NOVARTIS

Patient Safety & Pharmacovigilance

Gozetotide

AAA517

EU Safety Risk Management Plan

Active substance(s) (INN or common name)	gozetotide
Product(s) concerned (brand name)	Locametz
Document status	Final
Version number	2.1
Data lock point for this RMP	30-Sep-2024
Date of final sign off	04-Feb-2025

Template version 6.4, Effective from 12-Dec-2023

Rationale for submitting an updated RMP:

This EU RMP v2.1 is updated to implement the changes requested by the Rapporteur regarding the variation Type 1B EMEA/C/005488/IB/0014 (variation report issued on 08-Jan-2025) by removing the educational material (PET imaging reader training for HCPs) from the RMP and removing the important potential risk "PET imaging interpretation errors" from the list of safety concerns and reclassifying it as a 'risk not considered important'.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 2.0
Part I	None
Part II	Updated post-authorization exposure based on the data cut-off date 30-Sep-2024. The important potential risk "PET imaging interpretation errors" was removed from the list of safety concerns and reclassified as a 'risk not considered important'.
Part III	None
Part IV	None
Part V	Removed educational material for HCPs related to "PET imaging interpretation errors". Updated the text regarding risk minimization plan/measures to reflect the change by removing the "PET imaging interpretation errors" from the list of safety concerns as an important potential risk.
Part VI	Updated to reflect the changes in Part V.
Part VII	Annex 6: Removed text associated with educational material for HCPs as part of risk minimization measures related to "PET imaging interpretation errors". Annex 7: Removed MedDRA search terms for spontaneous post-marketing data associated with "PET imaging interpretation errors". Annex 8: Updated with summary of new changes made in the RMP.

Other RMP versions under evaluation

CCI

Details of the currently approved RMP:

Version number: 1.3

Approved with procedure: EMEA/H/C/005488/0000

Date of approval (opinion date): 09-Dec-2022

QPPV name: Dr. Justin Daniels

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of figures

None

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AOR	Adjusted Odds Ratio
aRMM	Additional Risk Minimization Measure
BMI	Body Mass Index
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
CMQ	Customised MedDRA Query
CO	Clinical Overview
CRPC	Castration-Resistant Prostate Cancer
CT	Computerized Tomography Scan
DaPCaR	Danish Prostate Cancer Registry
DDI	Drug-Drug Interaction
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ePLND	Extended Pelvic Lymph Node Dissection
EU	European Union
FDA	Food And Drug Administration
Ga	Gallium
GLP	Good Laboratory Practice
HCP	Health Care Professional
hERG	The Human Ether-À-Go-Go-Related Gene
HR	Hazard Ratio
Lu	Lutetium
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mPC	Metastatic Prostate Cancer
MRI	Magnetic Resonance Imaging
NOAEL	No-Observed-Adverse-Effect-Level
NPV	Negative Predictive Values
OS	Overall Survival
PASS	Post-Authorisation Safety Studies
PC	Prostate Cancer
PCSM	Prostate Cancer–Specific Mortality
PCWG3	Prostate Cancer Working Group 3
PET	Positron Emission Tomography
PPV	Positive Predictive Values
PSA	Prostate-Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
PSUR	Periodic Safety Update Reports

QPPV	Qualified Person for Pharmacovigillance
RLT	Radioligand Therapy
RMP	Risk Management Plan
rPFS	Progression-Free Survival
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SUVmax	Maximum Standardized Uptake Value
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
UK	United Kingdom
US	United States
USPI	United States Prescribing Information

