Medicines Evaluation Board

Public Assessment Report
Scientific discussion

Isoprotrace 10 microgram, kit for radiopharmaceutical preparation (gallium (^{68}Ga) gozetotide)

NL/H/5654/001/DC

Date: 25 August 2026

This module reflects the scientific discussion for the approval of Isoprotrace 10 microgram, kit for radiopharmaceutical preparation. The procedure was finalised on 10 January 2024. For information on changes after this date, please refer to section 'steps taken after finalisation' at the end of this PAR.

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List of abbreviations

(^{68}Ga)	Gallium-68
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AI	Acceptable Intake
ANOVA	Analysis of Variance
BCS	Biopharmaceutics Classification System (-based biowaiver)
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen / The Medicines Evaluation Board
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State(s)
CNS	Central Nervous System
DCP	Decentralised Procedure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERP	European Reference Product
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LALA	Locally Applied, Locally Acting
MAH	Marketing Authorisation Holder
PAR	Public Assessment Report
PD	Pharmacodynamics
PET/CT	Positron Emission Tomography–Computed Tomography
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PSMA	Prostate-specific membrane antigen
PSURs	Periodic safety update reports
QC	Quality Control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TFA	Trifluoroacetic Acid
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

Note: *Not all abbreviations may apply for this PAR.*

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member State have granted a marketing authorisation for Isoprotrace 10 microgram, kit for radiopharmaceutical preparation from Billev Pharma ApS.

This medicinal product is for diagnostic use only.

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

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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1. Rationale for the product

The marketing authorisation was applied for pursuant to Article 8(3) Full or full-mixed application (complete dossier) of Directive 2001/83/EC.

The MAH submitted a study report of a non-clinical safety study in combination with bibliographical references which is considered sufficient for an Article 8(3) mixed application. Furthermore, the MAH has requested and received a product-specific waiver for all subsets of paediatric populations, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

This application has been assessed with the Netherlands as Reference Member State (RMS) and as concerned Member State (CMS) Germany.

Authorisation of the product in the additional concerned Member States Cyprus, Denmark, Greece, Spain, France, Italy, Malta, and Sweden has been agreed on 3 February 2025 via the repeat-use procedure (RUP) NL/H/5654/001/E/001.

Authorisation of the product in the additional concerned Member States Austria, Belgium, Czechia, Finland, Luxembourg, Norway, Poland, Portugal, and Slovakia has been agreed on 1 February 2026 via the repeat-use procedure (RUP) NL/H/5654/001/E/002.

II.2. About the product

Pharmaco-therapeutic group (ATC Code): V09IX14 gallium (^{68}Ga) gozetotide.
Dispensing status: Prescription only.

This submission is literature-based. [^{68}Ga]Ga-PSMA-11 as a radioactive diagnostic agent is designed for molecular imaging and does not exert any pharmacodynamic effect.

The radiopharmaceutical preparation is for intravenous administration. The mechanism of action of [^{68}Ga]Ga-PSMA-11 is through PSMA binding and uptake into cancer tissue. [^{68}Ga]Ga-PSMA-11 has a high affinity for PSMA, which is highly expressed in prostate cancer. As the agent is retained in PSMA-positive lesions, visualisation of uptake is possible through Positron emission tomography–computed tomography (PET/CT). This effect is well-known and tested in many clinical studies.

Isoprotrace 10 microgram is a cold kit for radiopharmaceutical preparation of [^{68}Ga]gallium PSMA-11. The cold kit should be reconstituted and radiolabelled by the end-user using the eluate of one of the approved radionuclide generators. As this is a radiopharmaceutical product, it should only be received, used and administered by authorised persons and in designated clinical settings that comply with the regulations and/or appropriate licenses of the competent official organisations. The required precautions and instructions regarding these matters, have been included in the labelling, package leaflet and SmPC of the product.

II.3. General comments on the application

For this application, conditions pursuant to Article 21a or 22a of Directive 2001/83/EC have been agreed. Please refer to section IX of this PAR.

II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the medicinal product and batch release situated in the EU.

III. QUALITY ASPECTS

III.1. Introduction

Isoprotrace 10 microgram is a kit for radiopharmaceutical preparation for radiolabelling with gallium (^{68}Ga) chloride solution. The product is a white or almost white powder. Each vial contains gozetotide trifluoroacetate equivalent to 10 micrograms of gozetotide as active substance. The gallium-68 solution is obtained from a ^{68}Ge/^{68}Ga radionuclide generator and

decays by positron emission (energy 511 keV) with a physical half-life of 67.71 minutes to the stable zinc-68 isotope. The radionuclide is not part of the kit.

