30 May 2024
EMA/285852/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

GalliaPharm

International non-proprietary name: Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride

Procedure No. EMEA/H/C/006053/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

^{18}F	Fluorine-18
^{68}Ga	Gallium-68
^{68}Ge	Germanium-68
^{131}I	Iodine-131
AE	adverse event
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BCR	biochemically recurrent (prostate cancer)
BS	bone scintigraphy
BVC	best valuable comparator
CE	contrast enhanced
CI	confidence interval
CIM	conventional imaging
csPCa	clinically significant prostate cancer
CT	computed tomography
CTE	CT enterography
DOTA	1,4,7,10-tetraazacyclododecane-N, N', N''', N'''-tetraacetic acid
DOTA-NOC	DOTA-Phe^{1}-Nal^{3}-octreotide
DOTA-TATE	DOTA-D-Phe^{1}-Tyr^{3}-Thr^{8}-octreotate
DOTA-TOC	DOTA-D-Phe^{1}-Tyr^{3}-octreotide
DWI	diffusion-weighted imaging
EBR	early biochemical recurrence (of prostate cancer)
ECE	extracapsular extension
EDTA	ethylenediaminetetraacetic acid
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUS	endoscopic ultrasonography
F	female
FEC(H)	fluoroethylcholine
FDG	fludeoxyglucose
FDOPA	6-fluoro-L-3,4-dihydroxyphenylalanine
GBq	gigabecquerel

GEP	gastro-entero-pancreatic
GTV	gross tumour volume
IHC	immunohistocytochemistry
HBP	hepatobiliary phase imaging
HNPGL	head and neck paraganglioma
HP	histopathology
LAN	lanreotide
LN	lymph node
LND	lymph node dissection
LNM	lymph node metastasis (-es)
M	male
MA	marketing authorisation
MBq	megabecquerel
MCC	Merkel cell carcinoma
mCi	millicurie
MIBG	metaiodobenzylguanidine
mp	multiparametric
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mSv	millisievert
MSKCC	Memorial Sloan Kettering Cancer Center
MTC	medullary thyroid cancer
MTV	molecular tumor volume
N/A	not applicable
NaF	sodium fluoride
NF-PitNETs	nonfunctioning pituitary NETs
NET	neuroendocrine tumour
NPV	negative predictive value
PCa	prostate cancer
PET	positron emission tomography
PGL	paraganglioma
PHEO	pheochromocytoma
Ph. Eur.	European Pharmacopeia

p.i.	post injection
PIP	paediatric investigation plan
PPV	positive predictive value
PRRT	peptide receptor radiotherapy
PSA	prostate-specific antigen
PSMA	prostate surface membrane antigen
PSUR	periodic safety update report
PTEN	phosphatase and tensin homolog
PWAmpMRI	prostate/whole-abdomen MRI
RF	radiomics features
RP	radical prostatectomy
RT	radiotherapy
RT-qPCR	reverse transcription quantitative polymerase chain reaction
SI	small intestinal
SmPC	summary of product characteristics
SLND	salvage lymph node dissection
SPECT	single photon emission computed tomography
sRT	salvage radiotherapy
SST	somatostatin
SSTR	somatostatin receptor
SUV	standardised uptake value
SUV_{max}	maximum standardised uptake value
SVI	seminal vesicle infiltration
TRUS-GB	transrectal ultrasound-guided biopsy
TV	tumour volume
UCLA	University of California Los Angeles
UCSF	University of California San Francisco
US	United States of America
US FDA	United States Food and Drug Administration
USPI	United States Prescribing Information
VHL	von Hippel-Lindau (disease)
vs.	versus
WB DWI	whole-body diffusion-weighted imaging

WDTC	well-differentiated thyroid cancer
y	years

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eckert & Ziegler Radiopharma GmbH submitted on 24 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for GalliaPharm, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2021.

The applicant applied for the following indication:

This medicinal product is not intended for direct use in patients.

The eluate from the generator (gallium (^{68}Ga) chloride solution) is indicated for *in vitro* radiolabelling of specific carrier molecules, developed and approved for radiolabelling with such solution, to be used for positron emission tomography (PET) imaging.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/133/2011 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Antonio Gomez-Outes

The application was received by the EMA on	24 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 March 2023
The CHMP Co-Rapporteur's critique of the CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to GalliaPharm on	30 May 2024

2. Scientific discussion

2.1. Problem statement

The applicant is seeking marketing authorisation for the proposed medicinal product GalliaPharm (Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride), radionuclide generator based on full but mixed application according to Article 8 (3) of Directive 2001/83/EC with the results of a nonclinical dosimetry study and supportive published literature. GalliaPharm 0.74 -1.85 GBq, radionuclide generator has been approved in the EU via decentralised procedure (DCP) DK/H/2294 in 2014. The ^{68}Ge/ ^{68}Ga-generator has been used for more than 10 years to obtain a radiopharmaceutical precursor for the labelling of DOTA-conjugated peptides, mainly for use in the diagnostic imaging of NETs and meningiomas. Thus, to demonstrate the clinical utility of the ^{68}Ge/^{68}Ga-generator, information on the use of the ^{68}Ga-labeled peptides for the abovementioned indications is presented, based entirely on published data.

2.1.1. Disease or condition

Radionuclide generators are not intended for direct use in patients, and therefore are not indicated for a specific disease or condition. The target indication proposed by the applicant has been slightly updated as shown below:

Original version:

"This medicinal product is not intended for direct use in patients.

The eluate from the radionuclide generator (gallium (^{68}Ga) chloride solution) is indicated for in vitro radiolabelling of specific carrier molecules, developed and approved for radiolabelling with such solution, to be used for positron emission tomography (PET) imaging".

Current version:

"This radionuclide generator is not intended for direct use in patients.

The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalliaPharm is indicated for in vitro radiolabelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such eluate, to be used for positron emission tomography (PET) imaging."

Radionuclides have widely been used in medical applications such as diagnostic radiology for decades, with the first radiopharmaceuticals commercialised in 1950. Positron Emission Tomography (PET) is a powerful imaging technique that combines nuclear medicine with biochemical analysis. PET imaging / radionuclides-tracer-complex are used in many settings. The application of PET in clinical oncology is increasing since many molecular targets relevant to cancer can be labelled with positron emitter radionuclides. PET imaging can be used in cancer diagnosis, staging, and treatment planning.

2.2. About the product

This medicinal product is a shielded reservoir of the mother radionuclide ^{68}Ge adsorbed to titanium dioxide in a column system for elution of the intended daughter radionuclide, ^{68}Ga, with sterile ultrapure 0.1 mol/l hydrochloric acid. The eluate (gallium (^{68}Ga) chloride solution) is intended for *in vitro* radiolabelling of specific carrier molecules with the positron emitting radionuclide ^{68}Ga. The radiolabelled molecules are subsequently administered by the approved route and used for PET

imaging. The eluate produced by the generator ($^{68}GaCl_3$) is not intended for direct administration to patients.

The $^{68}Ge/^{68}Ga$-generator is provided in strengths ranging from 1.1 GBq to 3.7 GBq. It is produced under aseptic conditions to provide an eluate that is sterile and compliant with its specification.

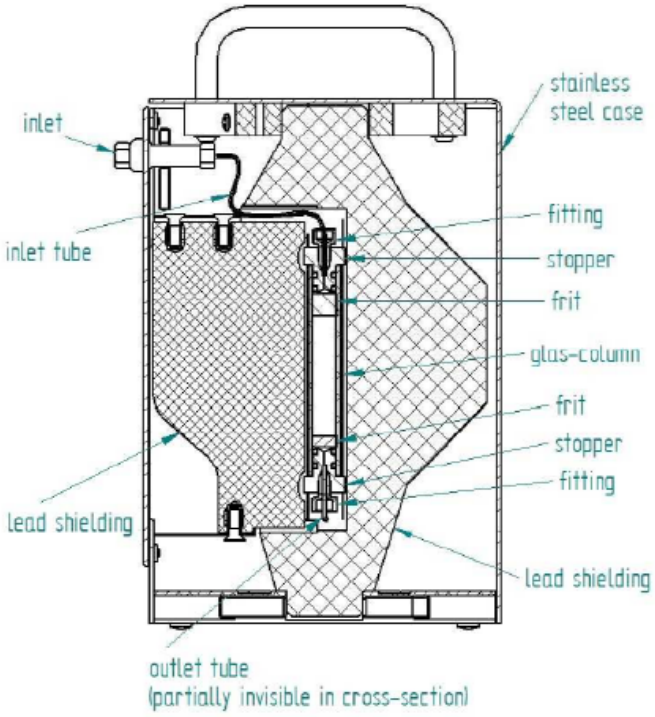
Germanium-68 as mother nuclide is adsorbed to titanium dioxide (TiO_2). ^{68}Ge decays to the daughter nuclide ^{68}Ga by electron capture with a half-life of 270.95 days. ^{68}Ga can be washed out from the generator with 0.1 mol/L hydrochloric acid (= "elution"). By elution, a solution of ^{68}Ga chloride in 0.1 mol/L hydrochloric acid is obtained. Subsequently, ^{68}Ga decays to stable Zinc with a half-life of 67.71 min, in 89% by positron branching accompanied by low photon emission (1.077 keV, 3.22%). The remaining 11% of ^{68}Ga decay by electron capture.

A radionuclide generator is a very uncommon pharmaceutical form used in nuclear medicine as daily source of a fast-decaying radionuclide.

The generator principle is that a radionuclide with a longer physical half-life (parent radionuclide and active substance no. 1) is fixed in the generator and decay into a radionuclide (child radionuclide and active substance no. 2) which can be separated from the generator and is used to radiolabel kits for radiopharmaceutical preparation to obtain together with the kit for the patient use suitable radiopharmaceutical.

The generator is presented as an unstained stainless-steel case with two handles and an inlet and an outlet port. Sterile 0.1 mol/L hydrochloric acid is used as solution for elution which is attached to the inlet port whereas the sterile eluate can be collected at the outlet port. Alternatively, the outlet port can be connected directly to a synthesis apparatus.

Figure 1. Sectional view of the $^{68}Ge/^{68}Ga$ generator



The table below summarises the total activity on the generator and the minimum activity obtained by elution at start of the shelf-life and after 12 months for all available strengths.

Table 1. Activity of the generator and activity obtained by elution

Strength, GBq	Activity inside the radionuclide generator at the start of shelf-life*, GBq	Activity inside the radionuclide generator at the end of shelf-life*, GBq	Eluted activity at the start of shelf-life**, GBq	Potential maximum amount of ^{68}Ga in 5 ml eluate, GBq / ng	Potential maximum amount of ^{68}Ge in 5 ml eluate, kBq / ng	Eluted activity at the end of shelf-life**, GBq
1.11	1.11	0.27	NLT 0.67	1.11 / 0.73	11.1 / 0.04	NLT 0.16
1.48	1.48	0.36	NLT 0.89	1.48 / 0.98	14.8 / 0.06	NLT 0.22
1.85	1.85	0.46	NLT 1.11	1.85 / 1.22	18.5 / 0.07	NLT 0.27
2.22	2.22	0.55	NLT 1.33	2.22 / 1.47	22.2 / 0.08	NLT 0.33
2.59	2.59	0.64	NLT 1.55	2.59 / 1.71	25.9 / 0.10	NLT 0.38
2.96	2.96	0.73	NLT 1.78	2.96 / 1.96	29.6 / 0.11	NLT 0.44
3.33	3.33	0.82	NLT 2.00	3.33 / 2.20	33.3 / 0.13	NLT 0.49
3.70	3.70	0.91	NLT 2.22	3.70 / 2.45	37.0 / 0.14	NLT 0.55

NLT = not less than

* The actual activity inside the radionuclide generator may deviate by ± 10 % from the nominal strength

** In equilibrium

The radionuclide generator provides after elution a sterile gallium (^{68}Ga) chloride solution for radiolabelling. The solution is clear and colourless.

Dosage form: Radionuclide Generator

Strength (Generator size): See Table 1 above

Therapeutic class or indication: V09X

This medicinal product is not intended for direct use in patients. The sterile eluate from the generator (gallium (^{68}Ga) chloride solution) is indicated for *in vitro* radiolabelling of specific carrier molecules, developed and approved for radiolabelling with such solution, to be used for positron emission tomography (PET) imaging.

It should be recognised furthermore that based on the DCP DK/H/2294 the applicant owns marketing authorisations in several member states for "GalliaPharm" radionuclide generators up to a strength of 1.85 MBq starting activity per radionuclide generator.

The ^{68}Ge/^{68}Ga-generator manufactured by Eckert & Ziegler Radiopharma GmbH under the trade name of GalliaPharm was approved in several EU/EEA countries by a decentralised procedure in 2014 (DK/H/2294/001/DC). According to the applicant, it is currently authorised in 16 European countries, United Kingdom (UK), Brasil (actual MA holder is a local company), and Canada. According to the applicant, in the United States of America (US), GalliaPharm is registered as an active pharmaceutical ingredient (API).

$^{68}GaCl_3$ is used for radiolabelling specific carrier medicinal products. $^{68}GaCl_3$ is used clinically in PET diagnostic imaging already for decades. In line with this EMA developed a Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator (EMA/CHMP/337681/2016) which came into effect on 1 August 2017. Furthermore, a European monograph exists for ^{68}Ge/^{68}Ga generators (Ph. Eur. 2464).

2.3. Type of application and aspects on development

As GalliaPharm is not used directly in the patients no clinical data can be generated and the product's PK, PD, efficacy and safety cannot be characterised in the classical sense. It is rather that the efficiency/effectiveness and safety of this product is defined by its technical/quality characteristics. Further, the Directive 2001/83/EC mentions radionuclide generators only within the context of quality assessment.

However, as per the rules defined in the Directive 2003/63, Annex I on radionuclide precursors:

"- Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

- However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented."

In accordance with these rules the applicant has provided published data to substantiate the claim of clinical utility.

The application for marketing authorisation relies upon scientific literature (clinical) and own non-clinical study.

No scientific advice from the EMA was received prior to this marketing authorisation application (MAA). Scientific advice has been sought prior to the first DCP MA application of GalliaPharm in 2013 from the German Federal Institute for Drugs and Medical Devices (BfArM) on 20 May 2010 and from the Danish Health and Medicines Authority (DKMA) on the 07 June 2012. The BfArM agreed that data on the dosimetry of the nuclides ^{68}Ge and ^{68}Ga are not considered necessary for approval of the generator. The DKMA recommended to use Article 8(3) for the application and agreed to the omission of module 2.7 Clinical Summaries, provided a short justification is given. The data on dosimetry was nevertheless obtained based on the study in rats.

The product information (PI) for this product is in line with the PI of the DCP-approved GalliaPharm, as well as with the EMA Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals (EMA/CHMP/167834/2011) and Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator (EMA/CHMP/337681/2016).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as radionuclide generator containing 1.11, 1.48, 1.85, 2.22, 2.59, 2.96, 3.33, and 3.70 GBq of Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride as active substance.

The radionuclide generator contains germanium (^{68}Ge) as mother nuclide which decays to the daughter nuclide gallium (^{68}Ga). The germanium (^{68}Ge) used to manufacture the (^{68}Ge/^{68}Ga) generator is carrier-free.

The radionuclide generator is a system for the elution of sterile gallium (^{68}Ga) chloride solution for radiolabelling in accordance with Ph. Eur. 2464. This solution is eluted from a column on which the mother nuclide germanium (^{68}Ge), parent of ^{68}Ga, is fixed. The system is shielded. The total radioactivity due to germanium (^{68}Ge) and gamma-ray-emitting impurities in the eluate is not more than 0.001%.

5 ml of the eluate from the radionuclide generator with highest strength (3.70 GBq) contain a potential maximum of 3.70 GBq of ^{68}Ga and 0.000037 GBq (37 kBq) of ^{68}Ge corresponding to its possible 0.001 % breakthrough in the eluate. These values equal 2.4 ng of ^{68}Ga and 0.14 ng of ^{68}Ge.

The quantity of gallium (^{68}Ga) chloride solution for radiolabelling Ph. Eur. that may be eluted from the radionuclide generator is dependent on the quantity of germanium (^{68}Ge) present on the date/time of elution, the volume of eluent used (typically 5 ml), and the time elapsed since the previous elution. If mother and daughter nuclides are in equilibrium, more than 60 % of the present gallium (^{68}Ga) activity can be eluted.

Other ingredients are:

Column matrix: titanium dioxide

Solution for elution: sterile ultrapure 0.1 mol/l hydrochloric acid

The product is available in a glass column which consists of a borosilicate glass tube (type I) and polyetheretherketone (PEEK) end plugs which are attached to PEEK inlet and outlet lines via HPLC-style fingertight fittings. These lines are connected to two ports that pass through the outer case of the radionuclide generator as described in section 6.5 of the SmPC.

The column is contained within the lead shield assembly. The shield assembly is secured in a stainless-steel outer case with two handles.