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	The active substance is obtained after radiolabelling of gozetotide, the drug substance of Locametz.
Pharmacotherapeutic group(s) (ATC Code)	V09IX14
Marketing Authorization Applicant	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Locametz
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** LOCAMETZ 25 micrograms kit for radiopharmaceutical preparation
	Summary of mode of action: Gallium (^{68}Ga) gozetotide binds to cells that express PSMA, including malignant prostate cancer cells, which over express PSMA. Gallium (^{68}Ga) is a radionuclide with an emission yield that allows PET imaging.
	Important information about its composition: Gallium (^{68}Ga) gozetotide solution for injection is a sterile, clear, colourless solution for intravenous administration, without undissolved matter and with pH between 3.2 to 6.5. After reconstitution, the gallium (^{68}Ga) gozetotide solution for injection also contains hydrochloric acid derived from the gallium-68 chloride solution.
	Physical Characteristics: Gallium-68 decays with a half-life of 68 minutes to stable zinc-68. Details on principle radiation emission data, and physical decay of gallium-68 are discussed in Table 4-6 and Table 4-7.
Hyperlink to the Product Information	[Current approved SmPC]
Indication(s) in the EEA	**Current:** This medicinal product is for diagnostic use only. Locametz, after radiolabelling with gallium-68, is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings: • Primary staging of patients with high-risk PCa prior to primary curative therapy, • Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,

	• Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate-cancer (mCRPC) for whom PSMA-targeted therapy is indicated.
Dosage in the EEA	**Current:** 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.
Pharmaceutical form(s) and strengths	**Current**: LOCAMETZ is a multidose kit for radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection, containing one vial of white lyophilized powder (powder for solution for injection). **For radiolabelling with gallium-68 chloride solution.** After reconstitution, LOCAMETZ contains a sterile solution for injection of gallium (^{68}Ga) gozetotide at an activity of up to 1369 MBq.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication and target population

2.1 Indication

This medicinal product is for diagnostic use only.

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

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

Diagnostic agents do not lend themselves to traditional epidemiological assessments of incidence and prevalence. As such, the data which follow focus on prostate cancer specifically.

Incidence:

Overall, the reported age-standardized incidence of prostate cancer in Europe ranged from 63.4 per 100,000 using GLOBOCAN data (Ferlay et al 2020) to 100.0-130.0 per 100,000 in France and Germany (Smith-Palmer et al 2019). The age-adjusted incidence reported for the US ranged from 73.3 per 1000,000 in men, based on GLOBOCAN data (Ferlay et al 2020), to 115.3 per 100,000 for the US "SEER 9 areas" (Howlader et al 2020). In regions other than Europe and the USA, the age-standardized PC incidence ranged from an annual incidence of 4.5 per 100,000 males (age-standardization not reported) in the United Arab Emirates

(Radwan et al 2018), to an age-standardized incidence of 70.3 per 100,000 in Oceania based on GLOBOCAN data (Ferlay et al 2020).

Prevalence:

Europe

Ferlay et al 2020 analyzed GLOBOCAN data and provided estimated numbers of prevalent PC cases in 2020 among all age groups. The GLOBOCAN data indicate that in 2020 the prevalence was 518.1 per 100,000 within Europe. Accordingly, Europe has the highest reported prevalence estimate amongst all GLOBOCAN data-based prevalence estimates.

United States

Data from the SEER Program (Howlader et al 2020) showed age-specific (crude) prevalence estimates on PC. The United States cancer prevalence estimates on 1st January 2017 were 900,214 cases diagnosed 0 to 5 years before. With respect to complete estimates, there were 3,170,339 men of all races living with PC in the United States in 2017. The counts are based on 2017 cancer prevalence proportions from the "SEER 13 Areas" (excluding the Alaska Native Registry) and 1st January 2017 US population estimates based on the average of 2016 and 2017 population estimates from the US Bureau of the Census. More recent data from 2020 from the GLOBOCAN program show a prevalence of 509.3 per 100,000 among all age groups in Northern America, which is the second highest prevalence estimate in the world region after Europe (Ferlay et al 2020).

Rest of World

Overall, the PCa prevalence estimates based on GLOBOCAN data (Ferlay et al 2020) in other regions in the world vary from 416.9 per 100.000 in Oceania, over 220.5 per 100.000 in Latin America and the Caribbean, to 49.6 per 100.000 in Asia, 6.9 per 100,000 in Africa, and 5% in Pakistan (Idrees et al 2018). (Idrees et al 2018) conducted a meta-analysis including data from 1994-2016 on PCa in Pakistan and showed that the prevalence of PC ranged from 2% to 8%, with an overall pooled prevalence estimate of 5%. An overview of prevalent PC cases among all age groups for all world regions based on GLOBOCAN 2020 data is provided by (Ferlay et al 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Prostate cancer incidence increases with age. Although only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer, the rate increases up to 1 in every 52 men for ages 50 to 59 years, and peaks even higher in the elderly. Nearly 60% of all prostate cancers are diagnosed in men over the age of 65 years. African-American men have the highest incidence of prostate cancer worldwide, are more likely to develop disease earlier in life when compared to other racial and ethnic groups, and are also prone to be diagnosed with more aggressive type of prostate cancer compared to White men. Rates are also very high among Caribbeans, and Black men in Europe, suggesting that they possess a common genetic background more prone to the development of the cancer (Rawla 2019).