The excipients are: hydrolysed gelatine, sodium acetate anhydrous and sodium chloride. After radiolabelling, the solution obtained also contains, as excipient, hydrochloric acid.

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

III.2. Active Substance

The structure of the active substance has been adequately proven, and its physico-chemical properties are sufficiently described. The active substance is PSMA-11 (gozetotide), an established active substance described in the PharmEuropa 34.1/Jan 2022. The active substance is used as a carrier only. It is an amorphous white to off white freeze-dried powder and is well soluble in water. PSMA-11 is classified as a peptide obtained by chemical synthesis and applied as a chemical precursor for radiopharmaceutical preparations. For this product, PSMA-11 is labelled with gallium-68 (^{68}Ga).

Polymorphism is not applicable as the material is dissolved in further processing of the drug product. PSMA-11 is supplied as trifluoroacetic acid (TFA) salt which can be seen as non-stoichiometric salt for which no clear ratio is expressed.

Manufacturing process
The manufacture of the active substance has been adequately described. The used starting materials, solvents and reagents are considered acceptable. Adequate tests and acceptable specifications have been adopted for these.

Quality control of the active substance
The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified in accordance with the applicable ICH Guidelines for impurities in new Drug Substances. The analytical methods applied are suitably described and non-compendial methods have adequately been validated. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements set by the active substance manufacturer and the drug product manufacturer. Batch analytical data demonstrating compliance with this specification have been provided for five batches (three batches tested by the active substance manufacturer and two batches tested by the drug product manufacturer). This is considered acceptable.

Stability of the active substance
Stability data have been submitted for three full scaled batches and one pilot batch of the active substances in accordance with the applicable European guidelines. Based on the data submitted, the re-test period for the active substance was confirmed for 24 months when stored under the stated conditions. This is acceptable.

III.3. Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients

is justified, and their functions explained. During the formulation development the pH, and appearance of the cake (freeze-dried product), and the radiopharmaceutical purity were monitored. The formulation was optimised to be in line with stated Ph.Eur. 3044 – Gallium (^{68}Ga) PSMA-11 injection acceptance criteria. Also, the reconstitution time of the cold kit, water content and osmolarity were evaluated and optimised for the reconstitution and radiolabelling procedure including further dilution with water for injection (WFI) or 0.9% sodium chloride when applicable. For the manufacturing development the focus lied on the lyophilisation process development for the cold kit. Three technical batches were manufactured to evaluate the final formulation and lyophilisation process for 3 months accelerated stability studies. The suitability of the radiolabelling procedure has been demonstrated on the extremes of volume and radioactivity on both fresh and aged kits. Furthermore, the difference in solutions obtained with both generators has been sufficiently discussed from a patient perspective.

Manufacturing process

The manufacturing process has been sufficiently described and critical steps identified. The manufacturing process has been validated according to relevant European/ICH guidelines. The radiolabelling procedures for the approved gallium generators have been provided.

The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for two full scaled batches and one smaller batch in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the current version of the Ph.Eur. requirements. These specifications are acceptable.

Microbiological attributes

The sterility test and acceptance criterion for the drug product is in line with the Ph.Eur monograph 0520 - Parenteral preparations and ICH Q6A and accepted. Furthermore, the container has been tested in accordance with the Ph. Eur. 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders. For this product the reconstituted, radiolabelled and possible diluted solution will be used within a short time, maximum 4 hours, and it is not expected that any microbial growth will be possible. The demonstration of the integrity of the container and self-sealing effect of the closure after multiple piercing is considered acceptable.

Quality control of the medicinal product

The medicinal product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for both the cold kit and the reconstituted and radiolabelled product and are as follows:

Cold kit - appearance of the cold kit, appearance of the reconstituted solution, reconstitution time, identification of PSMA-11, PSMA-11 content, gelatin content, water content, pH after reconstitution with different diluted HCl solutions (obtained from commercial available gallium generators), particulate matter subvisible particles, sterility and bacterial endotoxins test (BET).

Radiolabelled drug product - appearance, identification and radiochemical purity (RCP) tests on the radiolabelled product by both thin-layer chromatography (TLC) and high pressure liquid chromatography (HPLC) in line with Ph.Eur. 3044 and pH.

The release and shelf life specification is similar except for water content. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product and are in accordance with the EMA guideline on radiopharmaceuticals.