Accessories supplied with the radionuclide generator:

1. PP – container with the eluent, 250 ml sterile ultrapure 0.1 mol/l hydrochloric acid (PP = Polypropylene; a separate hanger is included for PP bottles)
2. Vented spike (ABS = Acrylonitrile Butadiene Styrene/PE = Polyethylene)
3. Adapter 1/16" to male LUER (PEEK)
4. Tubing 60 cm (PEEK)
5. Tubing 40 cm (PEEK)
6. Tubing 20 cm (PEEK)
7. Fingertight fitting 1/16" 10-32 (PEEK)
8. Fingertight fitting 1/16" M6 (PEEK)
9. Stopcock manifold (TPX = Polymethylpentene/HDPE = High Density Polyethylene)
10. Male LUER union (PP)

2.4.2. Active Substance

General information

The chemical name of the active substance is [^{68}Ge]germanium tetrachloride / [^{68}Ga]gallium trichloride corresponding to the molecular formula [^{68}Ge]$GeCl_4$ / [^{68}Ga]$GaCl_3$. It has a relative molecular weight of 209.74 g/mol / 174.29 g/mol. The structure is not applicable as the active substance is an inorganic substance.

The active substance used in the ^{68}Ge/^{68}Ga-generator is germanium (^{68}Ge) chloride and gallium(^{68}Ga) chloride in equilibrium, dissolved in diluted hydrochloric acid and adjusted to an activity concentration

ready for use in the manufacture of the medicinal product ("loading"/adsorption to a pre-assembled titanium dioxide matrix column). Therefore, it is called "germanium (^{68}Ge) chloride loading solution". The relevant characteristics of these simple inorganic substances are not their chemical structure, but their radiophysical properties. ^{68}Ge has a half-life of 270.95 days and decays entirely by electron capture into ^{68}Ga. ^{68}Ga has a half-life of 67.71 minutes and decays to stable ^{68}Zn either by positron-emission (89 %) or electron capture (11 %).

Manufacture, characterisation and process controls

The active substance is manufactured in four manufacturing sites.

The active substance of the generator is germanium (^{68}Ge) chloride/ gallium (^{68}Ga) chloride in equilibrium. The generator is thereby manufactured using a defined solution of the mother nuclide ^{68}Ge, the germanium (^{68}Ge) chloride loading solution. It is obtained from an intermediate, "raw" germanium (^{68}Ge) chloride (solution) manufactured by three manufacturing sites, by adjusting the parameters activity and volume to suitable, specified values. This final form of the active substance is ready for adsorbing ("loading") the mother nuclide ^{68}Ge onto titanium dioxide matrix column in course of the manufacture of the medicinal product.

The radionuclide germanium (^{68}Ge) is manufactured using the stable gallium (^{69}Ga) isotope which is irradiated in a particle accelerator with protons, whereby the nuclear reaction ^{69}Ga(p,2n)^{68}Ge produces the desired radionuclide ^{68}Ge. The irradiated gallium (^{69}Ga) target is then dissolved, ^{68}Ge is separated via extraction or purification and redissolved in diluted hydrochloric acid.

Diluted sterile hydrochloric acid is used to transform the intermediate in the usable loading solution, so that the intended radioactivity amount (of ^{68}Ge) can be loaded on the column of the generator.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The intermediate germanium (^{68}Ge) chloride solution, as well as the active substance, germanium (^{68}Ge) chloride loading solution, are packaged in sterile glass vials that are closed with rubber stoppers and crimped with an aluminium ring which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for: appearance (visual), identity ^{68}Ge (Gamma-ray spectroscopy), activity (Gamma-ray spectroscopy), activity concentration, specific activity (Gamma-ray spectroscopy, AAS, ICP-OES or spectro-photometry), radionuclidic purity (Gamma-ray spectroscopy), content of chemical impurities (AAA, ICP-OES or ICP-MS), hydrochloric acid concentration, residual solvents and volume.

The active substance may contain chemical (elemental) impurities that originate from the target composition. The specification for chemical impurities was set in accordance with the values determined during development. Bivalent and trivalent elements are not absorbed to titanium dioxide and therefore would be removed during the column loading and flushing steps in the course of the generator manufacturing.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 9 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The active substance is a simple, well- characterised inorganic solution. The decay pathway and half-life of ^{68}Ge are known. Therefore, and to avoid extensive experiments with high radioactivity amounts, it is considered appropriate to execute this study with one representative batch of the active substance solution, filled in the primary container. Storage only at ambient temperature is considered sufficient for the same reasons. The study was scheduled for 8 weeks.

Samples of the active substance batch were examined for identity, as well as for chemical and radionuclidic purity.

The identity of the active substance could be confirmed and the radionuclidic purity of the active substance solution did not change for the examined time. Thus, no new/ further radionuclidic impurities are formed by unexpected processes. The results for chemical purity also remained well within the specified limits and were nearly constant with only some very minor variability.

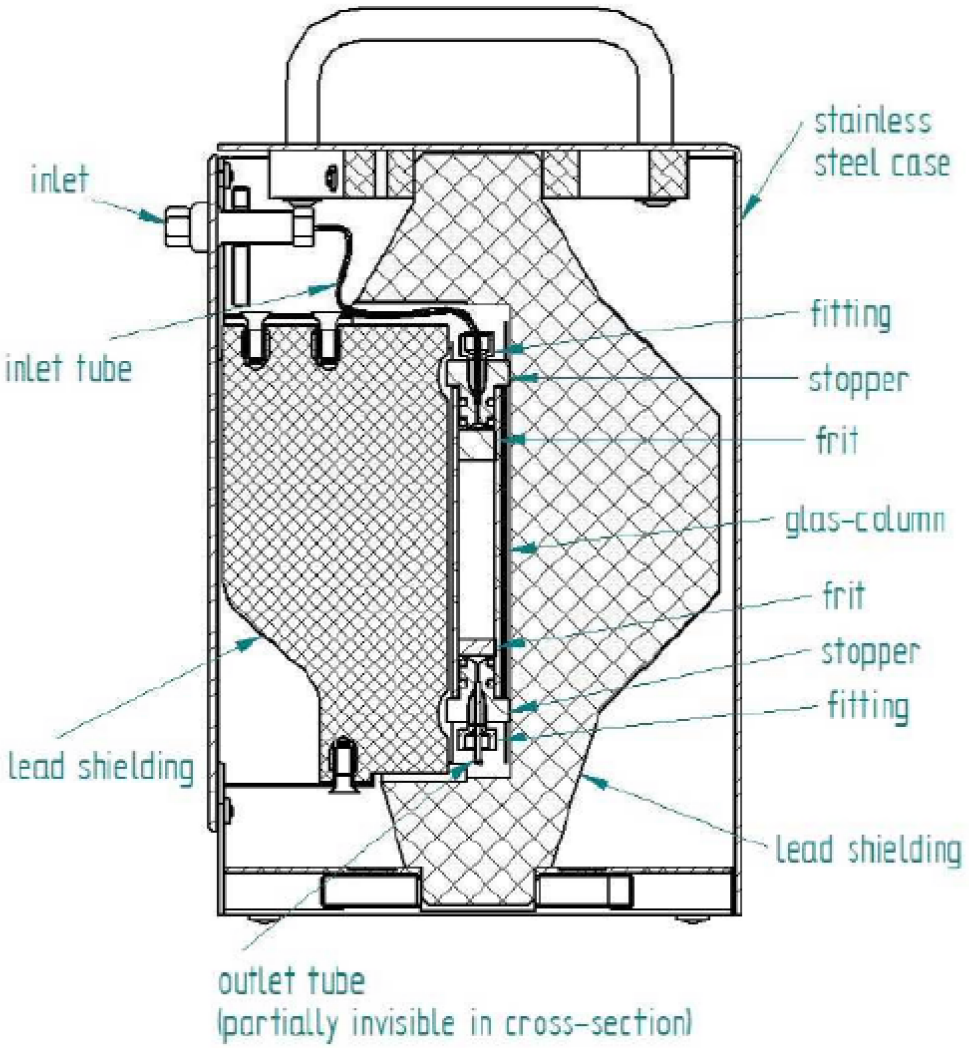
All in all, the results obtained so far (up to week 8 of storage) indicate that no unexpected physico-chemical processes occur in the active substance solution. Therefore, with the currently available data, the proposed shelf-life of 3 months is considered appropriate for the germanium (^{68}Ge) chloride loading solution.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The radionuclide generator is presented as a stainless-steel case with two handles and an inlet and an outlet port. The solution for elution is attached to the inlet port whereas the eluate can be collected at the outlet port. Alternatively, the outlet port can be connected directly to a synthesis apparatus. The radionuclide generator provides after elution a sterile gallium (^{68}Ga) chloride solution for radiolabelling (Figure 2).

Figure 2. Sectional view of the $^{68}Ge/^{68}Ga$ generator



The purpose of the GalliaPharm $^{68}Ge/^{68}Ga$ generator is to provide the radionuclide ^{68}Ga solved in sterile diluted hydrochloric acid by elution with 0.1 mol/l hydrochloric acid. ^{68}Ga is a carrier-free precursor for radiolabelling reactions.

The active substances are radioactive germanium (^{68}Ge) as parent radionuclide in equilibrium with its decay product the radioactive gallium (^{68}Ga), dissolved in dilute hydrochloric acid. Thus, it is present as germanium (^{68}Ge) chloride/ gallium (^{68}Ga) chloride in solution. ^{68}Ge is produced via a nuclear reaction by proton irradiation of a gallium-containing target (non-fission).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The finished product is a reservoir system with radioactive ^{68}Ge adsorbed to titanium dioxide in a column system designed to selectively elute the intended decay product ^{68}Ga with sterile ultrapure 0.1 mol/l hydrochloric acid. The combination of titanium dioxide as adsorption matrix and dilute hydrochloric acid solution as eluent is well established. Therefore, the objective for formulation development was to elucidate appropriate quality grades of the two excipients for an optimal adsorption/ elution performance, meaning good retention of ^{68}Ge to the "stationary phase"/ adsorption

matrix in a column system and a high yield of ^{68}Ga in eluates with minimal contamination by unintended co-elution of the parent radionuclide ^{68}Ge or by other chemical or radionuclidic impurities. Relevant for the manufacturing process of the generator, meaning the loading process to get the germanium-68 fixed for the complete shelf-life of the generator on its column, is to optimise the germanium-68 solution and its concentration of hydrochloric acid in such a way that the germanium-68 is completely absorbed on the column matrix. Titanium dioxide is an inert material that can easily be packed as stationary phase in columns. Tetravalent ions like $^{68}Ge^{4+}$ show good absorption to it, while bi- or trivalent ions like $^{68}Ga^{3+}$ do not. This makes the generator – principle by fixing the parent radionuclide on the column while the child radionuclide can be eluted possible.

Titanium dioxide was selected as column matrix together with 0.1 molar hydrochloric acid as mobile phase to build the core of the radionuclide generator binding the parent radionuclide Germanium-68 as tetravalent ion while the daughter product, the tri-valent Gallium-68 ion is solved in the hydrochloric acid and can be eluted. The applicant demonstrates the reliability of this chromatographic system.

Also the loading process itself is done in a certain frequence and speed to gain best results.

The titanium dioxide packed column is sterilised by gamma-radiation before the parent radionuclide is loaded. Gamma – radiation itself will not change the inorganic titan dioxide.

The germanium (^{68}Ge) chloride loading solution is not sterile but filtered through bacterial retention filter prior to entering the column (all solutions for flushing the column also pass this filter). The suitability of the aseptic manufacturing conditions to produce sterile, pharmaceutical grade generators was examined and confirmed in the course of the process validation. The loaded generator column is not finally sterilised by heat considering the risk to damage the liquid-filled column system and volatility of the parent radionuclide.

The glass of the column is specified as borosilicate glass Ph. Eur. type I, the usual standard for glass used to contain a sterile aqueous solution. Under aqueous acidic environment this type of glass is inert and does also not react with the parent radionuclide Germanium-68 or the daughter radionuclide Gallium-68. The O-Rings, frits and tubes are made of plastic materials as fluorinated rubber, polyether ether ketone (PEEK) and polyethylene (PE). It was demonstrated the stability of the plastic materials for a radiation dose of up to 50 kGy which is above the energy dose which will be deposit in the generator material during the generator's shelf-life.

The casing of the generator column including its tubing consists of a lead shielding as radiation shield and a steel container to give the heavy construction of the fragile generator column in the lead shielding stability and protection.

For the primary packaging material of the hydrochloric acid the applicant proposes two possibilities, a polypropylene bag or a polypropylene bottle which are sterilised by heat after filling.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The key to obtain a reliably working generator system is the quality of the stationary phase, in this case the titanium dioxide stationary phase, which needs to be slushed, washed and conditioned with 0.1 mol/L hydrochloric acid to obtain the optimal loading density of titanium dioxide into the generator column. The sterilisation of the cold prepared titanium dioxide column with γ-radiation is a standard process.

The 0.1 mol/L hydrochloric acid is an excipient. However, the separate preparation and sterilisation process of the hydrochloric acid is considered to be part of the finished product manufacturing process.

The 0.1 mol/L hydrochloric acid should be sterile because otherwise the sterility of the complete generator and the generator eluate, the [^{68}Ga]Gallium chloride solution for radiolabelling, is not assured for its shelf-life of up to 18 months. Therefore, the manufacturer who performs the sterilisation of 0.1 mol/l hydrochloric acid should possess a GMP certificate or a manufacturing authorisation covering the preparation and sterilisation process. During the assessment procedure, a GMP certificate for the manufacturer of 0.1 mol/l sterile hydrochloric acid was requested as Major Objection (MO). In response, the applicant provided the GMP certificate, and the issue was considered resolved.

The loading process of the germanium (^{68}Ge) chloride loading solution filtered through a sterile filter on the column is done in closed automatised systems in cleanroom areas assuring the sterile quality of the with germanium-68 loaded generator column. A final sterilisation by heat of the loaded column is not an option considering the risk that the generator column breaks and sets the volatile tetra – chloro (^{68}Ge)germanium free with a physical half life 271 days.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (gamma-spectrometry, Ph. Eur.), pH (indicator paper), chemical purity (AAS or ICP-MS), gamma emitting impurities (gamma spectroscopy), radiochemical purity (TLC), assay (Ph. Eur.), and microbiological quality (Ph. Eur.).

The provided specification is in compliance with the applicable Ph. Eur. monograph no. 2464.

The spectrum of potential impurities in the eluate of the generator is well characterised and controlled. It is determined solely by the inherent purity profiles of the active substance and the excipients, with no degradation or interaction products to be expected from these simple inorganic substances during the shelf-life of the generator.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 5 commercial scale batches of the generator and 3 commercial scale batches of the eluent 0.1 mol/l hydrochloric acid confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 8 commercial scale batches of finished product stored for up to 18 months under long term conditions (≤ 25°C), 2 commercial scale batches stored for up 9 months under intermediate conditions (30°C) and for 3 batches for up to 6 months under accelerated conditions (40ºC) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

To reduce the extent of radioactive material handling to a sufficient minimum, and to cover the entire range of intended strengths representatively, the stability studies were performed applying a bracketing design derived from ICH guidelines Q1A(R2) and Q1D. For this purpose, one generator for each of the three lowest strengths (1.11 GBq, 1.48 GBq and 1.85 GBq) were chosen to represent the lower part of the strength range and four generators of the highest strength (3.70 GBq) were chosen to cover the upper limit of the strength range. In addition, one generator of 0.74 GBq and one of 1.85 GBq were used for storage at intermediate temperature (30°C). This concept is justified based on the following considerations: The selected batches precisely cover the intended range of strengths (1.11 - 3.7 GBq) addressing the range's lowest and highest extremes, the qualitative and quantitative composition of all generator strengths is identical except for the amount of ^{68}Ge (i.e., the activity), and the manufacturing process is the same for all generator strengths. This was considered acceptable.

Samples were tested for visual presentation, ^{68}Ga yield, pH, radionuclidic, chemical, radiochemical, and microbiological purity. The analytical procedures used are stability indicating.

No significant changes have been observed under long term, intermediate and accelerated conditions.

The radionuclide generator might be exposed to low temperatures for a short time, e.g., during temporary storage or longer transport by plane or on roads. As the parent radionuclide ^{68}Ge is just adsorbed but not covalently bound to the titanium dioxide matrix, the effect of repeated short-termed storage of the generator at low temperatures (2 – 8°C) was evaluated. To this end, one representative generator was repeatedly moved from ambient temperature into a refrigerator (2 - 8°C) and back, in accordance with a pre-defined schedule. After an equilibration time of at least 12 h at each temperature, the generator was eluted for quality control analysis. The obtained data complied with the acceptance limits for visual presentation, pH, elution yield and all analysed purity parameters at all testing points, although a slight but completely reversable decrease of elution yield was observed at cold temperatures. No considerable differences between cold and ambient temperatures were observed for other parameters. These data indicates that exposure to low temperatures, even repeatedly, does not impair the quality and the performance of the ^{68}Ge/^{68}Ga generator.