Multivariate analyses showed that high occupational physical activity (AOR 6.7, 95% CI 1.3-35. 1), history of prostatitis (AOR 31.5, 95% CI 9.2-170.5), and old age (over 80 years vs 70 or young, AOR 299.1, 95% CI 5.3-16985.9) were associated with higher risk of PC (Hosseini et al 2010).

Obesity in general was found to be associated with more aggressive PC with higher risk of biochemical recurrence (HR = 1.20, p = 0.026), risk of castration-resistant prostate cancer (CRPC) (HR = 2.12, p = 0.026) and risk of PCSM (HR 3.38, p = 0.0170) (Vidal et al 2017). Another study showed similar results where high BMI was associated with a trend for greater risk of progression to CRPC (HR: 3.36, 95% CI: 0.96-11.71, p=0.063), risk of developing metastases (HR: 3.58, 95% CI: 0.77-16.65, p=0.027) and a trend toward worse PCSM (HR: 8.21 95% CI: 0.97-69.72, p=0.119) (Keto et al 2012).

The main existing PET imaging agents:

The European Commission granted a marketing authorization valid throughout the European Union for Axumin on 22-May-2017. The active substance in Axumin, fluciclovine (^{18}F), works by entering prostate cancer cells via structures (LAT-1 and ASCT2) that are present in high numbers on the surface of these cells.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality data in prostate cancer is limited across EU. (Morgan et al 2010) reported mortality of CRPC in the UK. Following the onset of CRPC, the mortality rate was 201.2 per 1,000 patient years compared with 86.7 per 1,000 for non-CRPC (Morgan et al 2010).

Helgstrand and colleagues reported five-year mortality in men with newly diagnosed mPC. The 5-year overall mortality in the Danish Prostate Cancer Registry (DaPCaR) cohort after diagnosis of de-novo metastatic PC was 78.5% (95% CI, 77.4%-79.5%). In the DaPCaR cohort, 5-year PC-specific mortality significantly decreased from 73.4% (95% CI, 71.2%-75.6%) for patients who were diagnosed during 1995 through 1999 to 56.8% (95% CI, 54.8%-58.8%; p<.0001) for the patients diagnosed during 2005 and 2009 (Figure 28) (Helgstrand 2018).

Five-year PCmortality was stable in the US for men diagnosed with de novo mPC from 1980-1994 and increased slightly for the 2005-2008 period; whereas, it decreased significantly by 16.6% (p<.0001) in the DaPCaR cohort from diagnosis period 1995-1999 to 2005-2009 (Helgstrand 2018).

The majority of men with localized PC died from other reasons (n=11,228, 23.9%) than PC (n=4058, 8.6%) during 1985-1994, while the majority of men with metastatic disease (48%) died from PC during the same period (Seikkula et al 2017).

Palliative radiation was the most common symptomatic skeletal event (83%), followed by spinal cord compression (10%), pathological fracture (6%), and surgery to bone (1%) with the majority of the patients having ≥2 symptomatic skeletal-related events (Saad et al 2018).

Important co-morbidities:

In a recent population-based study, patients with prostate cancer had a significantly higher risk of developing cardiovascular conditions (hazard ratio 1.37, 95% CI: 1.26–1.48), depression (1.86, 95% CI: 1.73–2.01), diabetes (1.30, 95% CI: 1.15–1.47), gastric acid disorders (1.48, 95% CI: 1.39–1.57), hyperlipidaemia (1.18, 95% CI: 1.09–1.29), osteoporosis (1.65, 95% CI: 1.48–1.85) and pain/pain-inflammation (1.47, 95% CI: 1.39–1.55) compared to the control patients. Notably, the hazard ratios for cardiovascular conditions and depression were highest in the first year and declined over time (Ng et al 2018).

