13 November 2025
EMA/CHMP/200195/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

GalenVita

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

Procedure No. EMEA/H/C/006639/0000

Note

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

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List of abbreviations

^{68}Ga	68 gallium
^{68}Ge	68 germanium
ASMF	Active substance drug master file
BRFS	Biochemical recurrence-free survival
CEA	Carcinoembryonic antigen
CT	Computed tomography
CXCR4	C-X-C chemokine receptor type 4
GEP-NET	Gastroenteropancreatic neuroendocrine tumour
DOTANOC	DOTA-1-Nal3-octreotide
DOTATATE	DOTA-D-Phe1-Tyr3-Thr8-octreotide
DOTATOC	DOTA-D-Phe1-Tyr3-octreotide
FAPs	Fibroblast activation proteins
FKM	Fluorine rubber
GBq	Gigabecquerel
GMP	Good manufacturing practice
HER2	Human epidermal growth factor receptor 2
ICH	International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals for Human Use.
ICP – MS	Inductively coupled plasma - mass spectrometry
IV	Intravenous
kGy	Kilogray (radiation dose)
MIA	Manufacturing and Inspection Authorisation
MRI	Magnetic resonance imaging
NETs	Neuroendocrine tumours
OMCL	Official Medicines Control Laboratory
PCa	Prostate cancer
PDE	Permitted daily exposure
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
PEEK	Polyethyletherketone

PE	Polyethylene
PET	Positron emission tomography
Ph. Eur.	European Pharmacopoeia
PRRT	Peptide receptor radionuclide therapy
QP	Qualified person
SPECT	Single photon emission computed tomography
SSTR	Somatostatin receptor
TIAC	Time-integrated activity coefficient
USP	U.S. Pharmacopeia
WEU	Well-established use

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Monrol Europe S.R.L. submitted on 22 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for GalenVita, 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 25 July 2024. During the procedure, the applicant's name was changed from Monrol Europe S.R.L. to Curium Romania S.R.L..

The applicant applied for the following indication:

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

The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalenVita 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

1.3. Information on paediatric requirements

Not applicable

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 appointed CHMP co-rapporteur had no such prominent role in scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	22 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	17 March 2025
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	31 March 2025
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	1 April 2025
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 April 2025
The applicant submitted the responses to the CHMP consolidated list of questions on	17 July 2025
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	27 August 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	13 October 2025
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	28 October 2025
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 GalenVita on	13 November 2025

2. Scientific discussion

2.1. Problem statement

GalenVita is a radionuclide generator. The radionuclide precursor produced by this generator, gallium chloride solution ($^{68}GaCl_3$), is exclusively used for *in vitro* radiolabelling of approved kits designed for the preparation of radiopharmaceuticals. Therefore, GalenVita, or its eluate gallium (^{68}Ga) chloride solution, are not intended for direct use in patients, and no specific condition/disease is claimed.

Radiopharmaceuticals labelled with ^{68}Ga are subsequently used for positron emission tomography (PET) imaging of different conditions. The specific disease or condition to be diagnosed depends entirely on the carrier molecules being labelled with the PET radionuclide gallium-68 and cannot be defined within the scope of this application.

$^{68}Ge/^{68}Ga$ generators are a common source of 68Ga in the absence of a cyclotron facility, that is not always affordable for diagnostic sites. Given the short half-life of ^{68}Ga, its delivery from a nearby cyclotron facility may be challenging. An on-site $^{68}Ge/^{68}Ga$ generator, such as GalenVita, allows to obviate the need for a nearby cyclotron facility and development of highly efficient distribution networks. Thus, the product opens the opportunity of gallium-labelling on-site as required and without a need of a cyclotron facility.

The product under evaluation is a radionuclide generator; therefore, the regulatory framework defined in the Directive 2003/63, Annex I on radionuclide precursors applies:

"- 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, the applicant has submitted published literature to support the clinical utility of $^{68}GaCl_3/^{68}Ga$.

2.1.1. Disease or condition

No specific disease/condition is claimed. The claimed indication is:

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

The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalenVita 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.

2.2. About the product

GalenVita is a radionuclide generator containing ^{68}Ge as mother nuclide which decays to the daughter nuclide ^{68}Ga. The germanium (^{68}Ge)/gallium (^{68}Ga) radionuclide generator is a system for the elution of gallium (^{68}Ga) chloride solution for radiolabelling in compliance with Ph. Eur. monograph 2464. This solution is eluted from a TiO2 column adsorbent on which the mother nuclide germanium (^{68}Ge), parent of gallium (^{68}Ga), is fixed. The system is shielded for radiation.