Based on available stability data, the proposed shelf-life of 18 months from calibration date, the calibration date and the expiry date are stated on the label eluate as stated in the SmPC (section 6.3) are acceptable.

Gallium (^{68}Ga) chloride solution for radiolabelling: After elution, immediately use the eluate.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, a major objection was raised by the CHMP in relation to the missing GMP certificate for the manufacturer of 0.1 mol/L sterile hydrochloric acid. The responses from the applicant to the MO was considered satisfactory and all the issues were considered to be resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The germanium (^{68}Ge) / gallium (^{68}Ga) generator from Eckert & Ziegler Radiopharma GmbH is a diagnostic precursor product. Its eluate containing the active substance ^{68}Ga chloride ($^{68}GaCl_3$) is without direct clinical application and is not intended to be administered directly to the patient. Instead, $^{68}GaCl_3$ is intended only for the in vitro radiolabelling of specific carriers for diagnostic imaging with PET. The pharmaceutical substance to be radiolabelled will be determined by the nature of the condition to be diagnosed.

$^{68}GaCl_3$ is clinically used in PET diagnostic imaging already for decades. In line with this, EMA developed a Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator (EMA/CHMP/337681/2016) which came into effect on August 1st, 2017. Furthermore, a European monography exists for ^{68}Ga chloride solution for radiolabelling produced by ^{68}Ge/^{68}Ga generators (Ph. Eur. 2464).

Prior to first approval, a nonclinical study had been carried out in rats to determine the distribution and dosimetry of ^{68}Ga and ^{68}Ge in case of accidental eluate injection (Study report GERGA and Autio et al., 2015). No other nonclinical or clinical studies were carried out by the applicant.

2.5.2. Pharmacology

$^{68}GaCl_3$ is a radiopharmaceutical precursor solution intended only for the in vitro radiolabelling of specific carrier molecules developed for PET imaging with ^{68}Ga.

^{68}Ga decays to stable zinc (^{68}Zn) with a half-life of 67.71 min. By the decay of 250 MBq ^{68}Ga (stated as the highest dose commonly used), only approximately 0.1 ng Zn is created.

Physical chemistry:

Molecular Formula:	$[^{68}Ge]GeCl_4$ / $[^{68}Ga]GaCl_3$
Molecular Weight:	209.74 g/mol / 174.29 g/mol
Structure:	not applicable as the active substance is an inorganic substance

Table 2. Radioactive properties of ^{68}Ge and ^{68}Ga (probability of decay in %)*, **

	^{68}Ge	^{68}Ga
Half-life	270.95 days	67.71 minutes
Type of physical decay	Electron capture	Positron emission
X-rays	9.225 keV (13.1 %) 9.252 keV (25.7 %) 10.26 keV (1.64 %) 10.264 keV (3.2 %) 10.366 keV (0.03 %)	8.616 keV (1.37 %) 8.639 keV (2.69 %) 9.57 keV (0.55 %)
Gamma-rays		511 keV (178.28 %) 578.55 keV (0.03 %) 805.83 keV (0.09 %) 1,077.34 keV (3.22 %) 1,260.97 keV (0.09 %) 1,883.16 keV (0.14 %)
Beta+		Energy max. Energy 352.60 keV 821.71 keV (1.20 %) 836.00 keV 1,899.01 keV (87.94 %)

Data derived from nudat (*www.nndc.bnl.gov*)

** This table is part of the Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator (EMA/CHMP/337681/2016).

2.5.2.1. Primary pharmacodynamic studies

^{68}Ga chloride is not intended to be administered directly to the patient. As a precursor, it should only be used for *in vitro* radiolabelling of appropriate carrier molecules for PET diagnostic imaging. Thus, the 'primary pharmacodynamic function' of ^{68}Ga chloride, or more specifically $^{68}Ga^{3+}$, is to provide an isotope for stable labelling for high clinical PET image contrast, with minimal retention due to rapid decay.

The element gallium does not appear to have a natural physiological function.

$^{68}GaCl_3$ has been specifically studied for tumour imaging in rats, but its high affinity for blood precludes its routine use for this purpose.

Historically, ^{68}Ga-EDTA has been investigated in animals for its use in detecting disruptions of the blood-brain barrier and for tumour imaging. However, to date the best described ^{68}Ga complexes are ^{68}Ga-DOTA-TOC and ^{68}Ga-PSMA-11.

^{68}Ga-DOTA-TOC was shown to be extremely stable *in vitro*, and to have high affinity for the somatostatin receptor (SSTR) subtype 2, but also subtype 3 and 5. This is associated with a high affinity for SSTR-expressing tissues, including SSTR-positive tumours, with very little uptake in other tissues (except kidneys), as shown in rats and mice. (Reubi et al., 2000; Zhang et al., 2011).

^{68}Ga-PSMA-11 is a urea based peptidomimetic that has a covalently bound chelator HBEDCC with extraordinary high thermodynamic stability constants of $>10^{39}$ at physiological pH. This enables the formation of a very stable ^{68}Ga-HBED-CC complex *in vivo* and in human serum for at least 72 h. (Eder et al., 2014).

2.5.2.2. Secondary pharmacodynamic studies

Since $^{68}GaCl_3$ obtained from the generator is not intended to be administered directly to the patients, no safety pharmacology testing was carried out.

Gallium in its ionic form has been investigated as a therapeutic agent for its normocalcaemic effects in hypercalcaemic rats and its anti-tumour activity in rats and mice. However, the doses investigated are in the range of mg/kg, not ng/kg, as would apply to the diagnostic use of ^{68}Ga.

2.5.2.3. Safety pharmacology programme

Any cardiac effects investigated with $^{68}GaCl_3$ occurred only at concentrations and doses greatly exceeding any potential exposure with ^{68}Ga obtainable from the generator and appeared to be protective rather than deleterious. (Leperre et al., 1994).

2.5.2.4. Pharmacodynamic drug interactions

No publications on pharmacodynamic drug interactions with $^{68}GaCl_3$ have been identified to date.

2.5.3. Pharmacokinetics

The eluate produced from the generator, consisting of $^{68}GaCl_3$ in 0.1 mol/l sterile ultrapure hydrochloric acid, is intended for the *in vitro* radiolabelling of medicinal products and is not administered directly to the patient. The pharmacokinetics of a ^{68}Ga-radiolabelled molecule will overall depend on the biological and chemical properties of the molecule to be radiolabelled and its mechanism of action in the human body.

With a physical half-life of 67.71 min, 97% of the radioactive ^{68}Ga decays to inactive ^{68}Zn within 6 h (equivalent to 5 half-lives). Therefore, in the case of ^{68}Ga, the biological half-life is determined by the physical half-life of ^{68}Ga, and is also 67.71 min.

The content of ^{68}Ge ("breakthrough") from the generator is < 0.001%, which is in line with Pharm. Eur. 2464, and is equivalent to < 0.14 ng ^{68}Ge per 5 ml eluate for a 3.7 GBq generator. According to published literature (Velikyan I., et al., 2013), after intravenous administration of $^{68}GeCl_4$, the elimination was fast with a half-life of ~0.6 h and no accumulation was observed in any organ including bone marrow.

A nonclinical distribution study had been carried out in rats to obtain extrapolated human dosimetry data after (accidental) intravenous administration of $^{68}GaCl_3$, and to ensure that the breakthrough of <0.001% ^{68}Ge specified for the generator does not lead to a radiation risk in any organ (Study report GERGA and Autio et al., 2015). All samples were measured for total radioactivity by gamma counting. No chemical analysis was carried out. Apart from blood, plasma, and urine, the organs with the highest ^{68}Ga radioactivity were the liver and the lungs, spleen and bone. In female rats, ^{68}Ga radioactivity in reproductive organs, i.e., uterus and ovaries, was comparable to that seen in the lungs (data not shown). In general, the pharmacokinetics (absorption, distribution, excretion) of unbound $^{68}Ga^{3+}$ is well known and had been investigated in detail in the past.

Absorption

For investigating pharmacokinetic parameters of ^{68}Ga after intravenous injection of diluted generator eluate in male and female rats, each animal (n=3-4 per sampling time) received 47 ± 4 MBq of $^{68}GaCl_3$ and the plasma ^{68}Ga concentration was determined at 5, 30, 60, 120, and 180 min after tracer injection. The average plasma concentrations are shown in Figure 3.

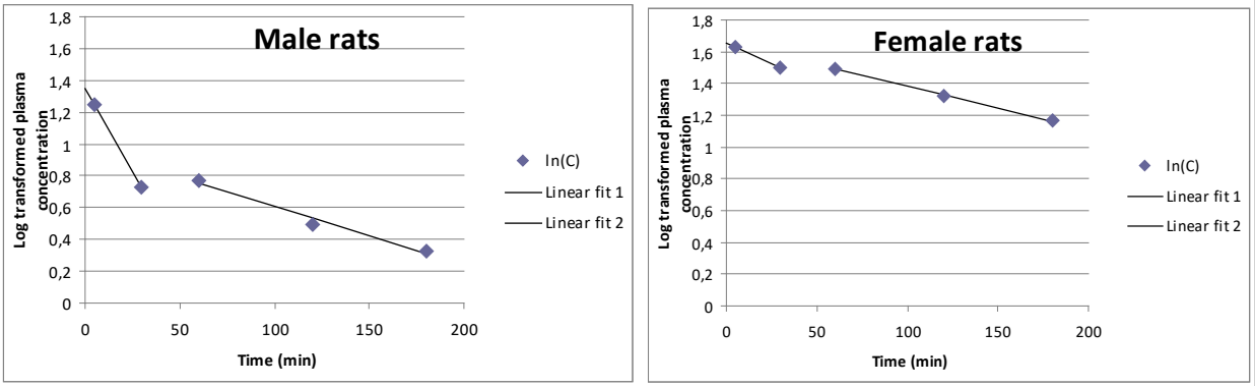
Maximum plasma concentrations were observed after 5 min (the first sampling time) and were 3.5%IA/g in males and 5.1%IA/g in females. The data were extrapolated by log-linear regression of the three last concentrations (60, 120, and 180 min) to estimate the total area under the curve (AUC_{0-inf}), total clearance, and terminal half-life. This resulted in an estimated terminal half-life of 188 h in male and 254 h in female rats, which is much longer than the physical half-life of ^{68}Ga of 67.71 min.

In the published literature, following intravenous administration of $^{72}GaCl_3$, biological half-life of 21 h was reported for Ga (Brucer M. et al., 1953). This value is based on samples taken at 6, 12, 24, 48 and 96 h after injection and may therefore be considered more accurate.

However, it should be noted that with a physical half-life of 67.71 min, 97% of the radioactive ^{68}Ga decays to inactive ^{68}Zn within 6 h (equivalent to 5 half-lives). Therefore, in the case of ^{68}Ga, the biological half-life is determined by the physical half-life of ^{68}Ga, and is also 67.71 min.

The absorption pharmacokinetics of ^{68}Ge was not determined separately, but the impact of the 0.001% ^{68}Ge breakthrough on the organ radiation exposure was investigated (see 'Distribution' below).

Figure 3. Average plasma radioactivity concentrations in %IA/g units for male and female rats after intravenous injection of 47±4 MBq diluted ^{68}Ge/^{68}Ga-generator eluate



Source: Study report GERGA; N=3-4 per sampling time: 5, 30, 60, 120 and 180 min after injection

Distribution

^{68}Gallium

In the GERGA study organ biodistribution was determined *ex vivo* at 5, 30, 60, 120 and 180 min after injection. The highest amount of ^{68}Ga radioactivity was detected in the blood, plasma, and urine.

Table 3. Ex vivo biodistribution of ^{68}Ga radioactivity in female rats as %IA/g

Test Article/Analyte: $^{68}GaCl_3$ / ^{68}Ga			**Location in CTD:** [4.2.2.3]				**Study code:** GERGA			
Species	**Rat**									
Gender (M/F)/Number of animals	**F/3-4**									
Weight of animals	244±8 g									
Vehicle/Formulation	^{68}Ge/^{68}Ga-generator eluate/^{68}Ga-eluate diluted with PBS (600−860 µl, pH 7±0)									
Method of Administration	intravenous									
Administration protocol	Single dose									
Radioactive dose per animal per dose	47±4 MBq									
Assay	gamma counter									
Tissue/Organ (data in % IA/g of single dose)	5 min		30 min		60 min		120 min		180 min	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adrenal glands	0.673	0.111	0.603	0.271	0.705	0.264	0.567	0.226	0.593	0.273
Blood	2.909	0.272	2.509	1.359	2.563	0.909	2.128	0.953	1.811	0.665
Bone (femur, both)	0.298	0.071	0.589	0.132	0.820	0.396	1.001	0.363	1.178	0.485
Bone marrow (femur, both)	0.586	0.133	0.296	0.051	0.705	0.242	0.790	0.366	0.825	0.332
Brain	0.075	0.006	0.079	0.040	0.084	0.025	0.080	0.041	0.060	0.024
Brown adipose tissue	0.405	0.017	0.605	0.229	0.471	0.213	0.376	0.201	0.403	0.156
Colon (minus contents)	0.289	0.095	0.668	0.283	0.615	0.337	0.531	0.302	0.632	0.332
Fat (intraperitoneal)	0.058	0.028	0.177	0.093	0.145	0.073	0.158	0.151	0.128	0.039
Heart	0.723	0.115	0.755	0.462	0.617	0.235	0.540	0.204	0.484	0.215
Ileum (minus contents)	0.271	0.040	0.550	0.191	0.465	0.070	0.631	0.426	0.535	0.305
Kidneys	0.773	0.173	0.875	0.328	0.823	0.301	0.722	0.324	0.829	0.262
Liver	1.225	0.374	1.529	0.450	1.490	0.516	1.597	0.627	1.863	0.699
Lungs	0.949	0.212	1.078	0.520	1.136	0.379	0.894	0.450	0.887	0.410
Ovaries	0.574	0.174	0.784	0.429	1.343	1.257	0.782	0.286	0.776	0.195
Pancreas	0.464	0.283	0.389	0.211	0.364	0.174	0.331	0.164	0.313	0.107
Plasma	5.083	0.486	4.491	2.419	4.451	1.523	3.742	1.602	3.207	1.278
Salivary glands	0.397	0.099	0.630	0.230	0.506	0.178	0.485	0.229	0.492	0.215
Skeletal muscle	0.132	0.048	0.253	0.080	0.214	0.118	0.190	0.078	0.194	0.105
Skin	0.096	0.029	0.341	0.142	0.312	0.176	0.265	0.089	0.318	0.092
Spleen	0.493	0.137	0.836	0.204	0.785	0.269	0.687	0.201	0.916	0.163
Stomach (minus contents)	0.261	0.060	0.384	0.117	0.471	0.196	0.441	0.255	0.474	0.195
Thymus	0.234	0.003	0.259	0.143	0.225	0.089	0.264	0.193	0.201	0.160
Thyroids	0.516	0.020	0.656	0.327	0.607	0.245	0.576	0.347	0.548	0.255
Urinary bladder (minus content)	0.256	0.080	0.442	0.172	0.636	0.311	0.734	0.187	0.587	0.202
Urine	0.417	0.134	13.162	3.607	3.526	1.783	5.228	2.368	2.644	0.706
Uterus	0.361	0.145	1.023	0.482	1.149	0.865	0.819	0.553	1.115	0.882
Residual carcass	0.200	0.010	0.318	0.036	0.266	0.025	0.269	0.023	0.277	0.035

%IA/g = Percentage of injected radioactivity per gram of tissue, PBS = phosphate-buffered saline, SD = standard deviation