Additionally, a longitudinal population-based cohort study in the General Practice Research Database of the UK found that compared with men with similar age but no prostate cancer, PC patients had higher incidence of urinary tract infection, impotence and breast disorder, and a 2.6-fold higher all-cause mortality (Li et al 2012).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
Single and repeat-dose toxicity: Single dose GLP toxicity studies of gozetotide in rats provided a systemic no-observed-adverse-effect-level (NOAEL) at the highest doses tested (1.33 mg/kg). This dose level provides a safety margin based on body surface area conversion of approximately 530-fold relative to the potential maximum human mass dose (25 µg) in a 1.7 m^2 patient.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Reproductive/Developmental toxicity Gallium (^{68}Ga) gozetotide is a microdose radiodiagnostic, therefore no reproductive and developmental toxicity studies were conducted with gallium (^{68}Ga) gozetotide or the gozetotide precursor as they are not required according to the relevant guidelines: CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) and Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (Guideline for Industry, FDA August 2018).	Beta, and gamma radiation cause deoxyribonucleic acid damage and damage male and female germ cells and a developing fetus. The risk is appropriately communicated in product labeling.
Carcinogenicity Gallium (^{68}Ga) gozetotide is a microdose radiodiagnostic, therefore no carcinogenicity studies have been conducted with gallium (^{68}Ga) gozetotide or the gozetotide precursor as they are not required according to the relevant guidelines: CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) and Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (Guideline for Industry, FDA August 2018).	Beta, and gamma radiation cause deoxyribonucleic acid damage and are inherently carcinogenic. The risk is appropriately communicated in product labeling.
Genotoxicity gallium (^{68}Ga) gozetotide is a microdose radiodiagnostic, therefore no genotoxicity studies have been conducted with gallium (^{68}Ga) gozetotide or the gozetotide precursor as they are not required according to the relevant guidelines: CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) and Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (Guideline for Industry, FDA August 2018). An in silico bacterial mutagenicity study was performed which indicated that gozetotide was not a bacterial mutagen and could be treated as a non-mutagenic compound (See results in Section 4.7).	Beta, and gamma radiation cause deoxyribonucleic acid damage and are inherently genotoxic. The risk is appropriately communicated in product labeling.

Safety Pharmacology:	
Cardiovascular Gozetotide was negative in the *in vitro* hERG and the *in vivo* cardiovascular safety pharmacology study in minipigs after administration of single doses up to 0.29 mg/kg.	Based on the current available data, there is no concern relevant to human usage.
Nervous system There were no effects of gozetotide on behavioral, neurologic or autonomic parameters in male Sprague Dawley (SD) rats after a single dose administration of up to 0.75 mg/kg.	Based on the current available data, there is no concern relevant to human usage.
Respiratory system There were no effects of gozetotide on respiratory parameters in male SD rats after a single intravenous administration of up to 0.75 mg/kg.	Based on the current available data, there is no concern relevant to human usage.
Drug-drug interactions	
No DDI studies were required with gallium (^{68}Ga) gozetotide or the PSMA-11 precursor, however in vitro assessments have been carried out with PSMA-11 in lieu of ^{68}Ga-PSMA-11. **CYP450 enzymes** Gozetotide is not a substrate of cytochrome P450 (CYP450) enzymes. It did not induce cytochrome P450 (CYP) 1A2, 2B6, or 3A4 and did not inhibit cytochrome P450 (CYP) CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 *in vitro.* **Transporters** Gozetotide is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 and OCT2 and not an inhibitor of BCRP, BSEP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 *in vitro*.	Based on the current available data, there is no concern relevant to human usage.

Conclusions:

No safety concerns were identified during the non-clinical program of gallium (^{68}Ga) gozetotide.

4 Part II Safety specification Module SIII Clinical trial exposure

Studies included in the clinical development program:

As of the data cut-off (27-Jan-2021), the safety and efficacy of gallium (^{68}Ga) gozetotide for identifying patients amenable to PSMA-targeted therapy were established in study PSMA-617-01 (VISION).