An adequate risk evaluation report on nitrosamines has been submitted. No risk for the presence of nitrosamines in the medicinal product was identified. This justifies the absence of any further testing for nitrosamine impurity in the active substance and medicinal product.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for four full scaled batches and two smaller batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of the medicinal product

Stability data on the product (cold kit) have been provided for four full scaled batches and two smaller batches stored at accelerated 25°C/ 60% RH (6 months) and long term 2-8°C (max 12 months). The batches were stored in 10 ml multi-dose vial (type I glass) closed with a rubber stopper (bromobutyl) and an aluminium cap with flip-off seal. The stability was tested in accordance with applicable ICH stability guidelines. Photostability studies were not performed, however, the photostability studies on the drug substance demonstrate that the drug substance is not stable when exposed to light. No clear trends are seen for any of the tested parameters at any of the storage conditions. Based on the data submitted, a shelf life of 2 years was granted. The labelled storage conditions are: ‘‘*Store in a refrigerator (2 °C – 8 °C). After reconstitution and radiolabelling: Store upright below 25 °C and use within 4 hours. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.”*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the excipient gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

III.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Isoprotrace 10 microgram has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and medicinal product.

IV. NON-CLINICAL ASPECTS

IV.1. Introduction

To support this application, the MAH submitted two non-clinical studies and results of published literature. The studies performed by the MAH were an extended single-dose toxicity study, and a genotoxicity study (Ames test). Both studies were performed under GLP.

IV.2. Pharmacology

The MAH provided literature demonstrating that in *in vitro* studies, [^{68}Ga]Ga-PSMA-11 binds with high affinity to the prostate-specific membrane antigen (PSMA) and is taken up in PSMA expressing cells. Therefore, [^{68}Ga]Ga-PSMA-11 can be expected to be a specific radio imaging ligand for PSMA expressing cells in PCa.

Several *in vivo* studies have been described that show successful imaging of PSMA-positive tumour specific distribution *in vivo*, which could be blocked by addition of 2-PMPA. PSMA showed good imaging results when compared to other compounds including [^{18}F]-AlF-PSMA 11 and [^{68}Ga]Ga-SC691. Salivary gland uptake was shown to be present. However, tumour uptake was significantly higher, and the intended dose for imaging is such that any interference is not anticipated. Expression levels of PSMA correlated with the visual positivity rate on [^{68}Ga]Ga-PSMA-11 PET and with the PSMA PET %IA/g. Another study showed that [^{68}Ga]Ga-PSMA-11, in a given PSMA+ lesion, is constant under several same-day or serial-day imaging conditions. A comparison of the L-isomer with the D-isomer of [^{68}Ga]Ga-PSMA-11 showed that the L-isomer (present in [^{68}Ga]Ga-PSMA-11) results in improved target-mediated binding properties. Another comparative study showed that [^{68}Ga]Ga-PSMA-11 is a suitable marker for PSMA-positive prostate cancer when comparing PSMA ligand based and non-PSMA-ligand based imaging agents for both PSMA+ and PSMA- tumours. As expected, [^{68}Ga]Ga-PSMA-11 could not detect neuroendocrine prostate cancer (NEPC), which is an aggressive and lethal variant of prostate cancer, and does not express PSMA (including Eder et al., 2012; Guan et al., 2021; Lütje et al., 2019; Osborne et al., 2017; Wang et al., 2018; Zhang-Yin et al., 2020).

Based on the dose used and high specificity PSMA-11, secondary pharmacology action is limited to imaging of other tissues or tumours also expressing PSMA.
A study describing the use of [^{68}Ga]Ga-PSMA-11 and [177Lu]Lu-PSMA-617 in imaging of triple negative breast cancer showed significant accumulation in triple negative breast cancer xenograft MDA-MB231, indicating that [^{68}Ga]Ga-PSMA-11 is an interesting imaging candidate for the identification of metastases of triple negative breast cancer (Morgenroth et al., 2019).

The MAH has addressed safety pharmacology as part of the extended single dose study. Although it can be agreed that PSMA-11 did not induce acute central nervous system (CNS) related, respiratory or cardiovascular effects, this was only evaluated by observation. In a large single arm clinical study with concomitant cardiovascular safety monitoring, no drug-related clinically relevant effects occurred. The included cardiovascular parameters (e.g., blood pressure, heart rate) remained normal and unchanged during and after the examination (Fendler et al., 2019).

While for CNS and respiratory effects it can be agreed that it is sufficiently addressed, cardiovascular safety aspects with regard to QT interval (electrocardiogram; Q wave and the T wave) do not appear to have been evaluated. Upon request, the MAH provided a discussion on the potential of PSMA-11 to induce QT interval prolongation, which was based on a

literature search and an estimation of systemic exposure, which were assessed to sufficiently justify the absence of dedicated cardiovascular studies (Orvos et al., 2019).