Table 4. Ex vivo biodistribution of ^{68}Ga radioactivity in male rats as %IA/g

Test Article/Analyte: $^{68}GaCl_3$ / ^{68}Ga					Location in CTD: [4.2.2.3]				Study code: GERGA	
Species	Rat									
Gender (M/F)/Number of animals	M/3-4									
Weight of animals	343±52 g									
Vehicle/Formulation	^{68}Ge/^{68}Ga-generator eluate/^{68}Ga-eluate diluted with PBS (600−860 µl, pH 7±0)									
Method of Administration	intravenous									
Administration protocol	Single dose									
Radioactive dose per animal per dose	47±4 MBq									
Assay	gamma counter									
Tissue/Organ (data in % IA/g of single dose)	5 min		30 min		60 min		120 min		180 min	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adrenal glands	0.635	0.404	1.119	0.088	0.338	0.040	0.355	0.174	0.268	0.009
Blood	1.556	0.476	0.303	0.047	1.175	0.128	0.970	0.165	0.761	0.093
Bone (femur. both)	0.285	0.100	0.387	0.188	0.500	0.176	0.657	0.240	0.770	0.218
Bone marrow (femur. both)	0.494	0.061	0.354	0.020	0.423	0.066	0.394	0.123	0.478	0.097
Brain	0.078	0.020	0.041	0.003	0.048	0.006	0.034	0.002	0.033	0.010
Brown adipose tissue	0.294	0.099	0.279	0.122	0.318	0.075	0.255	0.071	0.257	0.099
Colon (minus contents)	0.230	0.018	0.260	0.048	0.285	0.038	0.227	0.077	0.291	0.038
Fat (intraperitoneal)	0.050	0.019	0.069	0.013	0.090	0.031	0.069	0.046	0.053	0.004
Heart	0.494	0.075	0.338	0.070	0.320	0.032	0.270	0.053	0.224	0.023
Ileum (minus contents)	0.205	0.088	0.186	0.022	0.268	0.074	0.222	0.114	0.253	0.085
Kidneys	0.993	0.730	0.359	0.070	0.404	0.026	0.343	0.119	0.416	0.018
Liver	1.044	0.516	0.514	0.195	0.770	0.336	0.746	0.421	0.679	0.208
Lungs	0.608	0.028	0.479	0.045	0.484	0.196	0.455	0.079	0.379	0.044
Pancreas	0.246	0.042	0.207	0.067	0.212	0.031	0.181	0.034	0.168	0.022
Plasma	3.481	0.980	2.078	0.194	2.162	0.251	1.639	0.259	1.390	0.201
Salivary glands	0.351	0.079	0.304	0.018	0.336	0.058	0.331	0.075	0.316	0.049
Skeletal muscle	0.085	0.069	0.125	0.036	0.142	0.019	0.151	0.028	0.118	0.021
Skin	0.124	0.074	0.157	0.060	0.248	0.038	0.204	0.054	0.198	0.017
Spleen	0.520	0.114	0.383	0.099	0.516	0.193	0.582	0.255	0.555	0.150
Stomach (minus contents)	0.222	0.045	0.227	0.061	0.268	0.036	0.250	0.058	0.292	0.031
Testes	0.076	0.054	0.075	0.023	0.140	0.020	0.175	0.026	0.198	0.027
Thymus	0.190	0.033	0.137	0.055	0.182	0.050	0.141	0.051	0.116	0.074
Thyroids	0.536	0.040	0.355	0.057	0.403	0.131	0.415	0.106	0.434	0.137
Urinary bladder (minus content)	0.267	0.177	0.553	0.360	0.502	0.191	0.478	0.216	0.323	0.034
Urine	0.758	0.727	1.342	0.530	1.408	0.736	1.449	0.661	1.754	1.269
Residual carcass	0.177	0.082	0.218	0.051	0.207	0.039	0.215	0.048	0.231	0.017

%IA/g = Percentage of injected radioactivity per gram of tissue, PBS = phosphate-buffered saline, SD = standard deviation

After 1 h the activity was:

2.6%IA/g in the blood, 4.5%IA/g in the plasma and 3.5%IA/g in the urine in female rats

1.2%IA/g in the blood, 2.2%IA/g in the plasma and 1.4%IA/g in the urine in male rats.

After 3 h (the last sampling time) the remaining activity was:

1.8%IA/g in the blood, 3.2%IA/g in the plasma and 2.6%IA/g in the urine in female rats 0.8%IA/g in the blood, 1.4%IA/g in the plasma and 1.8%IA/g in the urine in male rats.

Apart from blood, plasma, and urine, the organs with the highest ^{68}Ga radioactivity were the liver (1.5%IA/g in female rats and 0.8% IA/g in male rats after 60 min) and the lungs, spleen and bone (0.8-1.1% IA/g in female rats and 0.5% IA/g in male rats after 60 min for each). In female rats, ^{68}Ga radioactivity in reproductive organs, i.e., uterus and ovaries, was comparable to that seen in the lungs (1.1-1.3% IA/g). In male rats, ^{68}Ga radioactivity in the testes was very low (≤ 2% IA/g at any time).

The distribution of ^{68}Ga after injection of ^{68}Ga chloride was also investigated by Ujula et al. (2010). Although the main aim of their studies was to investigate the potential of $^{68}GaCl_3$ for the imaging of pancreatic xenografts, ex vivo biodistribution to the blood, liver, lung, muscle, and skin was also assessed in 4 male tumour-bearing rats at 90 min after intravenous injection of 12 ± 3 MBq $^{68}GaCl_3$. These data are presented in Table 5 juxtaposed with 60- and 120-min data in male rats from the GERGA study. Apart from the higher levels observed in the liver in the study by Ujula et al., biodistribution pattern observed is similar between studies.

Table 5. Ex vivo biodistribution of ^{68}Ga radioactivity in male rats as %IA/g after intravenous administration of $^{68}GaCl_3$

	Study report GERGA Dose of 47±4 MBq, n=3-4				Ujula *et al.*, 2010 Dose of 12 ± 3 MBq, n=4	
	60 min		120 min		90 min	
Tissue/organ	Mean	SD	Mean	SD	Mean	SD
Blood	1.2	0.1	1.0	0.2	1.0	0.07
Liver	0.8	0.3	0.7	0.4	2.1	1.2
Lungs	0.5	0.2	0.5	0.08	0.7	0.3
Skeletal muscle	0.1	0.02	0.2	0.03	0.1	0.01
Skin	0.2	0.04	0.2	0.05	0.2	0.04

Sources: Study report GERGA, Ujula T., 2010, Ujula T. et al., 2010, 35; n = number of animals per time point

Further data on the biodistribution of gallium after intravenous injection of gallium chloride have been published by Brucer et al. They investigated ^{72}Ga biodistribution in male rats at 6, 12, 24, 48 and 96 h after intravenous injection of 0.7 to 8.0 mg $^{72}Ga^{3+}$/kg. The values are provided as % of the injected dose per organ, and Table 6 shows the comparison of results from Brucer et al. after 6 h (n=5) vs. the data from GERGA study after 3 h. For comparison purpose, 47±4 MBq of ^{68}Ga injected to male rats weighing on average 343±52 g in the GERGA study was converted to mg/kg and corresponds to approximately 0.9 x 10^{7} mg ^{68}Ga/kg. Clear difference can be seen in the liver uptake of ^{68}Ga after 3 h vs. that of ^{72}Ga after 6 h, with substantially higher values for ^{72}Ga despite longer period past-injection.

Table 6. Ex vivo biodistribution of Ga radioactivity in male rats as %IA/organ after intravenous administration of gallium chloride

	Study report GERGA ^{68}Ga Dose of approx. $0.9 \cdot 10^{-7}$ mg ^{68}Ga/kg, n=3-4 3 h		Brucer *et al.*, 1953 ^{72}Ga 0.7-2.6 mg ^{72}Ga/kg, n=5 6 h
Tissue/organ	Mean	SD	Mean
Kidneys	0.8	0.03	1.4
Liver	8.0	2.7	27.9
Plasma	ND	ND	8.9
Spleen	0.5	0.08	0.6
Residual carcass	ND	ND	31.2

Sources: Study report GERGA, Bruce et al., 1953; SD = standard deviation, n = number of animals per time point

The ^{68}Ga dosimetry data obtained in male and female rats in frame of the GERGA study were further used to estimate the human radiation dose giving an estimated effective dose of 0.048 mSv/MBq for a 57 kg woman and 0.033 mSv/MBq for a 70 kg male. The human data are included in the proposed summary of product characteristics.

The protein binding of ^{68}Ga was investigated by incubating $^{68}GaCl_3$ with increasing concentrations of human albumin for 1 h (Rovainen et al., 2004]). A protein binding of 10-20% was observed for concentrations up to 250 µM human albumin (the amount of $^{68}GaCl_3$ used in these experiments is not provided in the publication). This relatively low protein binding is consistent with the observation that Ga^{3+} behaves very similarly to Fe^{3+}, binding rapidly and mainly to transferrin (Bernstein LR., 1998). Although the affinity of transferrin for Fe^{3+} is approximately 300- 400 times higher than for Ga^{3+}

(Bernstein LR., 1998; Chitambar CR., 2010), the replacement of Ga^{3+} by Fe^{3+} is found to proceed very slowly, with an exchange half-life of 4.3 h (Bernstein LR., 1998). However, it should again be noted that ^{68}Ga decays to zinc with a half-life of 67.71 h. Thus, with ^{68}Ga, only 17% would remain after 4.3 h. Ionic zinc is Zn^{2+}, and therefore no longer competes for transferrin.

Germanium-68

The organ distribution of ^{68}Ge after intravenous injection of diluted generator eluate was investigated within GERGA study in male and female rats. The radioactivity resulting from ^{68}Ge breakthrough was determined based on a separate measurement of all samples after 24 h.

Table 7. Ex vivo biodistribution of ^{68}Ge radioactivity in female rats as %IA/g

Test Article/Analyte: $^{68}GaCl_3$ / ^{68}Ge					**Location in CTD: [4.2.2.3]**				**Study code: GERGA**	
Species	**Rat**									
Gender (M/F)/Number of animals	**F/3-4**									
Weight of animals	244±8 g									
Vehicle/Formulation	^{68}Ge/^{68}Ga-generator eluate/^{68}Ge-eluate diluted with PBS (600−860 µl, pH 7±0)									
Method of Administration	intravenous									
Administration protocol	Single dose									
Radioactive dose per animal per dose	47±4 MBq									
Assay	gamma counter									
Tissue/Organ (data in % IA/g of single dose)	5 min		30 min		60 min		120 min		180 min	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adrenal glands	6.45E-06	3.05E-06	3.39E-06	1.95E-06	ND	ND	2.69E-06	2.39E-06	1.15E-05	9.37E-06
Blood	3.71E-06	2.79E-06	2.39E-06	ND	8.29E-07	6.47E-07	7.18E-07	3.49E-07	2.67E-06	ND
Bone (femur, both)	8.95E-07	5.45E-07	6.99E-07	8.17E-07	5.51E-07	4.06E-07	4.83E-07	4.76E-07	9.64E-07	1.11E-06
Bone marrow (femur, both)	5.74E-06	3.07E-06	5.9E-06	2.1E-06	5.79E-06	ND	4.61E-06	1.55E-06	1.09E-05	6.31E-06
Brain	3.04E-07	2.83E-07	3.24E-07	2.1E-07	8.90E-08	1.18E-07	2.32E-07	9.24E-08	6.51E-07	ND
Brown adipose tissue	1.30E-06	6.11E-07	2.17E-06	1.41E-06	5.59E-07	2.66E-07	1.56E-06	1.27E-06	1.18E-06	1.53E-06
Colon (minus contents)	4.37E-07	1.88E-07	4.57E-07	4.26E-07	4.45E-07	1.10E-08	4.80E-07	5.20E-07	3.13E-07	3.3E-07
Fat (intraperitoneal)	2.99E-07	9.69E-08	1.06E-07	ND	7.55E-09	ND	2.65E-07	1.43E-07	1.27E-07	1.00E-07
Heart	4.01E-07	1.57E-07	1.38E-06	ND	9.97E-07	3.31E-07	5.69E-07	6.64E-07	7.77E-07	4.05E-07
Ileum (minus contents)	5.74E-07	4.4E-07	7.87E-07	4.66E-07	3.04E-07	2.41E-07	1.01E-07	1.48E-07	1.98E-07	ND
Kidneys	3.86E-06	4.95E-06	5.52E-06	1.68E-06	2.00E-06	1.28E-06	5.35E-06	ND	8.90E-06	1.21E-05
Liver	2.31E-05	9.88E-06	2.72E-05	1.25E-05	2.58E-05	8.30E-06	2.50E-05	8.42E-06	2.75E-05	6.55E-06
Lungs	1.91E-06	8.06E-07	1.4E-06	9.05E-07	8.81E-07	1.19E-07	6.41E-07	2.94E-07	6.47E-07	3.95E-07
Ovaries	2.38E-06	2.79E-06	4.79E-06	2.01E-06	1.38E-06	5.68E-07	4.19E-06	9.23E-07	7.83E-06	ND
Pancreas	6.77E-07	3.28E-07	5.81E-07	1.61E-07	2.64E-07	1.86E-07	5.42E-07	2.18E-07	4.29E-07	5.57E-07
Plasma	1.35E-06	1.23E-06	7.94E-07	ND	6.89E-07	5.31E-07	1.57E-06	9.01E-07	1.29E-06	ND
Salivary glands	1.36E-06	ND	1.91E-06	ND	4.83E-07	3.60E-07	4.98E-07	1.96E-07	2.04E-06	ND
Skeletal muscle	5.03E-07	ND	7.37E-07	1.77E-07	4.30E-08	3.25E-08	2.63E-07	3.64E-07	5.67E-07	ND
Skin	4.22E-07	1.90E-08	1.02E-06	1.02E-06	3.86E-07	2.28E-07	4.56E-07	4.99E-07	2.63E-07	2.58E-07
Spleen	6.98E-06	3.72E-06	1.65E-05	4.44E-06	1.41E-05	2.85E-06	1.20E-05	3.64E-06	1.72E-05	7.08E-06
Stomach (minus contents)	4.76E-07	2.07E-07	2.32E-07	1.3E-07	1.95E-07	5.62E-08	3.98E-07	3.05E-07	3.12E-07	3.49E-07
Thymus	1.31E-06	1.31E-06	2.95E-06	ND	9.27E-07	1.31E-06	2.40E-06	ND	1.74E-06	1.89E-06
Thyroids	1.66E-05	ND	9.17E-05	1.18E-04	2.74E-05	2.70E-05	2.87E-05	2.19E-05	2.13E-05	4.41E-07
Urinary bladder (minus content)	3.87E-06	4.31E-06	3.92E-06	4.35E-06	9.94E-06	9.73E-06	4.24E-06	4.47E-06	5.99E-06	3.55E-06
Urine	1.13E-05	1.48E-05	1.10E-04	2.31E-05	4.92E-05	4.66E-05	6.52E-05	3.02E-05	6.36E-06	8.03E-06
Uterus	6.01E-07	3.31E-07	7.58E-07	7.09E-08	5.87E-07	9.36E-07	6.74E-07	6.35E-07	3.84E-07	5.43E-07
Residual carcass	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

%IA/g = Percentage of injected radioactivity per gram of tissue, ND = not determined, PBS = phosphate-buffered saline, SD = standard deviation

Table 8. Ex vivo biodistribution of ^{68}Ge radioactivity in male rats as %IA/g

Test Article/Analyte: $^{68}GaCl_3$ / ^{68}Ge				Location in CTD: [4.2.2.3]				Study code: GERGA		
Species	Rat									
Gender (M/F)/Number of animals	M/3-4									
Weight of animals	343±52 g									
Vehicle/Formulation	^{68}Ge/^{68}Ga-generator eluate/^{68}Ge-eluate diluted with PBS (600−860 µl, pH 7±0)									
Method of Administration	intravenous									
Administration protocol	Single dose									
Radioactive dose per animal per dose	47±4 MBq									
Assay	gamma counter									
Tissue/Organ (data in % IA/g of single dose)	5 min		30 min		60 min		120 min		180 min	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adrenal glands	7.20E-06	ND	2.06E-06	ND	7.91E-07	ND	7.60E-06	5.62E-06	7.77E-06	ND
Blood	2.67E-06	1.61E-06	6.45E-06	ND	1.24E-06	6.18E-07	1.28E-06	1.26E-06	1.77E-06	2.37E-06
Bone (femur. both)	6.83E-07	3.91E-07	1.56E-06	ND	6.45E-07	5.47E-07	5.27E-07	8.60E-08	1.85E-07	ND
Bone marrow (femur. both)	3.89E-06	ND	ND	ND	4.30E-07	ND	4.20E-06	7.31E-07	5.68E-06	2.79E-06
Brain	1.72E-07	1.61E-07	ND	ND	2.28E-07	ND	2.57E-07	2.64E-07	ND	ND
Brown adipose tissue	1.01E-06	1.44E-06	ND	ND	2.03E-06	1.54E-06	1.32E-06	6.40E-07	7.51E-07	ND
Colon (minus contents)	2.10E-07	3.16E-08	4.84E-07	ND	1.85E-07	1.34E-07	4.19E-07	1.65E-07	3.46E-07	4.98E-08
Fat (intraperitoneal)	6.09E-08	8.11E-10	3.24E-08	1.10E-08	3.10E-08	2.01E-08	4.27E-07	6.37E-07	1.50E-07	2.23E-07
Heart	1.16E-06	ND	5.90E-07	ND	3.97E-07	2.32E-07	1.45E-07	7.13E-08	2.68E-07	1.48E-07
Ileum (minus contents)	5.83E-07	1.38E-07	5.29E-07	5.13E-07	5.82E-07	3.50E-08	1.06E-07	6.79E-08	4.71E-07	3.15E-07
Kidneys	5.45E-06	5.31E-06	4.06E-06	4.00E-06	4.34E-06	3.93E-06	2.62E-06	1.27E-06	5.68E-06	4.48E-06
Liver	1.27E-05	9.65E-06	1.25E-05	1.31E-05	1.34E-05	9.72E-06	1.34E-05	1.03E-05	8.96E-06	8.20E-06
Lungs	1.18E-06	5.44E-07	8.51E-07	1.00E-06	1.08E-06	6.72E-07	8.86E-07	2.62E-07	5.91E-07	2.76E-07
Pancreas	2.87E-07	1.27E-07	2.25E-07	2.81E-07	3.11E-07	1.18E-07	1.14E-07	7.74E-08	2.98E-07	4.93E-08
Plasma	2.48E-06	ND	2.98E-06	ND	1.11E-06	9.49E-07	1.37E-06	3.72E-07	5.33E-07	ND
Salivary glands	1.21E-06	1.37E-07	5.63E-07	5.09E-07	6.15E-07	5.62E-07	2.28E-07	1.68E-07	2.94E-08	ND
Skeletal muscle	3.42E-07	3.10E-08	7.08E-08	5.76E-08	3.90E-07	4.37E-07	2.92E-07	3.46E-07	1.10E-07	ND
Skin	5.84E-07	1.73E-07	ND	ND	1.94E-07	2.08E-07	5.23E-07	4.57E-07	4.03E-08	ND
Spleen	6.88E-06	4.31E-06	7.08E-06	6.58E-06	1.04E-05	8.23E-06	1.07E-05	8.43E-06	6.63E-06	6.84E-06
Stomach (minus contents)	4.62E-07	2.79E-07	6.69E-07	7.75E-07	3.60E-07	2.04E-07	5.34E-07	6.31E-08	1.25E-07	2.18E-09
Testes	3.37E-07	ND	4.65E-08	ND	7.52E-08	4.10E-08	5.49E-08	5.33E-08	5.22E-08	ND
Thymus	1.79E-07	ND	1.03E-06	1.20E-06	4.83E-07	3.56E-07	9.13E-07	1.12E-06	1.37E-06	ND
Thyroids	ND	ND	8.16E-06	7.95E-06	1.70E-05	8.11E-06	1.53E-06	ND	4.25E-05	4.13E-05
Urinary bladder (minus content)	7.09E-06	1.37E-06	1.11E-05	1.32E-05	1.09E-05	6.14E-06	4.73E-06	6.55E-07	3.94E-06	2.79E-06
Urine	1.08E-04	ND	4.53E-05	4.78E-05	1.86E-04	4.70E-05	1.08E-04	1.34E-04	7.11E-05	4.49E-05
Residual carcass	ND	ND	6.72E-06	ND	2.26E-06	4.52E-06	2.49E-06	4.99E-06	ND	ND