PSMA-617-01 (VISION): An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC).

The alternate primary efficacy endpoints of the VISION clinical study were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review per PCWG3 criteria.

As of data cut-off (27-Jan-2021), a total of 1003 adult male patients received gallium (^{68}Ga) gozetotide at median dose per body weight of 1.9 MBq/kg (range: 0.9-3.7 MBq/kg) and underwent PET/CT image acquisition at approximately 60 minutes (range: 50-100 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.

4.1 Part II Module SIII Clinical trial exposure

Table 4-1 SIII.1: Exposure by age group (Gozetotide Safety Analysis Set)

	Overall	
	Age < 65 (N=251)	**Age >=65 (N=752)**
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose (MBq)		
n	251	752
Mean	166.5	167.3
SD	22.42	23.35
Median	166.5	166.8
Min-Max	113-241	93-288
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose per body weight (MBq/kg)		
n	248	728
Mean	1.8	2.0
SD	0.37	0.41
Median	1.8	2.0
Min-Max	1-3	1-4
Data Cutoff Date: 27-Jan-2021 Source: Annex 7-Table GA-7-1		

Table 4-2 SIII.2: Exposure by race (Gozetotide Safety Analysis Set)

	Overall			
	White (N=868)	**Black or African American (N=66)**	**Asian (N=24)**	**Other/Missing (N=45)**
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose (MBq)				
n	868	66	24	45
Mean	167.6	172.1	161.1	155.2
SD	23.36	14.20	19.50	26.64
Median	166.9	173.9	166.5	155.4
Min-Max	93-288	144-204	117-192	99-200
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose per body weight (MBq/kg)				
n	843	65	24	44
Mean	2.0	1.9	2.1	1.8
SD	0.40	0.44	0.44	0.46
Median	1.9	1.9	2.0	1.7
Min-Max	1-4	1-3	1-3	1-3
Subgroups with at least 10 patients are presented Data Cutoff Date: 27-Jan-2021 Source: Annex 7-Table GA-7-2a				

Table 4-3 SIII.3: Exposure by region (PSMA-11 Safety Analysis Set)

	Overall	
	North America (N=714)	**Europe[1] (N=289)**
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose (MBq)		
n	714	289
Mean	170.8	158.2
SD	19.25	28.81
Median	170.2	157.0
Min-Max	93-237	96-288
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose per body weight (MBq/kg)		
n	710	266
Mean	2.0	1.9
SD	0.43	0.33
Median	1.9	1.9
Min-Max	1-3	1-4
Data Cutoff Date: 27-Jan-2021 Source: Annex 7-Table GA-7-3		

[1] Europe includes sites from Belgium, France, United Kingdom, Denmark, Sweden and Netherlands.

Table 4-4 SIII.4: Treatment Exposure by Ethnicity (PSMA-11 Safety Analysis Set)

	Overall		
	Hispanic or latino (N=18)	**Not hispanic or latino (N=858)**	**Not reported (N=127)**
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose (MBq)			
n	18	858	127
Mean	172.3	170.2	145.9
SD	23.24	20.86	26.35
Median	175.8	170.2	141.0
Min-Max	115-200	93-288	96-202
Gallium (^{68}Ga) gozetotide activity injected-decay corrected dose per body weight (MBq/kg)			
n	18	844	114
Mean	2.1	2.0	1.7
SD	0.37	0.40	0.31
Median	2.1	2.0	1.7
Min-Max	1-3	1-4	1-3
Source: Annex 7-Table GA-7-2b Data Cutoff Date: 27-Jan-2021			

Additional efficacy evaluation for gallium (^{68}Ga) gozetotide

Results from ongoing PSMA-617-01 (VISION) study, along with the below listed sources constitute the evidence and support for the successful use gallium (^{68}Ga) gozetotide in the detection of prostate cancer lesions in patients across the spectrum of prostate cancer.

Two studies conducted by Endocyte/AAA and 24 articles from published literature, together with the labels for the recently FDA-approved gallium (^{68}Ga) gozetotide for UCLA and UCSF, provide evidence and support for the successful use of gallium (^{68}Ga) gozetotide in the detection of prostate cancer lesions in patients across the spectrum of prostate cancer (gallium (^{68}Ga) gozetotide CO).

