handling” under “Other information”).

Patients should be well hydrated prior to gallium (^{68}Ga) gozetotide administration and should be advised to urinate immediately prior to and frequently during the first hours after image acquisition in order to reduce radiation exposure (see “Dosage/Administration”).

Individual benefit/risk justification

For all patients, the radiation exposure must be justified by the expected diagnostic benefit. The lowest radiation dose with which a diagnosis is still possible should always be chosen.

Sodium content

This medicinal product contains 28.97 mg sodium per vial, equivalent to 1.5% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

Based on *in vitro* interaction studies, gallium (^{68}Ga) gozetotide is not expected to have any clinically significant interactions with other medicinal products. No clinical drug interaction studies were performed.

In vitro evaluation of drug interaction potential

CYP450 enzymes

In vitro, gozetotide is not a substrate of cytochrome P450 (CYP450) enzymes, not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4 and not an inducer of CYP1A2, CYP2B6 and CYP3A4. Gallium (^{68}Ga) gozetotide is not expected to have any drug interactions with CYP450 substrates, inhibitors or inducers.

Transporters

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

Pregnancy/Breast-feeding

Locametz is not intended for use in females.

Pregnancy

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

Breast-feeding

There are no data on the presence of gallium (^{68}Ga) gozetotide in human milk, the effect on the breast-fed child or the effect on milk production.
Animal studies have not been conducted with gallium (^{68}Ga) gozetotide.

Fertility

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

Effects on ability to drive and use machines

The effect of gallium (^{68}Ga) gozetotide on the ability to drive or use machines has not been investigated.

Adverse effects

Summary of the safety profile

The safety profile of gallium (^{68}Ga) gozetotide was evaluated in 1,003 patients receiving gallium (^{68}Ga) gozetotide at a median dose of 1.9 MBq/kg body weight (range: 0.9-3.7 MBq/kg). Patients underwent PET/CT imaging to establish their eligibility for the VISION study based on the PSMA expression of their prostate cancer lesions.
In the VISION study patients received PSMA-targeted therapy plus best standard of care at the discretion of the physician or standard of care alone. Gallium (^{68}Ga) gozetotide was administered concomitantly with standard of care.
Mild to moderate adverse effects occurred after administration of gallium (^{68}Ga) gozetotide, with the exception of a grade 3 fatigue event (0.1%). No serious adverse drug reactions occurred.
The most common adverse drug reactions of any grade (incidence ≥0.5%) are fatigue (1.2%), nausea (0.8%), constipation (0.5%) and vomiting (0.5%).

Tabulated summary of adverse drug reactions

Adverse drug reactions observed in clinical studies (**Table 3**) are listed by MedDRA system organ class. Within each system organ class the adverse drug reactions are listed by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 3: Adverse drug reactions observed with gallium (^{68}Ga) gozetotide in the VISION clinical study

Adverse drug reactions	**Gallium (^{68}Ga) gozetotide 0.9-3.7 MBq/kg N=1003 n (%) All grades**	**Frequency category N=1003 All grades**
Gastrointestinal disorders		
Nausea	8 (0.8)	Uncommon
Constipation	5 (0.5)	Uncommon

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

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

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

In the event of an overdose of gallium (^{68}Ga) gozetotide the elimination of the radionuclide from the body should be increased by hydration and frequent bladder voiding. The effective radiation dose must be estimated.

Properties/Actions

ATC code

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

Physical characteristics

Gallium-68 decays with a half-life of 68 minutes to stable zinc-68. Gallium-68 decays as follows:

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

Gamma constant: 1.8E-4 mSv/hr per MBq at 1 metre.

Shielding lead [Pb]: Half value layer [HVL]: 6 mm; Tenth value layer [TVL]: 17 mm.