The MAH provided a discussion on potential interactions with [^{68}Ga]Ga-PSMA-11 of either similar molecules (2-PMPA) or upregulation of PSMA expression after androgen receptor blocking. Pharmacodynamic drug interaction has been demonstrated with 2-PMPA, a different ligand for the PSMA binding site. While such interaction is not of clinical relevance, the data indicate that pharmacodynamic interaction on the level of the PSMA binding site is possible, if other PSMA ligands are co-administered. But due to the high internalisation rate, the sensitivity of [^{68}Ga]Ga-PSMA-11 for pharmacodynamic interaction is limited (Wang et al., 2018).

As a standard treatment in prostate cancer patients is to block the androgen receptor (ARB), the effect of ARB on imaging quality was tested. ARB resulted in increased tumour expression of PSMA. This resulted in a trend towards better tumour to background ratio, i.e. better imaging (Lückerath et al., 2018).

IV.3. Pharmacokinetics

The MAH described the use of methods of analysis for animal studies. This is acceptable.

Intravenous administration of [^{68}Ga]Ga-PSMA-11 results in a rapid distribution in the whole body followed by a rapid elimination from systemic circulation. Plasma protein binding was found to be in the low range. For [^{68}Ga]Ga-PSMA-11, the protein-bound activity increasing from 40% to 55% over 4 hours (Ioppolo et al., 2020).

Besides the tumour tissue, the kidneys were the organs with highest radiation exposure, followed by the salivary and lacrimal glands, the spleen and the lungs. The liver was not a primary target of radioactivity. Some accumulation was seen in the non-tumour carrying prostate tissue in mice. Some uptake was also noted in the large intestine in one study. In rats, the superior cervical ganglion was found to specifically accumulate radioactivity, in line with the expression of PSMA in this ganglion. The mechanism of salivary gland uptake is not well understood but is most likely only partially mediated by PSMA expression. The distribution data observed in animals correlate well with dosimetry data reported in man. Organs of high exposure were the kidney and the urinary bladder followed by lower but significant exposure in the upper large intestine. The spleen and at a lower level the liver was also exposed (including Afshar-Oromieh et al., 2016; Cytogen, Label; Endepols et al., 2019; Giesel et al., 2017; Hohberg et al., 2016; Kim et al., 2021; Lütje et al., 2019; Osborne et al., 2017; Zlatopolskiy et al., 2019).

[^{68}Ga]Ga-PSMA-11 is stable in blood plasma, and gallium cannot be extracted with transferrin, further supporting complex stability. Metabolism is not reported for [^{68}Ga]Ga-PSMA-11. Due to the short half-life of the radioisotope [^{68}Ga], which decays to stable zinc with a half-life of 68.6 minutes, the primary route of metabolism can be expected to be the loss of the radioactive [^{68}Ga] which is chelated in the HBED-chelator moiety (Endepols et al., 2019; Ioppolo et al., 2020; Lütje et al., 2019).

The primary route of [^{68}Ga]Ga-PSMA-11 excretion is the urinary route (Chen et al., 2021; Afshar-Oromieh et al., 2012; Pfob et al., 2016).
High dose administration of monosodium glutamate was shown to reduce the unspecific uptake of [^{68}Ga]Ga-PSMA-11. This confirms the hypothesis that the glutamate transporter contributes to non-specific PSMA-11 internalisation. While this may not lead to improved imaging properties, it may reduce the radiation exposure to the kidneys and the salivary glands.

Administration of cold PSMA-11 was found to reduce the salivary gland and kidney exposure with the therapeutic ligand [177Lu]Lu-PSMA-617. Co-administration of up to 2000 picomoles of PSMA-11 largely reduced both the kidney and salivary gland uptake by >90% as compared to administration of [177Lu]Lu-PSMA-617 alone, with little impact on tumour uptake of [177Lu]Lu-PSMA-617 at the same time. Thus, unlabelled PSMA-11, if administered at high doses, may help to reduce the salivary gland and kidney damage induced by the therapeutic ligand [177Lu]Lu-PSMA-617[51] (Rousseau et al., 2018; Kalidindi et al., 2021).

No other pharmacokinetics studies have been mentioned by the MAH. This is acceptable.

IV.4. Toxicology

In an extended single dose rat study, there were no test-article related effects on clinical observations, body weight, food consumption, haematology, and clinical chemistry of intravenously administered 710 µg/kg PSMA-11. There were no histopathological changes, except for administration site reactions, including mild to marked haemorrhage and polymorphonuclear infiltration in the subcutis (Endepols et al., 2019). According to the MAH, this finding is accompanied with a normal healing process and is a reaction after application of any substance and not related with administrated test item. As this was only observed at day 2 necropsy and not at day 14 necropsy, this can be agreed with. Since the toxicokinetic aspects were not evaluated, a safety margin based on exposure could not be retrieved. However, a dose of 710 µg/kg PSMA-11 corresponds to 5000 times the clinical dose of 10 µg and therefore seems sufficiently high. Also taking into account that the product is indicated for one time use only.