Table 4-5 SIII.5: Overview of sources of efficacy data

Source of data	**Details**
Main study PSMA-617-01 (VISION)	An international, prospective, open-label, multicenter, randomized phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Reviewer variability study	Study using gallium (^{68}Ga) gozetotide PET/CT scans from Study PSMA-617-01 (reviewer variability study)
Published literature on technical performance	9 published prospective studies from a systematic literature search 4 published retrospective studies

Published literature on clinical impact on prostate cancer management	12 prospective published studies from a systematic literature review search*
Systematic literature reviews/meta-analyses	3 published articles
Labels	USPI for recently FDA-approved gallium (^{68}Ga) gozetotide from UCLA and UCSF
*Among the 12 prospective published studies on clinical impact on prostate cancer management, 4 overlap with the literature related to technical performance. Source: (gallium (^{68}Ga) gozetotide-CO)	

Table 4-6 SIII.6: Gallium (^{68}Ga) gozetotide PET/CT efficacy assessments

Criteria	Studies included
Technical performance: • Gallium (68Ga) gozetotide PET/CT identifies PSMA expression in primary tumors (relative to a standard of truth): sensitivity, specificity, and SUV_{max}. • Gallium (68Ga) gozetotide PET/CT scans are interpreted reliably across prostate cancer settings.	A retrospective study by (Woythal et al 2018) showed that gallium (68Ga) gozetotide PET detects PSMA expression and differentiates the higher extent of PSMA expression in cancerous prostate from that of normal prostate (a significantly higher mean SUV_{max} 14.06 ± 15.56 vs. 2.43 ± 0.63; $p < 0.001$), with high sensitivity (97%) and specificity (90%). A prospective study from (Basha et al 2019) showed that gallium (68Ga) gozetotide PET detects PSMA expression in primary prostate cancer tumors with high sensitivity and can correctly identify PSMA-positive prostate cancer during primary staging. The reliability of gallium (68Ga) gozetotide PET scan reads supports use in identifying PSMA-positive lesions, based on the results published literature (Landis and Koch 1977).
Diagnostic performance: • Adequate detection of PSMA expression in different anatomical locations outside the primary tumor. • Better sensitivity, specificity, PPV, NPV, accuracy and detection rate than comparator.	In van Kalmthout et al 2020, 103 adult male patients with biopsy-proven prostate cancer and intermediate- and high-risk features indicated for extended pelvic lymph node dissection (ePLND) underwent gallium (^{68}Ga) gozetotide PET/CT imaging. PET/CT scans were read by two independent blinded readers and ePLND was the histopathology reference standard for 96 out of 103 (93%) patients.
Clinical impact on patient management: The detection of PSMA-positive lesions leads to changes in treatment plans	Ability of gallium (^{68}Ga) gozetotide PET/CT to detect prostate cancer lesions that are not detected by other methods leads to more accurate staging and restaging (vs. comparator/conventional imaging) and has major impact on the planned treatment for patients with prostate cancer was demonstrated in studies (Fendler et al 2020, Hofman et al 2020).
Impact on clinical outcome:	Given the acknowledged diagnostic performance of gozetotide, gallium (^{68}Ga) gozetotide PET/CT scans have

The detection of PSMA-positive lesions can lead to better clinical outcome for patients treated with PSMA-targeted RLT.	been used to select patients to enter trials for PSMA-targeted therapy with 177Lu-PSMA-617 (Emmett et al 2019, Crumbaker et al 2020, Violet et al 2020, Yadav et al 2020a, Hofman et al 2021) and 225Ac-PSMA-617 (Yadav et al 2020b).

Source: (gallium (^{68}Ga) gozetotide CO)

Radiation dosimetry

Gallium-68 decays with a half-life of 68 min to stable zinc-68. The principal radiation emission data, and physical decay of gallium-68 are shown in Table 4-7 and Table 4-8.