%IA/g = Percentage of injected radioactivity per gram of tissue, ND = not determined, PBS = phosphate-buffered saline, SD = standard deviation

With all ^{68}Ga decayed to inactive zinc by this time, all this remaining activity could be attributed to ^{68}Ge. ^{68}Ge radioactivity was very low and for most of the samples reliable results could not be obtained as were below the sensitivity level of the gamma counter. The highest ^{68}Ge radioactivity was seen in the urine and liver (≤ 2 x 10^{-4} %IA/g, 5 min to 3 h after injection).

In general, the major concern was whether traces of ^{68}Ge would be deposited in the bone leading to significant radiation dose over time. The retention of ^{68}Ge in the bone and bone marrow was ≤ 10^{-5} %IA/g after 3 h, both in male and female rats (See Table 7 & Table 8). The biodistribution of intraperitoneally administered $^{68}GeCl_4$ (1.2 µCi = 0.04 MBq) in rats has been reported by Sabbioni et al. in 2010. At 24 h post-exposure, ^{68}Ge was poorly retained in rat tissues, with kidney, liver, intestine, femur, spleen, and the heart being the organs with the highest ^{68}Ge concentration. ^{68}Ge was rapidly cleared from blood, being almost equally distributed between plasma and red blood cells. The excretion was mainly via urine. The results of the GERGA study are thus in accordance with published by Sabbioni et al. data, except for the low ^{68}Ge-radioactivity observed in the bone.

Overall, the ^{68}Ge radiation exposure after injection of the generator eluate was too low in the rat study for human extrapolation. Konijnenberg et Breeman (2009) reported a human effective dose of 0.034 mSv/MBq, consisting of 0.016 mSv/MBq for ^{68}Ge and 0.018 mSv/MBq for ^{68}Ga formed during the uptake of ^{68}Ge in the body, with the highest radioactivity dose detected in the colon with 0.15 mGy/MBq.

Velikyan et al. carried out a ^{68}Ge organ biodistribution study in rats after intravenous administration of $^{68}GeCl_4$ (2013). After 7 days, only 1.8 ± 0.3% of ^{68}Ge remained in animals and the half-life for elimination was estimated to be 36 ± 5 min. The human estimates indicated that the whole-body effective dose was 0.0155 mSv/MBq for women and 0.0107 mSv/MBq for men. The dose limiting organs were the kidneys, with equivalent dose estimates of 0.185 mSv/MBq for women and 0.171 mSv/MBq for men, respectively. In osteogenic cells, the estimated organ specific dose was only 0.011 mSv/MBq for women and 0.0069 mSv/MBq for men, indicating that there is no selective bone uptake.

Using the effective doses reported by Velikyan et al. and the highest currently approved ^{68}Ga dose of 259 MBq (see Locametz prescribing information, US FDA), assuming a maximum of 0.001% ^{68}Ge breakthrough from the generator that would correspond to 0.00259 MBq ^{68}Ge, the whole-body effective doses would be 0.040 µSv for women and 0.028 µSv for men. These doses are at least 2.500- 3.000 times lower than the permitted effective doses ranges (starting at 0.1 mSv) that are currently recommended by the International Commission on Radiological Protection for use in healthy volunteers for biomedical research (ICRP Publication 103, 2007).

Metabolism

As an element, free ^{68}Ga is not metabolised. Since the complexing of ^{68}Ga with the most commonly used chelators, DOTA and PSMA-11, is irreversible (Eder M. et al., 2012; Riss PJ. et al., 2008) and no free ^{68}Ga is administered or released, the metabolism of the final product will depend on the carrier molecule.

Excretion

After intravenous injection of Ga chloride, gallium is predominantly excreted in the urine (GERGA study and (Ujula T., 2010; Ujula T. et al., 2010; Brucer M., 1953)). However, during clinical use the excretion will depend on the carrier molecule to be radiolabelled.

Pharmacokinetic drug interactions

No published pharmacokinetic drug interaction studies relevant to the use of the generator have been identified to date.

Other pharmacokinetic studies

No published other pharmacokinetic studies relevant to the use of the generator have been identified to date.

2.5.4. Toxicology

The eluate produced from the generator, consisting of $^{68}GaCl_3$ in 0.1 mol/l hydrochloric acid is intended for the in vitro radiolabelling of medicinal products and will not be administered directly to the patient.

An eluate of 5 mL produced from the generator corresponds to a potential maximum of 2.4 ng gallium.

Complexing of the eluate produced from the generator with DOTA and PSMA-11 is irreversible (Eder M. et al., 2012; Riss PJ. et al., 2008) and no free ^{68}Ga is administered or released. The non-clinical distribution study carried out in rats to obtain extrapolated human dosimetry data after (accidental) intravenous administration of $^{68}GaCl_3$ showed that most ^{68}Ga is contained in the blood and urine with some uptake also in the lungs, spleen and bone. However, due to the short half-life of ^{68}Ga, with almost complete decay to stable ^{68}Zn within 6 h, any exposure to gallium is short-lived. The study also demonstrated that the breakthrough of < 0.001% ^{68}Ge specified for the generator in line with Pharm. Eur. 2464 did not lead to accumulation in any organ. This is in line with published literature (Velikyan I., et al., 2013).

With regard to the element ^{68}Zn, the decay of 250 MBq ^{68}Ga produces only approximately 0.1 ng ^{68}Zn.

PET diagnostic agents are generally applied intravenously, although other routes of administration are conceivable. The eluate contains sterile ultrapure 0.1 mol/l hydrochloric acid, which is highly acidic at a pH of 1. With paravenous injection or infusion into small or collapsed large veins, tissue damage and necrosis can occur. In case of accidental use of the eluate, the catheter or affected area should be irrigated with isotonic saline solution (see SmPC).

Overall, the safety of the generator is determined by the safety and distribution of the ligand used, and not by any toxicity resulting from free ^{68}Ga or ^{68}Ga.

2.5.5. Ecotoxicity/environmental risk assessment

GalliaPharm is a ^{68}Germanium/^{68}Gallium chloride radionuclide generator to be used for *in vitro* labelling of various kits for radiopharmaceutical preparations which are used and administered only by authorised personal in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to national regulations on radioactive materials. Additionally, ^{68}Gallium chloride is an inorganic salt for which neither an ERA nor PBT screening are required according to the Guideline on the Environmental risk assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00_corr2). Furthermore, ^{68}Ga decays almost completely to naturally occurring ^{68}Zn within 6 hours.

Therefore, ^{68}Gallium chloride is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Good laboratory practices (GLP) were not applied to the dosimetry study GERGA, as the principles of GLP are usually not implementable for radiopharmaceuticals dosimetry studies demanded by the directive 2001/83/EC (Annex I, Part 3) and therefore deemed not obligatory for these studies, which is also laid down in the Article 6 of the draft guideline EMA/CHMP/SWP/686140/2018 on the nonclinical requirements for radiopharmaceuticals. This preclinical study in rats was conducted in 2011 in order to determine the distribution and dosimetry of ^{68}Ga and ^{68}Ge in case of accidental injection of the radioactive eluate itself. No information is available regarding GLP aspects of supportive published literature. Due to the extensive clinical experience with ^{68}Ga/ ^{68}Ga labelled molecules, lack of GLP compliance/information on GLP status is accepted and not considered being of concern given that the pharmacology and clinical safety profile of the product has been extensively studied in man.

Since $^{68}GaCl_3$ forms very stable complexes with no clinically relevant amounts of dissociated $^{68}Ga^{3+}$ administered with correct use, and since ^{68}Ga decays almost completely to ^{68}Zn within 6 hours, no pharmacodynamic effects are to be expected for the use of $^{68}GaCl_3$. Even with (accidental) injection of the eluate containing up to 3.7 GBq ^{68}Ga, the total amount of gallium administered would only be 2.4 ng, which is well below the doses (mg/kg) at which any unwanted pharmacodynamic effects might be observed. The distribution of ^{68}Ga after injection of ^{68}Ga chloride was investigated in the GERGA study and also by Ujula et al. (2010). Higher levels were observed in the liver in the study by Ujula et al. The reason for the different liver uptake is unclear but may be due to a strain difference since the study by Ujula et al. used athymic 6-week-old Hsd/RH-rnu/rnu rats, while mature Sprague Dawley rats were used in the GERGA study. Further data on the biodistribution of gallium after intravenous injection of gallium chloride have been published by Brucer et al. Clear difference can be seen in the liver uptake of ^{68}Ga after 3 h. However, this apparent increased accumulation of ^{72}Ga with time is of no relevance to ^{68}Ga, since only 3% of ^{68}Ga remains after 6 h due to the rapid decay to zinc.

The eluate produced from the generator, consisting of $^{68}GaCl_3$ in 0.1 mol/l sterile ultrapure hydrochloric acid, is intended for the in vitro radiolabelling of medicinal products and is not administered directly to the patient. The pharmacokinetics of a ^{68}Ga-radiolabelled molecule will overall depend on the biological and chemical properties of the molecule to be radiolabelled and its mechanism of action in the human body. With a physical half-life of 67.71 min, 97% of the radioactive ^{68}Ga decays to inactive ^{68}Zn within 6 h (equivalent to 5 half-lives). Therefore, in the case of ^{68}Ga, the biological half-life is determined by the physical half-life of ^{68}Ga, and is also 67.71 min.

A nonclinical distribution study had been carried out in rats to obtain extrapolated human dosimetry data after (accidental) intravenous administration of $^{68}GaCl_3$ (GERGA study). Apart from blood, plasma, and urine, the organs with the highest ^{68}Ga radioactivity were the liver and the lungs, spleen and bone. In female rats, ^{68}Ga radioactivity in reproductive organs, i.e., uterus and ovaries, was comparable to that seen in the lungs. In general, the pharmacokinetics (absorption, distribution, excretion) of unbound $^{68}Ga^{3+}$ is well known and had been investigated in detail in the past. In this study, the estimated terminal half-life rats is much longer (188 h in male and 254 h in female) than the physical half-life of ^{68}Ga (67.71 min). This may be due to a relatively high plasma concentration at the last study point (180 min), which may have resulted in a gross overestimation of the $AUC_{0\text{-}inf}$. Free Ga^{3+} is also known to be 'trapped' in the blood pool by complexing with transferrin (Bernstein LR., 1998), which is consistent with a slow plasma clearance also observed in this study. In the GERGA organ biodistribution study, the observed gender differences in ^{68}Ga biodistribution were most probably due to small number of animals. However, higher concentrations of some elements, including iron, have been previously observed in female vs. male rats (Uchino E. et al. 1990), and since Ga^{3+} is transported into tissues in a similar way as Fe^{3+}, this may explain part of the gender differences observed in GERGA study. With regards to the organ biodistribution, the results of the GERGA study are in accordance with published by Sabbioni et al. data, except for the low ^{68}Ge-radioactivity observed in the bone. This may be due to the small amounts administered with the generator eluate (only up to 0.001% of 47 MBq corresponding to 0.05 x 10-2 MBq), possibly resulting in less 'overflow' of ^{68}Ge into the bone.

The content of ^{68}Ge ("breakthrough") from the generator is < 0.001%, which is in line with Pharm. Eur. 2464, is equivalent to < 0.14 ng ^{68}Ge per 5 ml eluate for a 3.7 GBq generator. According to published literature [Velikyan I., et al., 2013] the elimination of ^{68}Ge was fast in rats with a half-life of ~0.6 h and no accumulation was observed in any organ including bone marrow.

The active substance ^{68}Ga decays almost completely to naturally occurring ^{68}Zn within 6 hours, therefore, ^{68}Gallium chloride is not expected to pose a risk to the environment. Furthermore, the handling and disposal of radioactive materials are subject to strict regulations, hence it can be expected that the environment will not be exposed to the generated ^{68}Gallium chloride.

2.5.7. Conclusion on the non-clinical aspects

The eluate of the $^{68}Ge/\ ^{68}Ga$ generator containing the active substance ^{68}Ga chloride ($^{68}GaCl_3$) is not intended to be administered directly to the patient. Instead, $^{68}GaCl_3$ is intended only for the in vitro radiolabelling of specific carriers for diagnostic imaging with PET. The pharmaceutical substance to be radiolabelled will be determined by the nature of the condition to be diagnosed.

^{68}Ga labelled carrier molecules are in clinical use for decades.

Even with accidental injection of the eluate itself no pharmacodynamic or toxicological effects are expected due to the extremely low amount of Ga present (2.4 ng).

The pharmacokinetics of ^{68}Ga and of the mother nuclide ^{68}Ge are known.

From a non-clinical point of view, no concerns are raised regarding the medicinal product in the intended clinical use.

2.6. Clinical aspects

2.6.1. Introduction

No clinical studies on the clinical pharmacology of ^{68}Ga-chloride have been performed since this substance is not intended to be administered directly to the patient. As a radionuclide precursor it should only be used for *in vitro* labelling of appropriate carrier molecules for PET diagnostic imaging.

The clinical data package is limited to the estimation of radiation dosimetry of $^{68}GaCl_3$ based on non-clinical evidence and estimated for the event of inadvertent use of the eluate and published efficacy and safety data from the studies evaluating ^{68}Ga-labelled carrier molecules: ^{68}Ga-DOTA-TOC being first reported in 2001, followed by the use of ^{68}Ga-DOTA-NOC in 2005, ^{68}Ga-DOTA-TATE in 2006, and ^{68}Ga-PSMA-11 in 2012.

GCP aspects

Not applicable as no clinical studies have been submitted.

2.6.2. Clinical pharmacology

No biopharmaceutical studies have been performed with the ^{68}Ge/^{68}Ga-generator, since only the final radiolabelled medicinal product is to be used. The final product characteristics depend mainly on the carrier to be labelled. Thus, no associated analytical methods have been developed. There are no published biopharmaceutical studies available for ^{68}Ga-chloride and no proprietary studies have been conducted.

Pharmacokinetics and pharmacodynamics of the ^{68}Ga-marked molecules will fully depend on the characteristics of the carrier molecules.

Therefore, the section of clinical pharmacology is limited to discussion of distribution and radiation dosimetry data collected in non-clinical setting, which have become the basis of the dosimetry information included in the SmPC.

2.6.2.1. Pharmacokinetics

No clinical studies were conducted. Non-clinical studies were performed with ^{68}Ga and ^{68}Ge chloride to investigate distribution and dosimetry and subsequently translate the data into humans (for the case of accidental use of the eluate), see section 2.5.3. In this report, only the short summaries are given on conducted methodology, which are also assessed.

Absorption

The eluate produced by GalliaPharm generator containing ^{68}Ga is intended to be administered intravenously consequently achieving the bioavailability of 100%.