Single-dose associated toxicity with gallium showed LD_{50} values of 46 mg/kg for rats and 43 mg/kg for rabbits (Dudley & Levine,1949).

No repeat-dose studies have been described by the MAH. This is acceptable, based on the intended single dose of 10 µg.

No toxicokinetic studies have been performed. The draft guideline on the non-clinical requirements for radiopharmaceuticals, EMA/CHMP/SWP/686140/2018, dated 15 November 2018, mentions that “According to microdose approach 1, outlined in ICH M3(R2), the results of an extended single dose toxicity study using the intended route of administration (usually i.v. route for radio diagnostics), with toxicokinetic data should be available for the non-radioactive part.” However, since the pharmacokinetic of [^{68}Ga]Ga-PSMA-11 has been adequately described in the overview, the absence of toxicokinetic data is justified. No interspecies comparison has been performed. This is acceptable, based on the single-dose use of 10 µg of [^{68}Ga]Ga-PSMA-11.

In a GLP-compliant Ames test conducted with PSMA-11, there was no evidence for mutagenicity of PSMA-11 when tested in the TA98, TA100, TA1535, TA1537 and TA102 *Salmonella typhimurium* strains up to cytotoxic concentrations in the presence and absence of S9.

No carcinogenicity studies have been performed as the medicinal product is intended for single dose use as a radio imaging agent. This is acceptable.
In an extended single dose toxicity study, reproductive organs were not found to be target organs of toxicity. No dedicated reproduction toxicity studies with [^{68}Ga]Ga-PSMA-11 are reported by the MAH, nor have those studies been conducted. Since the product is intended

for male patients only, this is acceptable. Potential effects on male fertility are sufficiently covered by the single dose study.

No clinically relevant signs of local irritation were reported in an extended single dose toxicity study (internal study report). The local tolerance of [^{68}Ga]Ga-PSMA-11 is supported by data reported following administration to patients in a large single arm clinical study.

Furthermore, the evaluation of excipients, impurities and potential degradation products did not reveal any toxicological concerns.

IV.5. Ecotoxicity/environmental risk assessment (ERA)

For the ecotoxicity / environmental risk assessment, the MAH has submitted the following study results:

Summary of main study results Phase I

The predicted local surface water concentration ($PEC_{surfacewater}$) is 0.000000137 µg/L. This value is more than 73000 times (i.e. nearly 5 orders of magnitude) below the action limit of 0.01 µg/L surface water. Therefore, no phase 2 is triggered based on the $PEC_{surfacewater}$.
The published log_D is reported as -2.91, and the calculated log_P is 0.20. Although no experimental data is submitted for assessment, the values reported are sufficiently low to conclude there is no risk of bioaccumulation.

Conclusions on studies:
The reported $PEC_{surface\ water}$ for [^{68}Ga]Ga-PSMA-11 is below the action limit of 0.01 µg/L and is not a PBT substance as log_{Kow} does not exceed 4.5. Consequently, a Phase II risk assessment is not required. No risks to the environment are to be expected when the medicinal product is used as recommended in the SmPC.

IV.6. Discussion on the non-clinical aspects

The submitted non-clinical safety study included in the non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Isoprotrace 10 microgram is adequate.

Since PSMA-11 (gozetotide) is a well-known substance, the submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Isoprotrace 10 microgram is adequate and is of sufficient high quality in view of the present European regulatory requirements.

V. CLINICAL ASPECTS

No bioequivalence study was submitted to support the application. The MAH justifies waiving of clinical studies by referring to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), appendix II - parenteral solutions on the following grounds: key evidence of favorable effects of ^{68}Ga-PSMA-11 have been investigated using available literature, focused mostly on meta-analysis and systematic reviews. The pharmacokinetics of the proposed formulation has not been studied in PK studies but is based on literature data. Only in the clinical pharmacology study by Kurash et al. (2020) the proposed product has been used. The MAH has provided sufficient justification that differences in excipients, cold-kit vs modular method and amount of gozetotide are not expected to lead to

differences in pharmacokinetics, efficacy or safety. Given the lack expected issues with efficacy or safety, the issue is not further pursued.

V.1. Pharmacokinetics

A literature review has been performed in order to summarise the clinical data available for [^{68}Ga]Ga-PSMA-11. No new study reports have been submitted. This is acceptable.

ADME
^{68}Ga-PSMA-11 is administered via the intravenous route. Therefore, bioavailability is 100%. Several studies were conducted in which organ uptake of Ga-PSMA-11 was investigated. Although small differences could be observed, the general pattern was consistent across studies, despite the differences in study protocols. Exposure was especially high in kidney, followed by submandibular glands, parotid glands, duodenum, spleen and liver (Demirici et al., 2016; Kurash et al., 2020; Prasad et al., 2016).