Table 4-7 SIII.7: Principal Radiation Emission Data (> 1%) for Gallium-68

Radiation/Emission	% Disintegration	Mean Energy (MeV)
beta+	88%	0.8360
beta+	1.1%	0.3526
Gamma	178%	0.5110
Gamma	3%	1.0770
X-ray	2.8%	0.0086
X-ray	1.4%	0.0086

Source: SmPC

Table 4-8 SIII.8: Physical Decay Chart for Gallium-68

Minutes	Fraction Remaining
0	1
15	0.858
30	0.736
60	0.541
90	0.398
120	0.293
180	0.158
240	0.086
360	0.025

Source: SmPC

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV. 1 Exclusion criteria in pivotal clinical studies within the development program

The majority of the clinically important exclusion criteria in the pivotal VISION trial are relevant for ^{177}Lu-PSMA-617 as the investigational treatment agent, and the ones specific to gallium (^{68}Ga) gozetotide are discussed in the table below.

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Known hypersensitivity to the components of the study therapy or its analogs	Reduction of the risk of hypersensitivity reactions on study	No	This is not an easily identifiable population. It would be expected to be such a small number of patients that the missing information would not impact the benefit-risk profile. It is proposed to include hypersensitivity as a potential risk, however, in patients who are not known to have prior relevant hypersensitivities.
Patients with severe renal impairment	Gallium (^{68}Ga) gozetotide is excreted by the kidney and severe impairment may increase systemic or local tissue exposure.	No	Gallium (^{68}Ga) gozetotide is administered as a single, low dose injection, with a maximum total peptide mass dose of 25 micrograms. Additionally, ^{68}Ga has a short physical half-life (68 mins), and shorter effective half-life of 54 minutes, and the resulting radiation as a result of a gallium (^{68}Ga) gozetotide administration is considered minimal. Based on these two considerations, an increase in exposure due to renal impairment would not be expected to compromise patient safety.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Treatment is intended to be administered to adult (often elderly) males with mPC. Therefore, as gallium (^{68}Ga) gozetotide is not indicated in females, the safety and efficacy of gallium (^{68}Ga) gozetotide in pregnant/breastfeeding women has not been assessed in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with severe hepatic impairment were not included, a limited number of patients with mild and moderate hepatic impairment were included in the gallium (^{68}Ga) gozetotide, clinical development program.
Patients with renal impairment	Patients with mild to moderate renal impairment were included in the clinical development program.
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Treatment exposure by ethnicity is discussed in Table 4-2
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

An estimate of patient exposure was calculated using the sales data of the Locametz kit. By nature of the imaging modality, patients typically receive one single dose. Locametz is a multidose kit that can be used for multiple patients and Novartis does not have information on how many patients are administered with any one kit. For this reason, patient exposure is estimated as one patient per kit sold, acknowledging that this may be an under-estimation of the actual patient number.

Cumulative, world-wide post-marketing exposure of Locametz (gozetotide) 25 micrograms, kit for radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection was 36,020. This patient exposure was until data cut-off date of 30-Sep-2024.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Unlike other prescription-based medicines, this radioligand imaging agent is administered to the patients under a very controlled setting, thereby resulting in a very low/no likelihood of misuse for illegal purposes.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 List of Safety Concerns not considered Important

Risk	Reason for non-inclusion as an RMP safety concern
Renal toxicity	Kidneys are a primary site of PSMA uptake, and gallium (^{68}Ga) gozetotide is rapidly excreted through the kidneys. However, given the microdose of gallium (^{68}Ga) gozetotide administered to the patient as a single dose for imaging purposes there is negligible risk of immediate or long-term renal toxicity. Available clinical safety data do not show renal events attributable to gallium (^{68}Ga) gozetotide. Therefore, the risk of renal toxicity is not important and does not require further investigation or mitigation.
Salivary gland toxicity	Salivary glands have been shown as a site of PSMA uptake. Dry mouth is a very common AE as reported in the pivotal VISION study, but these events are mild and reversible, may not always be attributed to gallium (^{68}Ga) gozetotide, and can be readily managed by symptomatic care. The risk of salivary gland toxicity is not important and does not require further investigation or mitigation.
Occupational and inadvertent exposure	The use of radioactive products implies a risk of exposing healthcare professionals preparing and administering the product. However, given the low radioactive dose (1.8-2.2 MBq/kg of body weight) together with the short physical half-life of the radionuclide gallium-68 (68 min), and shorter effective -half-life of 54 minutes administered to the patient as a single dose for imaging purposes in specialist centers and the guidance to the patients given at these centres, the risk of harmful exposure is considered negligible. This is not an important risk requiring further characterisation or special mitigation measures as patient release procedures implemented by specialist centers are considered adequate to address this risk.
Hypersensitivity	Hypersensitivity reactions can be potentially severe and based on mechanistic plausibility there is a theoretical potential risk of hypersensitivity reactions with imaging agents including gallium (^{68}Ga) gozetotide. Although a rare immunogenic reaction cannot be ruled out, based on current data with a low strength of evidence this risk is not considered to be important.
Injection site reactions	The medicinal product is administered intravenously and may provoke local reactions at the injection site such as pain, swelling, erythema and pruritus. There have been reports of local injection site reactions following administration, but they are uncommon, mild and reversible, and can be readily managed by symptomatic care. This is not an important risk requiring further characterisation or special mitigation measures.