Mechanism of action

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

Pharmacodynamics

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

Clinical efficacy

The efficacy of Locametz was established in the two following prospective studies:
In study 1, 300 adult male patients with untreated, biopsy-proven prostate cancer and high risk features were randomised 1:1 and underwent gallium (^{68}Ga) gozetotide PET/CT (N=148) or CT and bone scanning (N=152). A composite reference standard, including histopathology, imaging and clinical and biochemical findings, was available for 295 of 300 (98%) patients and the PET/CT scans were read by two independent readers. Gallium (^{68}Ga) gozetotide PET/CT had improved sensitivity and specificity compared to CT and bone scanning imaging as summarised in **Table 4**. Radiation exposure from gallium (^{68}Ga) gozetotide was lower (8.4 mSv, 95% CI: 8.1, 8.7) than CT and bone scanning radiation exposure (19.2 mSv, 95% CI: 18.2, 20.3).
A change in patient management intent occurred in 28% (95% CI: 21, 36) of patients undergoing gallium (^{68}Ga) gozetotide PET/CT and in 15% (95% CI: 10, 22) of patients undergoing CT and bone scanning. The change in patient management upon gallium (^{68}Ga) gozetotide PET/CT imaging included either a transition from curative to palliative treatment intent or a change in treatment approach (14% of patients each).

Table 4: Efficacy results in patients with untreated, biopsy-proven prostate cancer

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

[1]*Evaluable population*

In study 2, 635 adult male patients with histopathology-proven and biochemical recurrence (BCR) prostate cancer after prostatectomy (N=262), radiation therapy (N=169) or both (N=204) underwent gallium (^{68}Ga) gozetotide PET/CT or PET/MRI imaging. BCR was defined as serum PSA of ≥0.2 ng/ml more than 6 weeks after prostatectomy or as an increase in serum PSA of at least 2 ng/ml above nadir after definitive radiotherapy. Patients had a median PSA level of 2.1 ng/ml above nadir after radiation therapy (range: 0.1 to 1,154 ng/ml). A composite reference standard, including

histopathology, serial serum PSA levels and imaging (CT, MRI and/or bone scan), was available for 223 of 635 (35.1%) patients, while the histopathology reference standard alone was available for 93 (14.6%) patients. PET/CT scans were read by 3 independent readers blinded to clinical information other than the type of primary therapy and most recent serum PSA level.

Detection of PSMA-positive lesions occurred in 475 of 635 (75%) patients receiving gallium (^{68}Ga) gozetotide and the detection rate was significantly increased with PSA levels. The detection rate of gallium (^{68}Ga) gozetotide PET-positive lesions increased with increasing serum PSA levels (see "Warnings and precautions", "Risk of misinterpretation"). Sensitivity and positive predictive value (PPV) of gallium (^{68}Ga) gozetotide PET/CT imaging are summarised in **Table 5**. Inter-reader Fleiss kappa 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 5: Efficacy results in patients with histopathology-proven and BCR prostate cancer

	Composite reference standard N=223[1]	**Histopathology reference standard N=93[1]**
Sensitivity per patient (95% CI)	N/A	92% (84, 96)
Sensitivity per region (95% CI)	N/A	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

The total detection rate of ^{68}Ga-PSMA-11 PET (positive PSMA PET results, regardless of reference standard) was 75%. Detection rates increased significantly with PSA levels: 38% for <0.5 ng/ml (n=136), 57% for 0.5 to <1.0 ng/ml (n=79), 84% for 1.0 to <2.0 ng/ml (n=89), 86% for 2.0 to <5.0 ng/ml (n=158) and 97% for ≥5.0 ng/ml (n=173), p<0.001.

The efficacy of gallium (^{68}Ga) gozetotide as a method for identifying patients suitable for PSMA-targeted therapy was further established in the multicentre, randomised, open-label, phase III study VISION and in the VISION reviewer variability sub-study.

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

A total of 1,003 adult male patients received gallium (^{68}Ga) gozetotide at a median dose of 1.9 MBq/kg body weight (range: 0.9 to 3.7 MBq/kg) and underwent PET/CT imaging approximately 60 minutes (range: 50 to 100 minutes) after injection. Gallium (^{68}Ga) gozetotide PET/CT scans were assessed in conjunction with contrast-enhanced CT and/or MRI images and were read by independent central readers blinded to clinical information. Of 1,003 patients, 831 were identified as eligible for the VISION clinical study.