Distribution

One non-clinical study in rats was conducted to determine the distribution of ^{68}Ga and ^{68}Ge in case the generator eluate is accidentally intravenously administered to a patient (GERGA study).

The activity of ^{68}Ga was evaluated in various organs and tissues of 17 female and 17 male rats at five different time-points up to 180 min p.i. The urine was withdrawn from the urinary bladder by needle and syringe and measured to determine the activity concentration of ^{68}Ga in urinary bladder content. Blood was derived by cardiac puncture to obtain the activity concentration in blood and plasma. All

measurements were done with a gamma counter. The resulting data were reported as percentage of injected activity per gram of tissue (%IA/g), percentage of injected activity per organ (%IA/organ) and standardised uptake value (SUV) at each considered time-point combined for all female and all male investigated rats. Organ and tissue masses were also determined. Except for blood, bone, bone marrow, brown adipose tissue, fat, plasma, skeletal muscle, skin and urine, the masses were given for entire organs and tissues. Otherwise, the reported values were the masses of the withdrawn samples.

The activity of ^{68}Ga was slowly cleared from blood and excreted predominantly into the urine. Besides blood, organs and tissues that showed the highest uptake of ^{68}Ga (as %IA/organ) were (in descending order): liver, kidneys, ileum, lings, heart, pancreas and spleen (in the opposite order for male rats), stomach, colon and testes (in the opposite order for male rats), uterus, salivary glands and brain (data not shown). Although available as %IA/g, not for all examined regions the data were reported as %IA/organ.

All collected samples were measured to detect the residual ^{68}Ge. The ^{68}Ge breakthrough was monitored and lied typically below 0.001% if the generator was eluted regularly (data not shown). For most of the samples, the activity of ^{68}Ge was lower than the sensitivity level of the gamma counter and, thus, no reliable results could be obtained. The highest residual ^{68}Ge activity was detected in urine, liver, thyroid and spleen, respectively. The observed activity of ^{68}Ge in bone tissue was low. Except for the bone tissue, the distribution of ^{68}Ge determined in the conducted nonclinical study was similar to that reported by Sabbioni et al., 2010.

The distribution of ^{68}Ga after complexing with chelators like DOTA or ligands like PSMA-11 is driven by the distribution of the carrier molecule to be radiolabelled.

Radiation Dosimetry

The distribution data obtained in the GERGA study for ^{68}Ga in rats at 5 min, 30 min, 60 min, 120 min and 180 min p.i. were used to calculate the time-integrated activity coefficients (TIACs). These TIACs derived from rat data were extrapolated to the corresponding human TIACs using mass scaling by the following factor: $\frac{W_{\mathrm{TB,\,rat}}}{W_{\mathrm{Organ,\,rat}}} \times \frac{W_{\mathrm{Organ,\,human}}}{W_{\mathrm{TB,\,human}}}$, where $W_{\mathrm{TB,\,rat}}$ and $W_{\mathrm{TB,\,human}}$ are the body weights of rat and human, respectively; $W_{\mathrm{Organ,\,rat}}$ and $W_{\mathrm{Organ,\,human}}$ are the weights of the corresponding organs of rat and human, respectively. The masses of organs and tissues of rats published by Brown et al. and Lee et al. were used. For humans, the reference organ and tissue masses, as reported in the ICRP Publication 110, were assumed. The following source regions were considered in the dosimetry for adults: adipose/residual tissue, adrenals, blood, brain, cortical bone marrow, cortical bone mineral volume, heart wall, kidneys, left colon wall, liver, lungs, muscle, ovaries, pancreas, salivary glands, skin, small intestine wall, spleen, stomach wall, testes, thymus, thyroid, urinary bladder wall and uterus/cervix. In the dosimetry for other age groups adrenals, brain, cortical bone, heart wall, kidneys, liver, lungs, muscle, ovaries, pancreas, red marrow, small intestine, spleen, stomach, testes, thymus, thyroid, remainder, upper large intestine, urinary bladder content and uterus were employed as source regions. Dose coefficients for organ absorbed dose [mGy/MBq] after an injection of $^{68}GaCl_3$ were calculated for adults with the software IDAC-Dose 2.1 that utilises realistic anthropomorphic voxel phantoms (ICRP reference phantoms of adults) and for other age groups with the software OLINDA/EXM version 1.0 that uses the stylised mathematical paediatric phantoms. For the dosimetry using OLINDA/EXM the activity in blood was added to the source region "remainder". The dose coefficient for the effective dose [mSv/MBq] for adults was computed according to the formalism and the tissue weighting factors of the ICRP Publication 103.

The age stratified estimations of the coefficients of the absorbed organ doses for the case of an accidental injection of ^{68}Ga to blood are given in the tables below for women and men separately.

Extrapolating from the female rat data, the estimated absorbed dose coefficients for an adult reference female were the greatest in heart wall (0.0838 mGy/MBq), liver (0.0640 mGy/MBq), osteogenic cells (0.0567 mGy/MBq), lungs (0.0552 mGy/MBq), kidneys (0.0424 mGy/MBq) and spleen (0.0407 mGy/MBq).

Extrapolating from the male rat data, the estimated absorbed dose coefficients for an adult reference male were the greatest in heart wall (0.0335 mGy/MBq), osteogenic cells (0.0308 mGy/MBq), liver (0.0307 mGy/MBq), lungs (0.0262 mGy/MBq), spleen (0.0238 mGy/MBq), and kidneys (0.0221 mGy/MBq).

Overall, the estimated effective dose for adults after administration of 250 MBq $^{68}GaCl_3$ would reach 5.4 mSv (see tables below). This is well below the dose of 350 mSv (presuming the entire radioactive dose is from γ-radiation) at which transient, mild nausea or headache may first be experienced (Donnelly et al., 2010). Even in the heart wall in adult females, where the estimated absorbed dose coefficient was greatest, a single injection of 250 MBq would only result in a local exposure to approximately 21 mGy, almost a factor of 100 below the exposure of 2,000 mSv, above which acute radiation syndrome is produced (Donnelly et al., 2010).

In addition, the duration of radiation exposure after administration of any ^{68}Ga-containing product is very short, due to the short physical half-live of ^{68}Ga: after 6 h (5 half-lives) only 3% of the injected radioactivity remains.

As stated in the study report, it was impossible to derive TIACs for ^{68}Ge due to the very low ^{68}Ge levels detectable in rats and a short duration of the experiment (last measurement at 180 min p.i.) compared to the physical half-life of ^{68}Ge (270.95 d). Thus, no extrapolation of distribution data and no dosimetry for humans after an administration of ^{68}Ge was done in the frame of the conducted non-clinical study. For dosimetry of ^{68}Ge, the applicant has adopted the coefficient of the effective dose reported in the ICRP Publication 151.

Table 9. Human radiation dosimetry estimates for ^{68}Ga radioactivity for <u>women</u> after administration of $^{68}GaCl_3$, extrapolated from female rat data

Absorbed dose coefficients (mGy/MBq)						
	IDAC-Dose 2.1 v1.01	**OLINDA/EXM v1.0**				
Organ	**Adult (60 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adipose/residual tissue	0.0121	0.0199	0.0327	0.0531	0.1050	0.2680
Adrenals	0.0398	0.0304	0.0440	0.0618	0.0959	0.1020
Bone marrow	0.0299	0.0202	0.0331	0.0606	0.1540	0.6050
Bone surface	0.0169	ND	ND	ND	ND	ND
Brain	0.0081	0.0048	0.0061	0.0081	0.0126	0.0282
Colon wall	0.0210	0.0224	0.0373	0.0609	0.1170	0.2930
Heart wall	0.0838	0.0263	0.0407	0.0639	0.1150	0.2280
Kidneys	0.0424	0.0333	0.0474	0.0712	0.1280	0.3250
Liver	0.0640	0.0598	0.0906	0.1360	0.2630	0.6080
Lungs	0.0552	0.0497	0.0708	0.1090	0.2160	0.5840
Muscle	0.0131	0.0131	0.0248	0.0698	0.1370	0.1950
Osteogenic cells	0.0567*	0.0558	0.0869	0.1420	0.3310	1.0100
Ovaries	0.0372	0.0332	0.0944	0.1650	0.3720	0.7550
Pancreas	0.0309	0.0276	0.0533	0.0704	0.1490	0.4730
Salivary glands	0.0194	ND	ND	ND	ND	ND
Skin	0.0115	0.0115	0.0189	0.0311	0.0612	0.1570
Small intestine wall	0.0256	0.0273	0.0459	0.0749	0.1460	0.3630
Spleen	0.0407	0.0263	0.0403	0.0642	0.1180	0.3030
Stomach wall	0.0284	0.0188	0.0293	0.0482	0.0939	0.2540
Thymus	0.0129	0.0094	0.0115	0.0157	0.0261	0.0518
Thyroid	0.0265	0.0282	0.0434	0.0923	0.1730	0.2490
Urinary bladder wall	0.0174	0.0155	0.0251	0.0419	0.0770	0.2000
Uterus/cervix	0.0291	0.0325	0.4560	0.6900	1.2500	0.5360

* calculated in OLINDA v1.0 as not available in IDAC-Dose 2.1 v1.01.
ND = not determined as organ/tissue not available in OLINDA/EXM v1.0.
Calculations were performed either in IDAC-Dose 2.1 (for adults) or in OLINDA/EXM v1.0 as indicated. Time-points for measurements were 5, 30, 60, 120, and 180 min.

Table 10: Human radiation dosimetry estimates for ^{68}Ga radioactivity for men after administration of $^{68}GaCl_3$, extrapolated from male rat data

Absorbed dose coefficients (mGy/MBq)						
	IDAC-Dose 2.1 v1.01	OLINDA/EXM v1.0				
Organ	**Adult (73 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adipose/residual tissue	0.0065	0.0128	0.0210	0.0341	0.0672	0.1720
Adrenals	0.0189	0.0200	0.0289	0.0405	0.0628	0.0669
Bone marrow	0.0124	0.0149	0.0244	0.0454	0.1120	0.4180
Bone surface	0.0079	ND	ND	ND	ND	ND
Brain	0.0046	0.0034	0.0043	0.0056	0.0088	0.0196
Colon wall	0.0121	0.0162	0.0274	0.0449	0.0865	0.2150
Heart wall	0.0335	0.0195	0.0303	0.0478	0.0858	0.1710
Kidneys	0.0221	0.0239	0.0340	0.0510	0.0915	0.2340
Liver	0.0307	0.0388	0.0588	0.0881	0.1700	0.3940
Lungs	0.0262	0.0327	0.0466	0.0718	0.1420	0.3850
Muscle	0.0072	0.0111	0.0219	0.0658	0.1300	0.1800
Osteogenic cells	0.0308*	0.0402	0.0633	0.1050	0.2440	0.7550
Pancreas	0.0167	0.0211	0.0412	0.0540	0.1150	0.3720
Salivary glands	0.0132	ND	ND	ND	ND	ND
Skin	0.0073	0.0063	0.0102	0.0166	0.0326	0.0828
Small intestine wall	0.0126	0.0167	0.0282	0.0460	0.0892	0.2220
Spleen	0.0238	0.0259	0.0400	0.0634	0.1170	0.3060
Stomach wall	0.0145	0.0116	0.0179	0.0295	0.0573	0.1570
Testes	0.0098	0.0182	0.1210	0.1410	0.1910	0.2770
Thymus	0.0092	0.0082	0.0093	0.0122	0.0193	0.0384
Thyroid	0.0163	0.0248	0.0383	0.0825	0.1550	0.2200
Urinary bladder wall	0.0116	0.0095	0.0151	0.0252	0.0458	0.1190

* calculated in OLINDA/EXM v1.0 as not available in IDAC-Dose 2.1 v1.01.
ND = not determined as organ/tissue not available in OLINDA/EXM v1.0.
Calculations were performed either in IDAC-Dose 2.1 v1.01 (for adults) or in OLINDA/EXM v1.0 as indicated. Time-points for measurements were 5, 30, 60, 120, and 180 min.

The effective radiation dose of ^{68}Ga for an adult in the case of inadvertent direct administration of the eluate is 0.0216 mSv/MBq, resulting in an approximate effective radiation dose of 5.6 mSv from an accidental intravenously injected activity of 259 MBq.

The effective dose coefficients adopted from the ICRP Publication 151 for $^{68}GaCl_3$ if ingested or inhaled by mistake (0.11 mSv/MBq and 0.055 mSv/MBq, respectively) were provided.

2.6.3. Discussion on clinical pharmacology

Since neither the product, nor its produce – $^{68}GaCl_3$ – are intended for direct use in patients, no clinical pharmacology studies have been conducted, which is endorsed.

Non-clinical data from own study in rats (GERGA study), which were used for calculation of radiation exposure in humans in the event of accidental injection of the eluate (i.e. $^{68}GaCl_3$) of GalliaPharm, were presented. This was considered acceptable.

It must be noted, that the same preclinical study GERGA was submitted during the initial MAA of the similar $^{68}Ga/^{68}Ge$ generator (maximum strength of 1.85 GBq), that has been licenced via a DCP procedure (DK/H/2294) in numerous European countries. Also, the data obtained within the GERGA study have become the source of the dosimetry information included in the EMA Guideline on core SmPC and Package Leaflet for ($^{68}Ge/^{68}Ga$) generator (EMA/CHMP/337681/2016). Overall, the initial dosimetry information was acceptable, but it was no longer in compliance with the current standards and recommendations. Within the current application the dosimetry for the case of an accidental injection of ^{68}Ga was re-evaluated to improve the deficiencies following the recommendations of the assessment report.

The new dosimetry calculations were done based on the biodistribution data of ^{68}Ga in rats obtained within the GERGA study. The TIACs computed for rats in the preclinical study were scaled to derive the human TIACs using a mass-scaling method. In the re-evaluated dosimetry, the masses of organs and tissues of rats published by Brown et al. and Lee et al. and the corresponding masses for humans reported in the ICRP Publication 110 were used. Although a mass-scaling method is commonly used, it has a notable drawback: such scaling does not consider differences in metabolism between rats and humans. Hence, the resulting biodistribution and dosimetry in humans are to be used with caution considering very high possible uncertainties of the estimated doses. The uncertainty of the data obtained by scaling from animals to humans is also recognised in the provided report of the nonclinical study. The data on biokinetics of gallium in humans were not employed. The following source regions were considered in the re-evaluated dosimetry calculations for adults: adipose/residual tissue, adrenals, blood, brain, cortical bone marrow, cortical bone mineral volume, heart wall, kidneys, left colon wall, liver, lungs, muscle, ovaries, pancreas, salivary glands, skin, small intestine wall, spleen, stomach wall, testes, thymus, thyroid, urinary bladder wall and uterus/cervix. For other age groups the source regions employed were: adrenals, brain, cortical bone, heart wall, kidneys, liver, lungs, muscle, ovaries, pancreas, red marrow, small intestine, spleen, stomach, testes, thymus, thyroid, remainder, upper large intestine, urinary bladder content and uterus. Thus, additional source regions have been included compared to the initial application. The TIACs were re-evaluated using the current ICRP recommendations and models.

As requested, the usage of the TIAC in blood were improved: it was assigned to the source region ”blood” in dose calculations with IDAC-Dose 2.1 and added to the source region ”Remainder” when using the OLINDA/EXM v.1.0.

In line with the recommendations, in the re-evaluated dosimetry data set, the activity accumulated in the organs and tissues not explicitly considered as source regions was accounted for. It follows that this activity was assigned to the source region ”adipose/residual tissue” instead of ”other/remainder” (GERCA study, addendum). Although minor differences in the organ absorbed doses can be caused by this, this is considered appropriate, taking into account the uncertainties involved.

The IDAC-Dose 2.1 software that utilises realistic anthropomorphic voxel phantoms (ICRP reference phantoms of adults) was used to re-calculate the absorbed organ doses for adults, as recommended. Since the more realistic paediatric voxel phantoms are currently not available in the software IDAC-Dose 2.1, the stylised mathematical paediatric phantoms as implemented in the software OLINDA/EXM v.1.0 were employed for the dosimetry for other age groups instead. This is agreed.

In the initial assessment it was requested to include “urinary bladder content” as an explicit source region in dosimetric calculations. The applicant elaborated that this was not feasible due to (1) the small volumes of sampled urine and subsequently large uncertainties of the estimated sample weights;

(2) unknown total amount of urine in rats; (3) a lack of accuracy of the modelled time-activity curves for urinary bladder content. Although it is acknowledged that it is difficult to overcome this limitation, the omission of ”urinary bladder content” as a source region for the substance excreted predominantly into the urine leads to a possible underestimation of the effective dose. Thus, the applicant has added the following statement as a footnote to the dosimetry tables 3 and 4 in the SmPC: ”Due to the methodological limitations of the underlying distribution study in rats, it was not feasible to consider urinary bladder content as an explicit source region for the dosimetry. Since gallium (^{68}Ga) chloride is excreted predominantly into the urine according to the rat data, the reported effective dose is thus possibly underestimated”.