Similar organ distribution was also seen in the study where the Isoprotrace kit was investigated, indicating that similar distribution is to be expected for this product. This is also in line with the fact that the test and literature products are administered as aqueous intravenous solutions.
The major route of elimination is the renal pathway. The MAH has described the biological half-life (4.4 h), effective half-life (54 min) (Afshar-Oromieh et al., 2016; Green et al., 2017), and the percentage of Ga-PSMA-11 dose excreted into urine (14% in two hours) in section 5.2 of the SmPC (Sandgren et al., 2019).

Dosimetry
The MAH provided different sources for dosimetry assessment in different organs and tissues. The effective dose reported in these studies is consistent between 0.0171-0.023 mSv/MBq, indicating that an administered activity of 150 MBq results in an effective dose of 2.6-3.5 mSv, which was independent on study protocol and data analysis. The absorbed doses in organs between different studies appear more variable. The dosimetry study by Sandgren et al. (2019) is performed according to the most recent guidelines: ICRP Publication 103 (ICRP 103, 2007).

Special populations
No specific data was provided on the pharmacokinetics of Ga-PSMA-11 in special populations. For age (elderly and children) this not considered an issue, as the specific age-range that is expected for this compound is represented in the literature studies provided. In addition, gender effects are not relevant for this indication, which is specific for male subjects. The effects of weight, race and hepatic-impairment on pharmacokinetics were described by the MAH and appeared not to impact PK.

Drug-drug interactions
Data on interactions have not been provided. Ga-PSMA-11 is administered as a single microdose, which does not have a pharmacological effect. Moreover, Ga-PSMA-11 has a short biological half-life. This suggests that the risk for drug-drug interactions might be low.

V.2. Pharmacodynamics

[^{68}Ga]Ga-PSMA-11 as a radioactive diagnostic agent is designed for molecular imaging and does not exert any pharmacodynamic effect. The mechanism of action of [^{68}Ga]Ga-PSMA-11 is through PSMA binding and uptake into cancer tissue. [^{68}Ga]Ga-PSMA-11 has a high affinity for PSMA, which is highly expressed in prostate cancer. As the agent is retained in PSMA-

positive lesions, visualisation of uptake is possible through PET/CT (Ceci et al., 2019; Hope et al;, 2017; Lenzo et al., 2018; Silver et al., 1997). This effect is well-known and tested in many clinical studies. Potential uptake in healthy tissues and/or pathologies other than prostate cancer have been described and are reflected in the labelling.

No pharmacodynamic (PD) interactions were studied in humans given the low dose administered, single application and lack of potential of interaction. This is largely acceptable. However, while no PD interactions in the classical sense are expected, some concomitant medications may have impact on efficacy/diagnostic and technical performance of the product. Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to modulate PSMA expression. Impact of these therapies on diagnostic performance of [^{68}Ga]Ga-PSMA-11 has been reflected in the SmPC. However, the text is very general and does not state the directionality, which may depend on the duration of ADT, with PSMA increased with short-term ADT and decreased after long-term ADT, as well as on patient castration status (reduced in mCSPC and increased in mCRPC patients) (including Emmett et al., 2019a, b). Since this data is based on limited studies, the current text is considered sufficient, as the factors determining directionality of change are not fully crystalised. There currently is also no robust data available to suggest the optimal timepoint between ADT administration and PSMA PET imaging in order to reduce or increase (depending on the clinical needs) the effect of ADT on PSMA expression and its impact on PSMA PET imaging.

No clinical data on secondary pharmacology are available. In nonclinical studies addressing the risk for QT interval prolongation, no signs of interference were observed. This is considered acceptable. Overall, the pharmacodynamic section is currently sufficient.

V.3. Clinical efficacy

The use of molecular imaging represents a potential shift in the diagnostics of prostate cancer. The over-expression of PSMA in the majority of prostate cancers provides the opportunity for PSMA based imaging to become an important molecular marker in the diagnostics of this disease. Most importantly, PSMA PET has been adapted by the relevant national, European and international guidelines on prostate cancer. Currently, PSMA-11 is the most widely used agent for prostatic PET/CT diagnostic.

The efficacy of the current application relies on literature using several different gozetotide formulations. Limited bridging data could be presented. No further data could be retrieved from the publications. The MAH has provided sufficient justification that differences in excipients, cold-kit vs modular method and amount of gozetotide are not expected to lead to differences in pharmacokinetics, efficacy or safety. Given the lack expected issues with efficacy or safety, the issue is not further pursued. The MAH proposes use of [^{68}Ga]Ga-PSMA-11 PET/CT in two different indications, biochemical recurrence of prostate cancer and primary staging of prostate cancer.