A total of 125 gallium (^{68}Ga) gozetotide PET/CT baseline scans were evaluated in conjunction with contrast-enhanced CT and/or MRI images by three independent people blinded to clinical information to assess inter-reader variability. Of the 125 PET/CT scans, 20 were used to assess intra-reader reproducibility. Inter-reader Fleiss kappa was 0.60 (95% CI: 0.50, 0.70) across the three independent readers, while intra-reader Cohen kappa was 0.78 (95% CI: 0.49, 0.99), 0.76 (95% CI: 0.46, 0.99) and 0.89 (95% CI: 0.67, 0.99) for each reader.

Elderly patients

In the VISION clinical study 752 of 1,003 (75%) patients were aged 65 years or older. No overall differences in safety and efficacy were observed between these patients and younger patients.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Intravenously injected ^{68}Ga-PSMA-11 was rapidly cleared from the blood and predominantly taken up by the kidneys (7%), liver (15%), spleen (2%) and salivary glands (0.5%).
Based on *in vitro* data, gozetotide mainly distributes to plasma, with a mean blood-to-plasma ratio of 0.71. Gozetotide is 33% bound to human plasma proteins.

Metabolism

Based on *in vitro* data, gozetotide undergoes hepatic and renal metabolism to a minor extent.

Elimination

It is likely that gallium (^{68}Ga) gozetotide is mainly eliminated via the kidneys. Approximately 14% of the gallium (^{68}Ga) gozetotide dose administered is excreted in the urine 2 hours post injection.

Pharmacokinetics in special populations

Hepatic impairment

Gallium (^{68}Ga) gozetotide pharmacokinetics and biodistribution have not been investigated in patients with hepatic impairment. It is unlikely that hepatic impairment affects gallium (^{68}Ga) gozetotide pharmacokinetics to any clinically relevant extent.

Renal impairment

Gallium (^{68}Ga) gozetotide pharmacokinetics and biodistribution have not been investigated in patients with renal impairment. As gallium (^{68}Ga) gozetotide is likely to be primarily excreted renally, increased exposure is to be expected in patients with renal impairment.

Further information

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

Preclinical data

Safety pharmacology

Gozetotide was evaluated in safety pharmacology and single-dose toxicity studies. Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single-dose toxicity.

Carcinogenicity and reproductive toxicity

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

Other information

Incompatibilities

This medicinal product may only be mixed with the medicinal products specified under “Instructions for use and handling”.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Shelf life after opening

After reconstitution store gallium (^{68}Ga) gozetotide solution for injection upright at a temperature below 30°C and use within 6 hours.

Special precautions for storage

Before reconstitution: Do not store above 25°C. Storage of the radiolabelled product must meet the legal requirements on the storage of radioactive materials.

Instructions for use and handling

Before reconstitution the content of Locametz is not radioactive. After reconstitution the gallium (^{68}Ga) gozetotide solution for injection should be handled using appropriate safety measures to minimise radiation exposure. Waterproof gloves, effective radiation protection and other appropriate safety measures should be used when preparing and handling the gallium (^{68}Ga) gozetotide solution in order to avoid unnecessary radiation exposure to workers, clinical personnel and other persons.

Preparation

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

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

The instructions for use from the germanium-68/gallium-68 generator manufacturer must also be followed.

Step 1: Reconstitution

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

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

Follow the generator-specific reconstitution procedures as shown in Table 6 and in Figures 1 and 2. Then continue with step 2.