Effective dose coefficients for adults after an injection of $^{68}GaCl_3$ reported by the applicant in the addendum to the conducted nonclinical study were computed according to the formalism and the tissue weighting factors of the ICRP Publication 103 (2007). These are the current ICRP recommendations.

In summary, the estimated effective radiation dose of ^{68}Ga for an adult is 0.0216 mSv/MBq, resulting in an approximate effective radiation dose of 5.6 mSv from an accidental intravenously injected activity of 259 MBq. The duration of radiation exposure after administration of any ^{68}Ga-containing product being very short, due to the short physical half-live of ^{68}Ga, no specific action is required in case of accidental injection with the eluate from the ^{68}Ge/^{68}Ga generator containing $^{68}GaCl_3$.

For dosimetry of $^{68}GeCl_4$, the applicant adopted the effective dose coefficients reported in the ICRP Publication 151 “Occupational intakes of radionuclides: part 5” (2022). This was considered acceptable.

An issue of an accidental intake of $^{68}GaCl_3$ via other incorporation ways such as ingestion or inhalation has also been discussed. The effective dose coefficients as reported in the ICRP Publication 151 for ^{68}Ga if accidentally ingested or inhaled (0.11 mSv/MBq and 0.055 mSv/MBq, respectively), have been adopted. These effective dose coefficients (and the respective effective doses when similar activity is administered) after accidental ingestion or inhalation of $^{68}GaCl_3$ are notably higher (about 5 times and 2-2.5 times, respectively) than the dose coefficients after an accidental injection of $^{68}GaCl_3$ to blood, or i.v. administration of ^{68}Ga-labelled frequently used carriers. However, it is acknowledged that the accidental exposure to $^{68}GaCl_3$ is a generic risk and is unlikely to occur if the SmPC recommendations and warnings are followed.

2.6.4. Conclusions on clinical pharmacology

No clinical studies have been conducted. The applied methodology to calculate dosimetry in humans is considered compliant with current standards and is therefore acceptable.

2.6.5. Clinical utility

In total, >270 publications were submitted describing use of ^{68}Ga-marked carrier molecules – DOTA-TOC (edotreotide), DOTA-NOC, DOTA-TATE and PSMA-11 (gozetotide) - in the indications of neuroendocrine tumours (NETs), meningiomas and prostate cancer (PCa):

- >40 publications on ^{68}Ga-DOTA-TOC in NETs (mostly GEP-NETs, but also nonfunctioning pituitary NETs, paraganglioma, head and neck paraganglioma, pheochromocytoma),
- >40 publications on ^{68}Ga-DOTA-NOC in NETs (mostly GEP-NETs, but also Merkel cell carcinoma, paraganglioma, pheochromocytoma, pulmonary carcinoma, etc.),
- >60 publications on ^{68}Ga-DOTA-TATE in NETs (mostly GEP-NETs but also pheochromocytoma, paraganglioma, medullary thyroid carcinoma, hormone-producing pituitary microadenoma, pulmonary carcinoma, etc.),

- 8 publications on ^{68}Ga-DOTA-TOC in meningiomas, two publications on ^{68}Ga-DOTA-TATE in meningiomas,
- >30 publications on ^{68}Ga-PSMA-11 in primary PCa imaging,
- >30 publications on ^{68}Ga-PSMA-11 in recurrent PCa diagnostics,
- 20 publications on ^{68}Ga-PSMA-11 in detection of PCa metastases, and
- 10 publications on impact of ^{68}Ga-PSMA-11 on diagnostic thinking and patient management.

Studies evaluated diagnostic performance, but also, impact on patient management and decision-making have been studied.

- DOTA-TOC

NETs

In the prospective studies identified in literature from 2014 to 2022, reported ^{68}Ga-DOTA-TOC PET/CT sensitivities for detecting various NETs were in the range from 63 to 100% depending on the lesion location and lesion size. Specificities higher than 90% were reported. These studies also suggested that the use of ^{68}Ga-DOTA-TOC has an impact on the clinical management of NETs and may be of prognostic value as well.

DOTA-TOC (edotreotide) labeled with ^{68}Ga has gained marketing authorisation in Europe in 2016 with the brand name SomaKit TOC (Marketing authorisation holder: Advanced Accelerator Applications, France) via the centralised procedure (EMEA/H/C/004140) in the following indication:

"after radiolabelling with gallium (^{68}Ga) chloride solution, the solution of gallium (^{68}Ga) edotreotide obtained is indicated for PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases."

A ready-to-use preparation of ^{68}Ga-labelled DOTA-TOC for intravenous use (brand name: TOCscan/Sogacin, previously: IASOtoc; Marketing Authorisation Holder: ITM Medical Isotopes GmbH) has been authorised in 2016 via a decentralised mutual recognition procedure (procedure number: FR/H/0611/001/MR) in France, Austria and Germany.

Meningioma

Six studies investigated the value of ^{68}Ga-DOTA-TOC PET or PET/CT in addition to the MRI or comparison to the PET/MRI hybrid scans for radiation planning. Overall, all lesions detected by MRI/CT could be also detected by ^{68}Ga-DOTA-TOC PET and additional lesions were discovered. ^{68}Ga-DOTA-TOC PET was able to add information with regard to tumour extent, especially in difficult areas such as the base of the skull or intracranial expansion. In one study tumour volume was modified compared to CT and MRI based on ^{68}Ga-DOTATOC PET in 72% of patients (Nyuyki et al). Many authors conclude that ^{68}Ga-DOTATOC PET data improve interpretation of imaging data revealed by MRI alone.

- DOTA-NOC

NETs

The largest studies evaluating diagnostic performance of ^{68}Ga-DOTA-NOC PET in the diagnostics of NETs were conducted by Ambrosini et al., 2012b (n=1239) and Haidar et al., 2017 (n=445). Sensitivity and specificity around 90% were reported in these larger studies.

- DOTA-TATE

NETs

Sadowski et al., 2015 (the largest prospective study evaluating 136 patients with blinded image interpretation) showed that ^{68}Ga-DOTA-TATE PET/CT imaging detected 95.1% of lesions (95% CI, 92.4% to 96.8%), anatomic imaging detected 45.3% of lesions (95% CI, 37.9% to 52.9%), and ^{111}In-pentetreotide SPECT/CT detected 30.9% of lesions (95% CI, 25.0% to 37.5%), with a significant difference between imaging modalities. On the basis of findings with ^{68}Ga-DOTA-TATE PET/CT, 43 of 131 patients (32.8%) had a change in management recommendation. In patients with carcinoid symptoms but negative biochemical testing, ^{68}Ga-DOTA-TATE PET/CT detected lesions in 65.2% of patients, 40% of which were detected neither by anatomic imaging nor by ^{111}In-pentetreotide SPECT/CT.

A kit preparation for ^{68}Ga-labeling of DOTA-TATE (NETSPOT™, AAA) was approved by the US FDA on June 1st, 2016, by Swissmedic in Switzerland on October 26th, 2018, and by Health Canada on July 3rd, 2019, for PET imaging to localise NETs overexpressing somatostatin receptors after gallium (^{68}Ga) radiolabelling.

Meningioma

Rachinger et al., 2015 showed that uptake of ^{68}Ga-DOTA-TATE was different in tumour and tumour-free tissue and ^{68}Ga-DOTA-TATE PET compared to MRI led to the diagnosis of additional, so far undiagnosed meningiomas in 9/21 patients. The authors therefore concluded that ^{68}Ga-DOTA-TATE PET has significant impact on the diagnosis and management of meningiomas, particularly with tumours in complex locations or at recurrent stage.

Kunz et al., 2017 (retrospective study) showed that higher SUVmax values were observed in patients with transosseous meningiomas vs. patients with extraosseous tumours ($p<0.001$). Compared to CE-MRI, ^{68}Ga-DOTA-TATE PET/CT demonstrated higher sensitivity (98.5% vs. 53.7%, respectively), while maintaining high specificity (86.7% vs. 93.3%, respectively) in the detection of osseous involvement. The authors concluded that ^{68}Ga-DOTA-TATE PET/CT provides improved detection of the transosseous extension of intracranial meningiomas compared to CE-MRI.

- PSMA-11 (gozetotide)

The largest prospective study conducted in the diagnostics of primary PCa staging with ^{68}Ga-PSMA-11 is the study by Hope et al., 2021. In this study, a total of 764 men underwent ^{68}Ga-PSMA-11 PET imaging scan for primary staging, and 277 of 764 (36%) subsequently underwent prostatectomy with lymph node dissection (efficacy analysis cohort). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for pelvic nodal metastases were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85), respectively. Images were interpreted in blinded fashion by several readers and reference standard of truth was histopathology.

In the setting of biochemical recurrence (BCR) of PCa the largest prospective, multicentre trial with blinded reads by Fendler et al. (2019; n=635) demonstrated an overall 75% detection rate with a direct correlation to the prostate specific antigen (PSA) level and as such ranging from 37% for PSA<0.5 ng/mL to 97% for PSA ≥5 ng/mL. An 84% PPV was observed in this study when the ^{68}Ga-PSMA-11 PET/CT findings were verified by HP, increasing to 92% when a verification was conducted using composite reference standard that included HP and other imaging modalities.

^{68}Ga-PSMA-11's ability to detect metastases compared ^{11}C-choline was studied by Schwenck et al. (2017) in a prospective, open label study in a mixed population of patients with primary and recurrent PCa (n=123; the largest study presented). The overall detection rates of ^{68}Ga-PSMA-11 and ^{11}C-choline PET/CT did not differ significantly (83% vs. 79%, respectively). In patients with BCR, 39% of

LNM were detected only by ^{68}Ga-PSMA-11 PET/CT, while 6% showed only ^{11}C-choline uptake, resulting in LNM detection rates of 94% vs. 71%, respectively. In patients with PSA <1 ng/mL LN metastases were detected mostly only by means of ^{68}Ga-PSMA-11. Similarly, of 380 detected bone lesions, 36% were only visible in ^{68}Ga-PSMA-11 scans, resulting in 98% detection rate vs. 64% observed for ^{11}C-choline.

Lengana et al. (2018b) conducted a head-to-head comparison of ^{68}Ga-PSMA-11 PET/CT diagnostic accuracy vs. that of technetium-99m-based bone scintigraphy (^{99m}Tc-BS) for detecting bone metastases in PCa patients sent for the initial skeletal scanning. Histologic correlation and clinical follow-up were used for verifying imaging findings. ^{68}Ga-PSMA-11 PET/CT showed significantly higher sensitivity and accuracy than ^{99m}Tc-BS in detecting bone metastases (96.2% vs. 73.1%, and 99.1% vs. 84.1%, respectively).

By analysing ^{68}Ga-PSMA-11 PET/CT findings in 69 patients with metastatic PCa within a prospective multicentre CPCT-02 clinical trial, de Jong et al. (2020) demonstrated 70% success rate of ^{68}Ga-PSMA-11-guided bone biopsies, showing additional positive clinical impact of this tracer.

High impact on patient management and decision-making have been reported in the presented 5 publications (Roach et al., 2018, Sonni et al., 2020, Fendler et al., 2020, Emmett et al., 2020 and Ekmekcioglu et al., 2021) reaching levels of >50% in some settings.

Gozetotide (PSMA-11) under the trade name Locametz (Marketing authorisation holder: Novartis Europharm Limited) was approved in the EU as a kit for radiopharmaceutical preparation via a centralised procedure (EMEA/H/C/005488) on 09.12.2022 in the indication:

"… 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 (see section 4.4)."

2.6.6. Discussion on clinical utility

Clinical utility data and additional analyses

As the product under evaluation is not intended for direct use in patients, it was considered acceptable that no specific indication was targeted, and no proprietary clinical data were provided.

In accordance with Annex I, Part III, Section 2.2 of Directive 2001/83/EC, as amended, stating "[…] information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented", published clinical data were submitted to support the claim of clinical utility. This was considered acceptable.

The following key areas of clinical utility of $^{68}GaCl_3$ as the eluate of GalliaPharm, have been discussed:

Diagnostics of

- Brain lesions (using ^{68}Ga-EDTA, only of historical interest)
- Neuroendocrine tumours
- Meningiomas
- Prostate cancer (using ^{68}Ga-PSMA-11)

Four main carrier molecules currently being in clinical use after labelling with ^{68}Ga have been presented: DOTA-TOC, DOTA-TATE, DOTA-NOC and PSMA-11.

The areas discussed in respect to the clinical utility, and the number of the published studies is considered sufficient.

The broadest evidence of clinical utility of ^{68}Ga-labelled carrier molecules has been provided for ^{68}Ga-DOTA-TOC, DOTA-NOC and DOTA-TATE in diagnostics of NETs (primarily in GEP-NETs) and for ^{68}Ga-PSMA-11 in diagnostics of PCa (primary imaging, recurrence diagnostics). Evidence of use of ^{68}Ga-labelled DOTA molecules is very limited in meningioma diagnostics.

The presented data suggest that ^{68}Ga-DOTA-TOC (edotreotide) and ^{68}Ga-PSMA-11 (gozetotide) show good levels of diagnostic performance (e.g., sensitivity, detection rates, accuracy, etc.) in diagnostics of GEP-NETs and PCa (primary imaging, diagnostics of recurrent PCa, etc.) with relevant impact on diagnostic thinking and patient management. Place in diagnostic imaging and positive benefit-risk ratio has been established for these two carrier molecules, and they have gained marketing authorisation throughout the Europe in the recent years.

Edotreotide is approved under the brand names SomaKit TOC and TOCscan/Sogacin, and gozetotide under the brand name of Locametz.

The remaining carrier molecules, i.e., DOTA-NOC and DOTA-TATE are still in their experimental development stage. However, it must be noted, that use of ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE (together with ^{68}Ga-DOTA-TOC) is recommended by a number of European and international scientific societies, such as, EANM (Virgolini et al., 2010 and Bozkurt et al., 2017 – updated guideline), European Neuroendocrine Tumor Society (ENETS) (Sandin et al., 2017) and European Society for medical Oncology (ESMO) (Pavel et al., 2020) in the diagnostics of NETs. Broad integration of ^{68}Ga-labeled DOTA-conjugates in various clinical practice guidelines is also considered supportive for the claim of clinical utility, especially within the context of this application.

In conclusion, while majority of the submitted evidence contains exploratory small studies, the totality of published evidence, but most importantly, availability of the licenced radiopharmaceuticals approved for use after radiolabelling with $^{68}GaCl^3$ are considered sufficient to substantiate the claim of clinical utility of GalliaPharm and its eluate $^{68}GaCl^3$ in PET diagnostics.

2.6.7. Conclusions on the clinical utility

GalliaPharm is a radionuclide generator. Proof of efficacy within the context of this application is not required, but demonstration of clinical utility is expected. Overall, the presented evidence indicates, that ^{68}Ga is broadly used for labelling purposes in PET diagnostics. Moreover, a ^{68}Ga/^{68}Ge generator by the same Applicant, as well as the carrier molecules to be labelled with ^{68}Ga have already gained approval in the Europe, so that clinical utility of $^{68}GaCl_3$ can be considered sufficiently substantiated.

2.6.8. Clinical safety

Safety profile of the ^{68}Ga-labelled molecules will depend on the characteristics of these molecules and are not of relevance within the context of this Application.

Discussion on safety has been focused on radiation exposure to the patients, comparison of effective dose to other diagnostic agents and on the safety of ^{68}Ga-DOTA-conjugates and ^{68}Ga-PSMA-11. Also, world-wide marketing experience has been summarised. See detailed description of the dosimetry information in 2.6.2.

2.6.8.1. Patient exposure

According to the sales volumes of GalliaPharm (DCP MA, max strength 1.85 GBq), a total of 1,488 GalliaPharm radionuclide generators were sold from the date of its first approval in Italy in 2014 up to 15 March 2022 - the data lock point of the last prepared Periodic Safety Update Report (PSUR). Applying the calculation approach used for the PSUR, which is based on several reasonable assumptions (230 working days per year [a shelf-life of one generator], 1.5 eluates obtainable per working day on average, and one eluate used for one patient), a total number of 513,360 patients is estimated to have been potentially exposed to the product during this time.

2.6.8.2. Radiation exposure

Overall, the estimated human organ specific doses and the averaged effective dose after accidental administration of 259 MBq $^{68}GaCl_3$ would reach 5.6 mSv in adults. This is well below the dose of 350 mSv (presuming the entire radioactive dose is from γ radiation) at which transient, mild nausea or headache may first be experienced (Donnelly et al., 2010).

The effective dose of $^{68}GaCl_3$ (if injected accidentally) is somewhat higher than those of ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TOC, and ^{68}Ga-PSMA-11.

Table 11. Effective doses of ^{68}Ga radiopharmaceuticals and in humans

Radiopharmaceutical	Effective dose (mSv/MBq)	Reference
^{68}Ga-DOTA-NOC	0.025	Pettinato *et al*., 2008
^{68}Ga-DOTA-TOC	0.023	Hartmann *et al*., 2009
^{68}Ga-PSMA	0.022[1]	Sandgren *et al.,* 2019
^{68}Ga-eluate	0.0483[2], 0.0338[3]	Study report GERGA

[1] Measured in 6 low-risk prostate cancer patients injected with 133–178 MBq ^{68}Ga-PSMA, [2]obtained by using female rat data; [3]obtained by using male rat data.

mCi = millicurie, MBq = megabecquerel, PSMA = prostate specific membrane antigen.