The largest body of evidence, supporting the efficacy of [^{68}Ga]Ga-PSMA-11 PET/CT is available in the field of recurrent prostate cancer, also known as biochemical recurrence (BCR). This is defined by a rise in prostate specific antigen after primary curative therapy (usually radical prostatectomy or radiotherapy). Measuring sensitivity and specificity is often not feasible due to the lack of a histopathological reference in most studies. Therefore, detection rate was often used in the evaluation of the diagnostic agent. Several large meta-analyses are published, providing evidence on the usefulness of [^{68}Ga]Ga-PSMA-11 PET/CT in this clinical setting. Detection rates, as reported in these studies, are as high as 95%,

especially in patients, presenting with PSA levels over 2 ng/mL. Limited data is available on the sensitivity and specificity of [^{68}Ga]Ga-PSMA-11 PET/CT in BCR, where histopathology is used as gold standard. However, these studies provide excellent data, with sensitivity, specificity, negative predictive value, positive predictive value, most often ranging from 90 – 100% (i.e. the meta-analyses by Hope et al., 2019). Furthermore, the MAH has demonstrated that [^{68}Ga]Ga-PSMA-11 PET/CT leads to a change in patient management in roughly half the patients, which is considered as a substantial benefit to patient care.

For primary staging, evidence is somewhat less extensive but has been growing fast in recent years. Both meta-analyses of retrospective studies and a recent prospective study (Hofman et al., 2020) demonstrated [^{68}Ga]Ga-PSMA-11 PET/CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning. Furthermore, the latest guideline from ESMO (Parker et al., 2020) recommends that for primary staging the patients with intermediate-risk disease are staged for metastases using MRI or CT (abdomen and pelvis) and bone scan and those with high-risk disease using CT (chest, abdomen and pelvis) and bone scan. However, it should be noted that the joint European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG) (EAU - EANM - ESTRO - ESUR - ISUP – SIOG) guideline states (grade 1b evidence) that *PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management."*

Overall, the totality of the evidence presented is considered sufficient to substantiate the use of [^{68}Ga]Ga-PSMA-11 PET in the indication of primary staging in the patients with high-risk PCa. This is due to the fact that the key efficacy study included patients mostly with high-risk PCa (about 90% in van Kalmthout et al., 2020) as defined by the joint European clinical guideline on diagnosis and management of PCa by Mottet et al., 2022. Importantly, data on impact of [^{68}Ga]Ga-PSMA-11 PET on clinical outcomes are lacking, which raises concerns of "overtreatment" of PCa. The renowned expert groups (Mottet et al., 2022) do not recommend the use of ^{68}Ga-PSMA PET the patients with intermediate-risk PCa.
Therefore, adaptation of the claimed indication with restriction of the target population to high-risk PCa patients was requested. However, the MAH proposed to also include patients with intermediate risk for the primary staging indication. The MAH refers to the EANM/SNMMI guideline and proposes to align the indication with the guideline. Importantly, guideline recommendations, while valuable, cannot replace data and are, thus, not acceptable as supportive evidence. As stated by the MAH the guideline was based on the publications by Hofman et al., 2020, Hope et al., 2021 and Calais et al., 2019. For the prospective, phase III clinical study by Calais et al., 2019, only the study protocol is available in public domain. Hofman et al., 2020 and Hope et al., 2021 were already assessed previously and deemed insufficient to support the indication of primary staging in intermediate risk. Hofman et al., 2020 remains a study with high uncertainty because of questionable methodology (surrogate SOT definition) and unclear proportion of high-risk vs intermediate-risk population (study population is referred to as "biopsy-proven prostate cancer and high-risk features"). In the surgery cohort by Hope et al., 2021 a total of 49 patients with intermediate risk disease and 225 with high risk disease were included. Subgroup analyses according to risk stratification demonstrated that in the patients with intermediate risk the sensitivity was 25 [7-59] % whereas it was 42 [31 – 54] % in those with high risk. Based on the lower sensitivity and small sample size, this study does not support an intermediate risk indication. The MAH has amended the indication to only include the primary staging of high-risk patients. Similar to biochemical recurrence, primary staging also leads to a change in patient management in roughly half of the patients. Whether this leads to better outcomes remains unknown and this is adequately reflected in the SmPC.

With regards to the posology, the current joint Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine (EANM) guideline recommends a dose of 1.8–2.2 MBq (0.049–0.060 mCi) per kilogram bodyweight and most of the studies discussed in the clinical overview are within this range. The proposed posology of the current MAH follows this recommendation and the recently approved Locametz. The posology is acceptable.