Table 6: Reconstitution with Eckert & Ziegler GalliaPharm and IRE ELiT Galli Ad generators

If Eckert & Ziegler GalliaPharm generator is used	**If IRE ELiT Galli Ad generator is used**
• Connect the male luer of the outlet line of the generator to a sterile elution needle (size 21G-23G). • Connect the Locametz vial directly to the outlet line of the generator by pushing the elution needle through the rubber septum. • Elute directly from the generator into the Locametz vial.	
Perform the elution manually or by means of a pump according to the generator instructions for use.	Connect the Locametz vial through the vent needle with 0.2 micron sterile air filter to a vacuum vial (25 ml minimum volume) by means of a sterile needle (size 21G-23G) or to a pump to start the elution.
Reconstitute the lyophilised powder with 5 ml of eluate.	Reconstitute the lyophilised powder with 1.1 ml of eluate.

If Eckert & Ziegler GalliaPharm generator is used	If IRE ELiT Galli Ad generator is used
At the end of the elution disconnect the Locametz vial from the generator by removing the elution needle and the vent needle with the 0.2 micron sterile air filter from the rubber septum. Then, invert the Locametz vial once and place it upright.	At the end of the elution first withdraw the sterile needle from the vacuum vial or disconnect the pump in order to establish atmospheric pressure into the Locametz vial. Then disconnect the bottle from the generator by withdrawing both the elution needle and the vent needle with the 0.2 micron sterile air filter needle from the rubber septum.

Figure 1: Reconstitution procedure for Eckert & Ziegler GalliaPharm generator

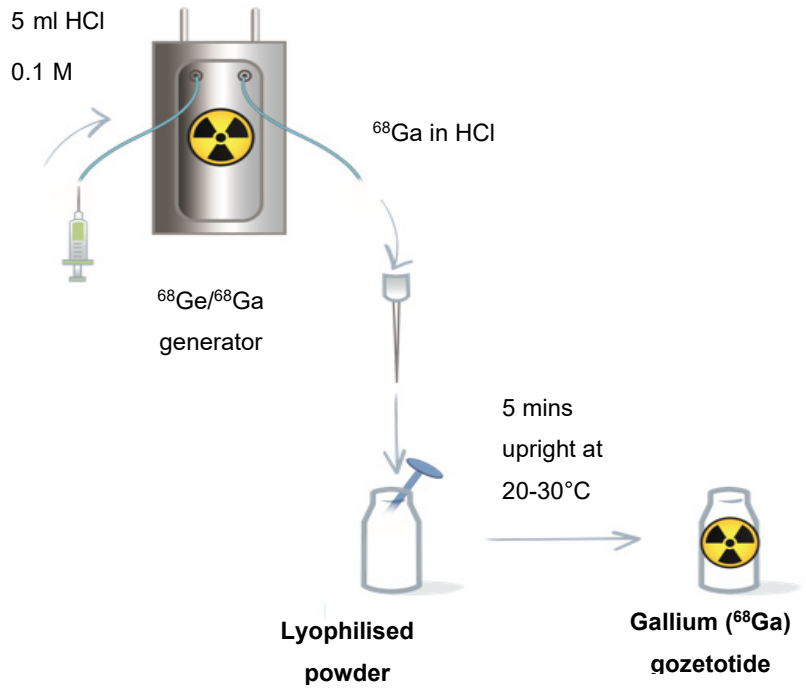
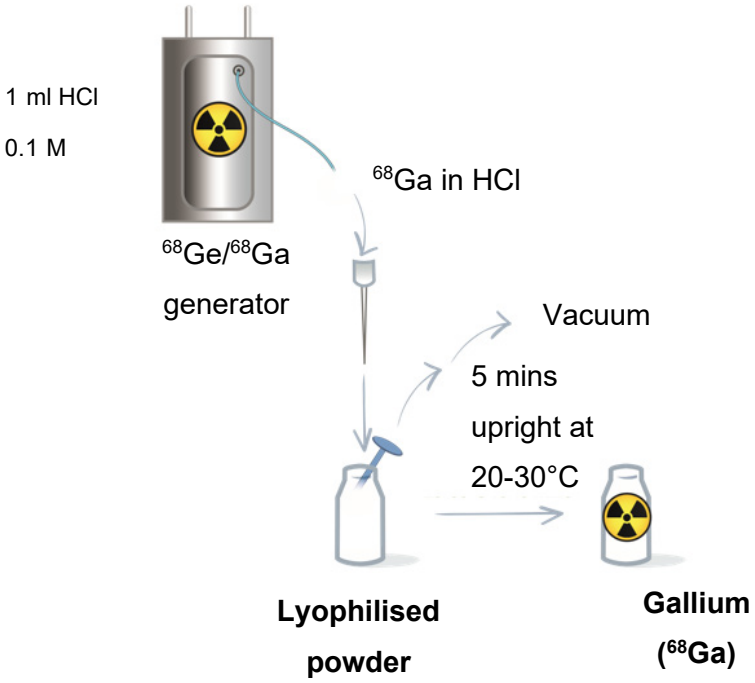