2.6.8.3. Safety of ^{68}Ga-DOTA-conjugated peptides and ^{68}Ga-PSMA-11

No adverse events (AEs), no significant AEs, or no AEs with the grade > 1 have been reported on ^{68}Ga-PSMA-11 in the following studies evaluating safety: Nielsen *et al.,* 2017 (n=88), Fendler *et al*., 2019 (n=635), Hope *et al*., 2021 (n=764) and Zhang J. *et al.,* 2019 (n=54). Highest proportion of patients reporting AEs was 6% and was reported in a large study by Hope et al., over the follow-up period of 1-3 days post-procedure.

In the procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides, the following cautionary considerations are listed (Bozkurt et al., 2017):

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is or may be pregnant, a clinical decision is necessary considering the benefits against the possible harm of carrying out any procedure.
- Breastfeeding. If radiopharmaceutical administration is considered necessary, breastfeeding should be interrupted and can be restarted after elapsing of seven physical half-lives of radionuclide in a radiopharmaceutical, when the level of radiation in the milk will not result in a radiation dose to the child greater than 1 mSv.
- The ionising radiation from ^{68}Ga-DOTA-conjugate peptides administration must be carefully evaluated in subjects under 18 years of age. However, the dosimetry of ^{68}Ga-somatostatin analogues is more favourable than that of ^{111}In-pentetreotide.
- It has been recommended to temporarily withdraw somatostatin analogue therapy (when possible) to avoid possible SSTR blockade. In some patients the withdrawal of therapy might not be tolerated.

Of these, the recommendations regarding pregnancy and breastfeeding apply to any radiopharmaceutical and therefore apply to the ^{68}Ge/^{68}Ga-generator:

- When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.
- Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and the foetus.

- Before administering a radiopharmaceutical to a mother who is breast-feeding, consideration should be given to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding. If the administration is considered necessary, breast-feeding should be interrupted and the expressed feeds discarded.

2.6.8.4. Post marketing experience

The currently applied highest strength for GalliaPharm (3.7 GBq) has never been marketed. However, another version of this generator with lower strength (max. 1.85 GBq) has been approved in numerous countries in Europe. To date, 8 PSURs for this lower strength generator have been prepared and submitted to EMA and national agencies within EU. No safety concerns for the generator have been identified so far from post-marketing sources. No serious AEs from clinical trials sponsored by Eckert & Ziegler Radiopharma GmbH were received during the entire reporting interval from 09 September 2014 to 15 March 2022. No information from long-term follow-up of patients from clinical trials with GalliaPharm is available.

The last PSUR, covering the interval from 16 March 2019 to 15 March 2022, was included in the submission.

2.6.9. Discussion on clinical safety

GalliaPharm is a radionuclide generator, therefore its safety profile is dependent on its technical features and functioning. Thus, as long as the quality requirements and specifications are clearly defined and complied with, risks related to GalliaPharm are considered very low. The use of ^{68}Ga-labelled medicinal products is contraindicated in case of hypersensitivity to the active substance or to any of the excipients listed.

Theoretical risks may emerge from inappropriate handling and maintenance procedures, which may impact the quality of the eluate (e.g., ^{68}Ge breakthrough, low purity, lack of sterility), or lead to radiation exposure of the hospital staff (exposure through surface, inhalation, etc.) or patients (e.g., through an accidental use of the eluate directly in the patients). Possible ^{68}Ge breakthrough represents a certain degree of risk.

In order to minimise the above risks handling and maintenance procedures for GalliaPharm (e.g., storage, instructions for preparation of the eluate) have been reflected in the SmPC in detail and can be regarded sufficient, as risk minimisation measures.

^{68}Ge breakthrough

A small amount of ^{68}Ge is washed from the radionuclide generator column with each elution. ^{68}Ge breakthrough is expressed as a percentage of total ^{68}Ga activity eluted from the column, corrected for decay, and does not exceed 0.001 % of the eluted ^{68}Ga activity. ^{68}Ge breakthrough can, however, increase above 0.001 % if the radionuclide generator is not eluted for several days. Therefore, if the radionuclide generator has not been eluted for 96 hours or more, it should be pre-eluted with 10 ml of sterile ultrapure 0.1 mol/l hydrochloric acid at least 7 hours prior to the intended use (the time between the pre-elution and the elution for radiolabelling can be reduced if the intended radiolabelling procedure does not require maximum achievable eluate activity). When this instruction is followed, the ^{68}Ge breakthrough should constantly stay below 0.001 % in eluates obtained for radiolabelling. For testing the ^{68}Ge breakthrough, the activity levels of ^{68}Ga and ^{68}Ge in the eluate should be compared. For further details see Ph. Eur. monograph 2464. Appropriate warnings and instructions have been included in the PI to inform health care providers.

External radiation exposure

The average surface or contact radiation for the radionuclide generator is less than 0.14 µSv/h per MBq of ^{68}Ge, but local hot spots of higher radiation can occur. Nevertheless, a 3.70 GBq radionuclide generator will reach an overall average surface dose rate of approx. 518 µSv/h. It is generally recommended that the radionuclide generator is stored within auxiliary shielding to minimise dose to operating personnel.

Generally, ^{68}Ge/^{68}Ga-generators are being routinely used for decades in nuclear medicine and generic safety risks related to inappropriate handling and maintenance are estimated as low. It is the current assumption that additional product-specific risks related to handling and maintenance procedures which would exceed the context of routine measures taken for other generators are not to be expected.

Non-clinical studies (own and published) have been presented to address the risk of direct application of the $^{68}GaCl_3$ eluate to patients. Radiation dosimetry has been calculated for $^{68}GaCl_3$ and humans based on these data and in accordance with the current standards. The effective dose resulting from an accidental intravenously injected activity of 259 MBq is estimated as 5.6 mSv for an adult and is roughly in the range of the effective dose of various diagnostic agents, including ^{68}Ga-marked radiopharmaceuticals (e.g., SomaKit TOC, Locametz).

Accidental administration of gallium (^{68}Ga) chloride solution for radiolabelling containing 0.1 mol/l hydrochloric acid may also cause local venous irritation and, in case of paravenous injection, tissue necrosis. The catheter or affected area should be irrigated with 9 mg/ml (0.9 %) sodium chloride solution for injection.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. Human radiation dose in case of an inadvertent administration of the eluate should be estimated using the information given.

Recommendations to increase hydration and voiding in order to reduce the dose/overdose in such event have been included in section 4.9 of the SmPC to minimise the risk of radiation exposure to patients. No toxic effects are to be expected from the free ^{68}Ga after an inadvertent administration of the eluate. The administered free ^{68}Ga decays almost completely to stable ^{68}Zn within a short time (97 % are decayed in 6 hours). During this time, ^{68}Ga is mainly concentrated in the blood/plasma (bound to transferrin) and in the urine. The patient should be hydrated to increase the excretion of the ^{68}Ga. Forced diuresis as well as frequent bladder voiding are recommended. Forced diuresis as well as frequent bladder voiding are recommended. This is agreed.

In summary, majority of the theoretical risks represent generic risks related to use of radionuclide products and have been addressed in the SmPC. Overall, the product can be considered to have favourable safety profile, provided that all quality requirements are fulfilled and adhered to.

2.6.10. Conclusions on the clinical safety

The product has a favourable safety profile. Theoretical relevant risks are being adequately addressed in the SmPC. This medicinal product is for use in designated nuclear medicine facilities only and should only be handled by specialists experienced with in vitro radiolabelling. The gallium (^{68}Ga) chloride solution is not intended for direct use in patients but is used for in vitro radiolabelling of various kits for radiopharmaceutical preparation. The route of administration of the ^{68}Ga-labelled radiopharmaceutical is defined in the Summary of Product Characteristics/package leaflet of the respective kit for radiopharmaceutical preparation and should be adhered to.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 12. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

Table 13. Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)	Routine risk communication: • Instruction / information in SmPC section 12 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The first eluate obtained from the generator should be discarded due to potentially increase ^{68}Ge-brekthrough. • It is recommended to test the first eluates and the eluates obtained in routine use throughout the shelf-life of the generator for ^{68}Ge-breakthrough in accordance with Ph. Eur. monograph 2464. • The radionuclide generator should be pre-eluted 7 hours (or less if appropriate) prior to eluting for radiolabelling if the generator has not been used for a period of 96 hours or more to avoid elevated ^{68}Ge-breakthrough levels. Other routine risk minimisation measures beyond the Product Information: • The product is a radiopharmaceutical. Its receipt, use, and administration are restricted to authorised persons in designated clinical settings. • Legal status: prescription only

Table 14. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)	**Routine risk minimisation measures:** • Extensive information and instructions in SmPC section 12. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 01 (DLP: 31/07/2022, date of final sign off: 26/06/2023) is acceptable.

In addition, minor revisions are recommended to be taken into account with the next RMP update: (i) a unique RMP version number should be assigned to each RMP submitted for evaluation; (ii) the DLP should not be more than six months before the RMP sign-off date; (iii) the wording of the indication provided in Part I should be aligned with the indication stated in the SmPC.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to GalliaPharm 0.74 -1.85 GBq, radionuclide generator in the scope of the decentralised procedure (DCP) DK/H/2294 in 2014. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The subject of this centralised application is $^{68}Ge/^{68}Ga$-generator (proposed name: GalliaPharm 1.11 – 3.70 GBq, radionuclide generator), a device that produces an eluate containing the active substance gallium (^{68}Ga) chloride ($^{68}GaCl_3$). $^{68}GaCl_3$ is a precursor, that is used for in-vitro radiolabelling of specific carrier molecules, which are subsequently utilised in PET diagnostics.

Neither the generator itself, nor the eluate are directly used in the patients. Therefore, disease or conditions these will be utilised for will depend on the selected carrier molecules to be labelled with ^{68}Ga. Currently, ^{68}Ga-labelled tracers are being mainly applied in the PET diagnostics of NETs and prostate cancer.

Since GalliaPharm, or its eluate are not used in patients, no clinical studies have been conducted and assessment of efficacy in the usual sense is neither possible, nor applicable. Also, no specific indication referring to concrete condition has been claimed.

The final agreed indication correctly reflects the main function of the product and is also in line with the EMA "Guideline on Core SmPC and Package Leaflet for $^{68}Ge/^{68}Ga$-generator" (EMA/CHMP/337681/2016) stating:

"This radionuclide generator is not intended for direct use in patients.

The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalliaPharm is indicated for in vitro radiolabelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such eluate, to be used for positron emission tomography (PET) imaging".

3.1.1. Disease or condition

No specific indication is targeted. However, the key areas of clinical utility of the eluate of the product are diagnostic PET imaging of cancer (primarily GEP-NETs and prostate cancer).

3.1.2. Available therapies and unmet medical need

Currently, two $^{68}Ge/^{68}Ga$ radionuclide generators have been approved via decentralised procedures in a relatively large number of European member states:

- In 2014, marketing authorisation has been granted for the $^{68}Ge/^{68}Ga$-generator GalliaPharm by Eckert & Ziegler Radiopharma GmbH (Berlin, Germany; DK/H/2294/001/DC; authorised in: AT, BE, CZ, DK, FI, FR, DE, ES, IE, IT, LV, NL, NO, PL, SE, SK), which is similar version of the product under discussion but with lower strength (max. 1.85 GBq).
- GalliAd, 0.74-1.85 GBq, radionuclide generator, IRE-Elit, Belgium has been authorised via a decentralised procedure (DK/H/2690/001/DC) in AT, BE, DE, DK, ES, FI, FR, IT, LU, NL, NO, and SE in 2018.

In 2016 DOTA-TOC (edotreotide) was authorised with the brand name SomaKit TOC (Marketing authorisation holder: Advanced Accelerator Applications, France) via the centralised procedure (EMEA/H/C/004140) for radiolabelling with gallium (^{68}Ga) chloride solution and subsequent use for PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-

differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases.

More recently, on 09.12.2022, gozetotide (PSMA-11) under the trade name Locametz (Marketing authorisation holder: Novartis Europharm Limited) was approved in the EU as a kit for radiopharmaceutical preparation via a centralised procedure (EMEA/H/C/005488) in the indication:

"… 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 (see section 4.4)."

It is assumed, that utilisation of the above diagnostic products in the diagnostic imaging of oncological diseases may be limited by the absence of a licenced on-site $^{68}Ge/^{68}Ga$ generator in the European members states, where GalliaPharm or GalliAd have not been marketed. Although, alternatively an access to ^{68}Ga could be gained e.g., through a cyclotron facility, these are not affordable for all diagnostic centres and quick delivery of the radionuclide from a nearby device may be difficult. These countries are assumed to be facing an unmet medical need.

3.1.3. Main clinical studies

Not applicable.

3.2. Favourable effects

GalliaPharm can provide a consistent supply of a high-quality precursor $^{68}GaCl_3$, that can be further used for labelling of the licenced carrier molecules edotreotide and gozetotide to support the diagnostics of GEP-NETs and prostate cancer by means of PET.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties related to the favourable effects of the product.

3.4. Unfavourable effects

Potential unfavourable effects of the product may be radiation exposure of the hospital/clinic staff, increased exposure to ^{68}Ge (because of ^{68}Ge breakthrough), excess radiation exposure of the patients (e.g., direct accidental use of the eluate). These unfavourable effects may emerge through inadequate handling and maintenance of the product, or its eluate and are mostly generic in nature.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties related to the unfavourable effects of the product. All possible risks have been adequately addressed through appropriate warnings and recommendations on handling and maintenance of the product in the product information.

3.6. Effects Table

Not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

^{68}Ga based radiotracers are broadly used in the PET/CT diagnostics of oncological diseases. Their clinical utility has been shown in this application. Common source of ^{68}Ga in the absence of ^{68}Ge/^{68}Ga generator is a cyclotron facility that is not always affordable for diagnostic facilities. Given the short half-life of ^{68}Ga, its delivery from nearby cyclotron facility may be challenging. An on-site ^{68}Ge/^{68}Ga generator, such as GalliaPharm, is expected to cover the logistical hurdles. This is especially important in the countries where no ^{68}Ge/^{68}Ga generators have been licensed.

Thus, GalliaPharm is expected to facilitate an access to improved cancer diagnostics across Europe, which is regarded a clinically relevant effect.

The unfavourable effects of GalliaPharm are limited and generic. Risk minimisation measures are basically covered through routine radiation protection procedures and rules. Additional potential risks to the patients are currently regarded as low, as these can be minimised through quality control procedures and adequate instructions and training of the medical personnel.

3.7.2. Balance of benefits and risks

The key benefit of the ^{68}Ge/^{68}Ga radionuclide generator under evaluation is its ability to provide a consistent supply of ^{68}Ga directly at the site of its subsequent utilisation.

Risks related with GalliaPharm are dependent on its technical functionality, handling, maintenance and quality control procedures (e.g. radiation exposure to hospital staff, ^{68}Ge breakthrough, eluate of inadequate quality). These risks are mostly generic and can be minimised through adequate quality control, training of the medical personnel and supply of detailed information. These are addressed adequately in the PI.

Relevant for the sterility of the radionuclide generator and its sterile eluate [^{68}Ga]Gallium chloride solution for radiolabelling is, beside the sterile manufacturing process of the generator column itself, also the continuous use of sterile 0.1 mol / L hydrochloric acid to elute the desired [^{68}Ga]Gallium chloride solution for radiolabelling. Beside the necessity to use a sterile 0.1 mol / L hydrochloric acid the hydrochloric acid should be ultra-pure with a very low amount of metal ions, because metal ions can come into concurrence to the [^{68}Ga]gallium ions disturbing the metal complex reaction of [^{68}Ga]gallium ion during the radiolabelling procedure.

More relevant theoretical safety risk, not related to the quality of the product is the risk that $^{68}GaCl_3$ may be applied directly by mistake. To reflect the consequences of such inadvertent exposure,

dosimetry table has been included in the product information and recommendations on patient management are being given. These are considered adequate.

As ^{68}Ga decays to Zn in the body additional exposure to Zn is the consequence of administration of ^{68}Ga-labelled tracer molecules. Amount of additional Zn due to a single application of ^{68}Ga is, however, considered negligible.

In principle, as various types of radionuclide generator have been in use for decades, including the one that is similar to the product under evaluation, and as the generator under evaluation will only be used by well-trained staff in specialised facilities, probability of the occurrence of generic risks is considered as very low.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of GalliaPharm is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of GalliaPharm is favourable in the following indication(s):

This radionuclide generator is not intended for direct use in patients.

The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalliaPharm is indicated for *in vitro* radiolabelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such eluate, to be used for positron emission tomography (PET) imaging.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.