Gallium-68 (Ga-68) is the decay product of germanium-68 (Ge-68) which has a half-life of 270.95 days and decays via electron capture. Ga-68 is a positron emitter with a half-life of 67.71 min. It decays via 1.92 MeV positron emission (89%) and electron capture (11%) to stable Zinc-68.

The strength of the generator is between 0.74 – 3.70 GBq. Four ml of eluate contains a potential maximum of 3700 MBq of ^{68}Ga and 37.0 kBq of ^{68}Ge (0.001% breakthrough in the eluate, consistent with the Ph. Eur. monograph). This corresponds to 2.4 ng of gallium and 0.14 ng of germanium.

Table 1. Active substance composition per unit

Active Substance	Quantity/ Unit	Function
Germanium-68 chloride ($^{68}GeCl_4$) / gallium-68 chloride ($^{68}GaCl_3$)	0.74 – 3.70 GBq at calibration	Mother radionuclide / Daughter radionuclide

Table 2. Activity on the radionuclide 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 4 ml eluate, GBq / ng	Potential maximum amount of ^{68}Ge in 4 ml eluate, kBq / ng	Eluted activity at the end of shelf-life**, GBq
0.74	0.74	0.29	NLT 0.41	0.74 / 0.49	7.4 / 0.03	NLT 0.16
1.11	1.11	0.44	NLT 0.61	1.11 / 0.73	11.1 / 0.04	NLT 0.24
1.48	1.48	0.58	NLT 0.81	1.48 / 0.98	14.8 / 0.06	NLT 0.32
1.85	1.85	0.73	NLT 1.02	1.85 / 1.22	18.5 / 0.07	NLT 0.40
2.22	2.22	0.87	NLT 1.22	2.22 / 1.47	22.2 / 0.08	NLT 0.47
2.59	2.59	1.02	NLT 1.42	2.59 / 1.71	25.9 / 0.10	NLT 0.56
2.96	2.96	1.16	NLT 1.63	2.96 / 1.96	29.6 / 0.11	NLT 0.64
3.33	3.33	1.31	NLT 1.83	3.33 / 2.20	33.3 / 0.13	NLT 0.72
3.70	3.70	0.91	NLT 2.04	3.70 / 2.45	37.0 / 0.14	NLT 0.50

NLT = not less than
* The actual activity inside the radionuclide generator may deviate by ± 10 % from the nominal strength
** In equilibrium

2.3. Type of application and aspects on development

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

In accordance with Article 10a of Directive 2001/83/EC, the application relies on well-established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal

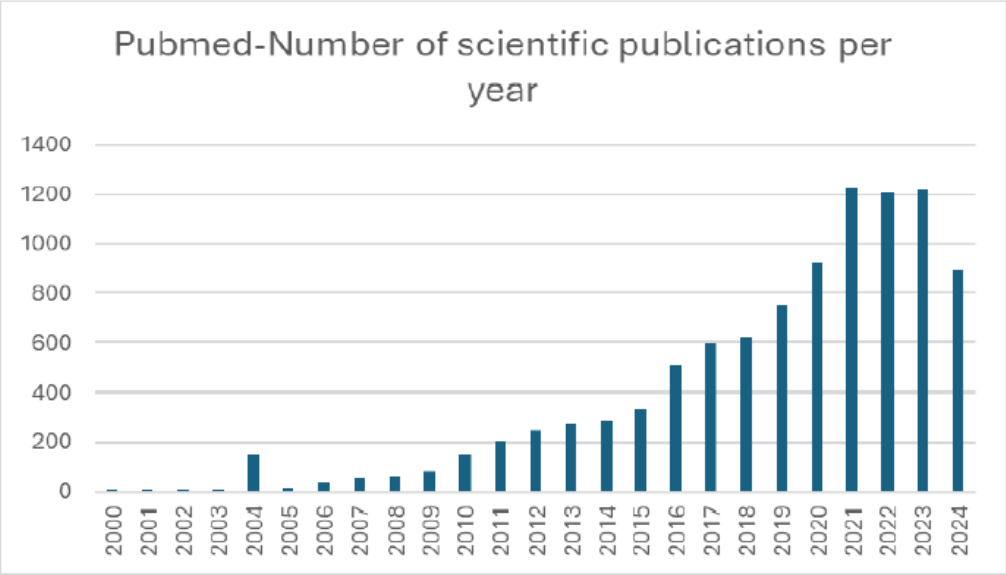
product has been in well-established medicinal use in the European Union for more than 10 years, with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply. Supporting the application as a well-established use, the fulfilment of the requirements of Article 10a was assessed as follows:

Duration of well-established use over more than 10 years in the European Community: The first $^{68}Ge/^{68}Ga$ generator was developed in 1960 (Gleason et al., 1960) followed by a new type of $^{68}Ge/^{68}Ga$ generator with titanium oxide (TiO2) based column matrix and providing ionic $^{68}Ga3+$ in 0.1 M HCl (Razbash et al., 2015). The latter has become the base of modern generators and is since then widely used. GalenVita is also a titanium oxide-based generator with 0.1 HCl elution solvent. Ga-68 labelled somatostatin derivatives have been successfully used for the diagnosis of neuroendocrine tumours as early as 2000 (Hofmann et al., 2001).

Continued scientific interest:

There is continued and growing scientific interest in the use of ^{68}Ga-labelled tracers documented by an increasing total number of publications listed in PubMed during the last 24 years. A PubMed search using the terms "68Ga" OR "68-Gallium" OR "Gallium-68" OR "Ga68" OR "Ga-68" OR "68-Ga"revealed about 8592 publications. Those include clinical trials, meta-analyses, systematic reviews, and reviews.

Figure 1. Number of scientific publications per year



Up to date, approximately 20 on-going trials have been listed in EU and there is a large number of studies registered on www.clinicaltrials.gov (using the terms "gallium-68" OR "68Ga").

Quantitative evaluation of the well-established use (exposure and spread across countries): a lists of published studies using ^{68}Ga-labeled carrier molecules, such as DOTATOC, DOTANOC, DOTATATE, NODAGA-LM3, DOTA-LM3, NODAGA-JR11, DOTA-JR11, and PSMA, was provided. These publications describe more than 15,000 patients exposed to ^{68}Ga-labeled ligands in the European Community (Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Serbia, Switzerland, and UK).

Systematic use of $^{68}GaCl_3$ is supported by multiple recommendations issued in various clinical guidelines. For instance, the European Association for Nuclear Medicine (EANM) nuclear medicine guide from 2020 describes and recommends the use of 68Ga in the Chapter 10.3.1 "68Ga-labelled PSMA" (https://nucmed-

guide.app/chapter/89) and Chapter 10.6 "68Gallium- Somatostatin Analogues" (https://nucmed-guide.app/chapter/92). Additionally, kits for radiopharmaceutical preparation for use after labelling with ^{68}Ga have been approved via centralised procedure. These products are utilised in diagnosis of various cancers. A PubMed search using the terms "68Ga" OR "68-Gallium" OR "Gallium-68" OR "Ga68" OR "Ga-68" OR "68-Ga", contained 1,700 published case reports of use of ^{68}Ga-labelled molecules (approved and in an experimental setting), starting from 2004.

Coherence of scientific assessments:

As per Annex 1, Part III, point 2.2 of Directive 2001/83/EC as amended in Directive 2003/63/EC, Annex I:

"Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radiolabelling purposes. However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented".

The efficacy and safety characteristics of ^{68}Ge/^{68}Ga generators depend on the carrier molecule that is radiolabelled with the gallium (^{68}Ga) chloride solution obtained from the eluate. Therefore, no clinical studies investigating the efficacy and safety of the proposed medicinal product have been conducted by the applicant.

Therefore, in accordance with the requirements to substantiate the well-established medicinal use of the active substance as medicinal product for at least 10 years in the Community, as set out in Annex 1 Part III of Directive 2001/83/EC, as amended, the applicant presented comprehensive data from published clinical trials and on the clinical utility of ^{68}Ga-labelled tracer molecules, focusing mainly on carriers used in diagnostic imaging targeting different types of neuroendocrine tumours (NETs), meningiomas and prostate cancer (PCa).

To comply with the rules defined in the Directive 2003/63, Annex I on radionuclide precursors the Applicant has submitted more than 80 publications to support this MAA.