V.4. Clinical safety

While there is a large pool data on [^{68}Ga]Ga-PSMA-11 PET for efficacy, there are surprisingly few studies or meta-analyses focusing on safety of [^{68}Ga]Ga-PSMA-11. The most comprehensive review up to date has been performed in 2017 by Nielsen et al., 2017 who did not identify any serious safety concern related to the use of [^{68}Ga]Ga-PSMA-11. Very few adverse reactions, such as injection site pain and rash have ever been reported, none of which was serious enough to require any medical intervention. This is not unexpected, given the low dose, lack of specific pharmacodynamics, and single dose application. Overall, [^{68}Ga]Ga-PSMA-11 appears to be very well tolerated and safe.

V.5. Summary Pharmacovigilance system

The MAH has submitted a signed Summary of the MAH's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

V.6. Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Isoprotrace 10 microgram. At the time of approval, the accepted version of the RMP was version 0.4 (DLP: 16 November 2023) with sign-off date 20 December 2023.

Table 1. Summary table of safety concerns as approved in the RMP

Important identified risks	None
Important potential risks	• PET imaging interpretation errors
Missing information	None

The Member States agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

V.7. Discussion on the clinical aspects

No bioequivalence studies have been performed, the clinical aspects of the product have been discussed and supported based on literature data. Bridging to the products used in the literature has been sufficiently justified. This is acceptable.

VI. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation (EMEA/H/C/004140) for content and EndolucinBeta 40 GBq/mL radiopharmaceutical precursor, solution (EMEA/H/C/003999) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VII. POST-APPROVAL COMMITMENTS (PAC's)

The following post-approval commitments apply:

- Type IB variation (category C.I.11.z): to update the RMP post RUP and to remove the PET-imaging interpretation errors from the list of important potentials risks in the safety specifications thereby rendering the educational material redundant is accepted.

At the time of writing this PAR, this commitment has been fulfilled via NL/H/5654/001/IB/001 (see variation table at the end of this PAR).

VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application is partially based on published data on the pharmacology, efficacy and safety of [^{68}Ga]Ga-PSMA-11 as a radioactive diagnostic agent. Bridging of the data in the literature to the current product has been adequately performed. Isoprotrace 10 microgram has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

Based on the review of the data on quality, safety and efficacy, the Benefit/Risk ratio of Isoprotrace 10 microgram, kit for radiopharmaceutical preparation is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The Member States, based on the data submitted, considered that the Benefit/Risk ratio of the product is positive and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 January 2024.

IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N.A.

IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

Initial conditions (as included in MRP/RUP AR) and, if any, additional conditions agreed during MRP):

- Additional risk minimisation measures (including educational material)

The educational material should contain the following key elements:

Safety concern: PET imaging interpretation errors.

Additional Risk minimisation measures: Educational material for HCPs.

Objective:
Medical practitioners qualified to interpret PET scans obtained with gallium (^{68}Ga) gozetotide will have access to self-training material for the interpretation of gallium (^{68}Ga) gozetotide PET scans, to reduce the potential risk of PET imaging interpretation errors.

Rationale for the additional risk minimisation activity:
The educational material provides HCPs with detailed information in order to reduce the potential risk of incorrect interpretation of gallium (^{68}Ga) gozetotide PET scans.

Target audience and planned distribution path:
• Target audience: Medical practitioners intended to read gallium (^{68}Ga) gozetotide PET images.
• Planned distribution path: An online or/and in-person (when online training is not accessible).

Plans to evaluate the effectiveness of the interventions and criteria for success:
• Evaluation of effectiveness of the educational material among medical practitioners qualified to interpret PET scans.
• The criteria for successful effectiveness will be based on frequency of ADRs concerning PET imaging interpretation errors.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5654/001 /E/001	Repeat-use application for new CMS: CY, DK, EL, ES, FR, IT, MT and SE.	Yes	3-2-2025	Approved	N.A.
NL/H/5654/001 /IB/001	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan.	No	18-4-2025	Approved	N.A.
NL/H/5654/001 /II/002	Updates to Mod. 3.2.S, regarding the manufacturing of the active substance.	No	8-6-2025	Approved	N.A.
NL/H/5654/001 /E/002	Repeat-use application for new CMS: AT, BE, CZ, FI, LU, NO, PL, PT and SK.	Yes	1-2-2026	Approved	N.A.
NL/H/5654/001 /IB/003	To extend the shelf-life of the finished product from 2 to 3 years.	Yes	6-5-2026	Approved	N.A.
NL/H/5654/001 /II/004	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. - To add a $^{68}Ge/^{68}Ga$ radionuclide generator.	Yes	21-6-2026	Approved	N.A.