Figure 2: Reconstitution procedure for IRE ELiT Galli Ad generator



Step 2: Incubation

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

Step 3: Specifications and quality control

Perform the quality controls in **Table 7** behind a lead glass pane for radioprotection purposes.

Table 7: Specifications of the gallium (^{68}Ga) gozetotide solution for injection

Test	Acceptance criteria	Method
Appearance	Clear, colourless and without undissolved matter	Visual inspection

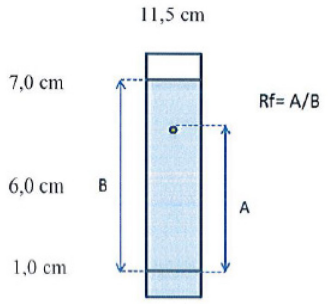
Test	Acceptance criteria	Method
Labelling efficiency	Non-complexed gallium-68 species ≤3%	Instant thin-layer chromatography (ITLC, see details below)

Determine labelling efficiency of gallium (^{68}Ga) gozetotide solution for injection via instant thin-layer chromatography (ITLC).

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

ITLC method

a. Develop the ITLC SG strip for a distance of 6 cm from the point of application (i.e. to 7 cm from the bottom of the ITLC strip).



b. Scan the ITLC SG strip with a radiometric ITLC scanner.

c. Calculate labelling efficiency by integration of the peaks on the chromatogram. **Do not use the reconstituted product if the percentage (%) of non-complexed gallium-68 species is higher than 3%.**

The retention factor (R_f) specifications are as follows:

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

Step 4: Method of administration

a. Aseptic technique and radioprotection measures must be used when withdrawing and administering gallium (^{68}Ga) gozetotide solution for injection.

b. Prior to use visually inspect the prepared gallium (^{68}Ga) gozetotide solution for injection behind a lead glass pane for radioprotection purposes. Only solutions that are clear, colourless and without undissolved particles should be used (see “Composition”).

c. After reconstitution gallium (^{68}Ga) gozetotide solution for injection can be diluted with water for injections or sodium chloride 9 mg/ml (0.9%) solution for infusion up to a final volume of 10 ml.

d. Using a single-dose syringe fitted with a sterile needle (size 21G to 23G) and protective shielding, aseptically withdraw the prepared gallium (^{68}Ga) gozetotide solution for injection prior to administration (see “Dosage/Administration”).
e. The total radioactivity in the syringe must be verified with an activimeter immediately before and after gallium (^{68}Ga) gozetotide administration to the patient. The activimeter must be calibrated and comply with international standards (see “Dosage/Administration”).

Waste disposal

Radioactive unused products or waste materials may only be disposed of as per prevailing Swiss radiation protection regulations.

Swissmedic number

68685

Pack sizes

Pack containing 1 multidose kit for preparation of gallium (^{68}Ga) gozetotide solution for injection. Locametz is supplied in one 10 ml type I Plus glass vial closed with a rubber stopper and sealed with a flip-off cap.
[A]

Marketing authorisation holder

Advanced Accelerator Applications International SA, 1204 Geneva

Information last revised

October 2022