Given the above, well-established use (WEU) according to article 10a of Directive 2001/83/EC is supported by bibliographic literature provided by the applicant.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as radionuclide generator containing 0.74 GBq, 1.11 GBq, 1.48 GBq, 1.85 GBq, 2.22 GBq, 2.59 GBq, 2.96 GBq, 3.33 GBq, and 3.70 GBq of germanium (^{68}Ge) chloride / gallium (^{68}Ga) chloride as active substance. The strength of the radionuclide generator is defined by the amount of the parent radionuclide germanium-68 fixed on the generator column declared as the amount of radioactivity per generator at its calibration date.

The radionuclide generator contains germanium (^{68}Ge) as mother nuclide which decays to the daughter nuclide gallium (^{68}Ga). The germanium (^{68}Ge) used for the production of the (^{68}Ge/^{68}Ga) generator is carrier free. The total radioactivity due to germanium (^{68}Ge) and gamma-ray-emitting impurities in the eluate is no more than 0.001%.

The product 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 gallium (^{68}Ga), is fixed. The system is shielded.

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 4 ml) and the elapsed time since the previous elution. If mother and daughter nuclides are in equilibrium, more than 55 % of the present gallium (^{68}Ga) activity can be eluted. 4 ml of the eluate from the radionuclide generator with highest strength (3.70 GBq) contains by theoretical 100 % gallium-68 elution a potential maximum of 3700 MBq of ^{68}Ga and 37.0 kBq of ^{68}Ge (0.001 % breakthrough in the eluate). This corresponds to 2.4 ng of gallium and 0.14 ng of germanium. It should be noted that a theoretical 100 % elution is not possible, the applicant guarantees only for an elution yield of 55 % gallium-68.

Other ingredients are:

Column matrix: titanium dioxide

Solution for elution: 0.1 mol/l hydrochloric acid

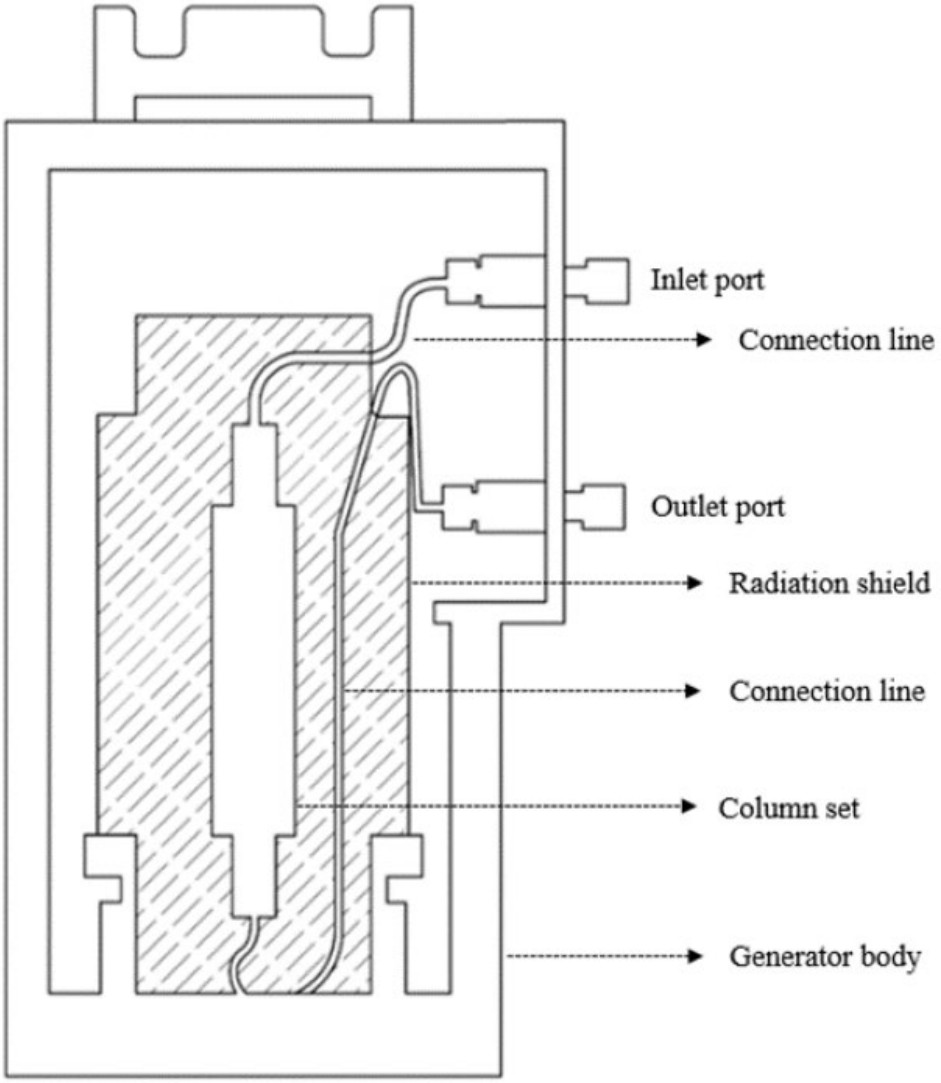
The primary packaging of the generator consists of a PEEK (polyetheretherketone) column and PEEK upper and bottom caps which are attached to PEEK inlet and outlet lines via HPLC-style finger tight fittings as stated in section 6.5. of the SmPC. These lines are connected to two unions that pass through the outer case of the GalenVita generator. The column is contained within the radiation shield assembly.