PET imaging interpretation errors	Distribution of PSMA in the body is not specific to the prostate gland and prostate tumor tissue but can be physiologically present in other tissues such as lacrimal glands, salivary glands, liver, spleen and bowel which may complicate the interpretation of the images. Gallium (^{68}Ga) gozetotide uptake is not specific to prostate cancer and may occur in other types of cancers and non-malignant tissues. If the PET scan is not performed according to instructions, e.g., gallium (^{68}Ga) gozetotide radiation level is lower than recommended, timing between administration of gallium (^{68}Ga) gozetotide and scanning, the image quality may be impaired, which may also complicate the interpretation. The risk of PET imaging interpretation errors can be minimized when the scans are interpreted by adequately trained Nuclear Medicines Specialist in the context of the patient's clinical history, histopathological and/or other diagnostic procedures. This is usually the case per standard of care in clinical practice. Available clinical trial data and post-authorization safety data do not show events of PET imaging interpretation errors attributable to gallium (^{68}Ga) gozetotide. Therefore, the risk of PET imaging interpretation errors is not an important risk and does not require further characterization or special mitigation measures.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There are no important potential risks identified for gallium (^{68}Ga) gozetotide.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

According to the variation assessment report EMEA/H/C/005488/IB/0014 (08-Jan-2025), "PET imaging interpretation errors" was reclassified from "Important potential risks "to a "Risk not considered important for inclusion in the list of safety concerns in the RMP".

8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

There are no important identified risks, important potential risks, and missing information identified as safety concerns for gallium (^{68}Ga) gozetotide.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

None

Other forms of routine pharmacovigilance activities for risks

None

10.2 Part III.2. Additional pharmacovigilance activities

None

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

No post authorization efficacy studies are planned or ongoing.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Not applicable.

12.2 Part V.2. Additional Risk minimization measures

Not applicable.

12.3 Part V.3. Summary of risk minimization measures

Not applicable.

13 Part VI: Summary of the risk management plan for LOCAMETZ (gallium (^{68}Ga) gozetotide)

This is a summary of the RMP for LOCAMETZ. The RMP details important risks of LOCAMETZ, how these risks can be minimized, and how more information will be obtained about LOCAMETZ's risks and uncertainties (missing information).

LOCAMETZ's SmPC and its package leaflet give essential information to healthcare professionals and patients on how LOCAMETZ should be used.

This summary of the RMP for LOCAMETZ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LOCAMETZ's RMP.

13.1 Part VI: I. The medicine and what it is used for

This medicinal product is for diagnostic use only.

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

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

LOCAMETZ is a multidose kit for radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide solution for injection, containing one vial of white lyophilized powder (powder for solution for injection). LOCAMETZ is for radiolabeling with gallium-68 chloride solution.

Further information about the evaluation of LOCAMETZ’s benefits can be found in LOCAMETZ’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of LOCAMETZ, together with measures to minimize such risks and the proposed studies for learning more about LOCAMETZ's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of LOCAMETZ are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LOCAMETZ. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

13.2.2 Part VI - II B: Summary of important risks

Not applicable.

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of Locametz.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Locametz.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

None

Annex 6 - Details of proposed additional risk minimization activities

Not applicable.