Accessories supplied with the radionuclide generator:

1. 1 x 220 ml sterile 0.1 mol/l hydrochloric acid in polypropylene bag
2. 1 x B-safe spike
3. 2 x Adapter male LUER
4. 1 x Stopcock manifold
5. 1 x Inlet extension line
6. 1 x Outlet Extension line

The generator column and its tubing are sterile and provide with the eluent sterile 0.1 mol / L hydrochloride acid a sterile gallium-68 chloride solution for radiolabelling.

Figure 2 Sectional view of the radionuclide generator.



2.4.2. Active Substance

General information

ctive substances of radionuclide generators are the parent radionuclide (in this case gemanium-68 fixed in the radionuclide generator on the generator column with the stationary phase titanium dioxide) and the daughter radionuclide (in this case the gallium-68 which can be eluted from the generator in diluted hydrochloric acid). The counter ion chloride is mentioned because electroneutrality is always necessary since the mother radionuclide germanium-68 is put on the generator column solved in hydrochloric acid and the daughter radionuclide gallium-68 is eluted in hydrochloric acid. Because the chemical substance amount of the radioactive metals is very low, these substances are dissolved in aqueous solutions. An isolation of the parent radionuclide by drying of the aqueous solution will lead to gaseous tetrachloro[^{68}Ge] germanium, which makes the handling of germanium-68 in hydrochloric acid challenging.

The best description of the chemical form of the parent radionuclide and the daughter radionuclide would be that these metal ions will be dissolved in hydrochloric acid while the germanium-68 is fixed to the radionuclide generator column the , in this case fixed to the stationary phase titanium oxide.

The chemical name of the active substances is [^{68}Ge] germanium tetrachloride / [^{68}Ga] gallium trichloride corresponding to the molecular formula [^{68}Ge] $GeCl_4$ / [^{68}Ga] $GaCl_3$. They have 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.

Germanium-68 chloride solution is a clear, colourless aqueous solution and very soluble in hydrochloric acid.

For radionuclides their radioactive decay properties are an important characteristic. In the case of a radionuclide generator dedicated to supply the daughter radionuclide in a repeated rhythm, the physical half-life (radioactive decay) of the parent nuclide should be significantly longer that of the daughter radionuclide, so that the parent radionuclide can provide the daughter radionuclide continuously. The parent radionuclide germanium-68 has a physical half-life of 271 days. The daughter radionuclide gallium-68 decays by positron emission with a physical half-life of 67.71 minutes, which makes it suitable to be used as radionuclide in positron emission tomography (PET).

Germanium-68 and gallium-68 are declared as the active substances of the radionuclide generator, however they are not intended to be directly used in a clinical indication. Gallium-68 is indicated for use as a radionuclide precursor for the *in vitro* radiolabelling of a 'cold' non – radioactive chemical precursor to produce a clinically relevant diagnostic active substance that can be used for PET imaging.

Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturing sites. Satisfactory GMP documentation has been provided for both manufacturing sites.

Detailed information on the manufacturing of the active substance by the two manufacturing sites has been provided in the restricted parts of the respective ASMFs and it was considered satisfactory. Both ASMFs were previously assessed and approved as part of marketing authorisation applications for other radionuclide generator(s) in Europe

Germanium 68 by the first manufacturer is produced by purification of gallium-nickel plated metal targets that have undergone proton irradiation and is synthesised in 9 main steps: target planting, target irradiation, target dissolution, normality adjustment, purification by distillation, pH adjustment, normality reduction, product formulation and dispensing.

Germanium 68 by the second manufacturer is synthesised in 7 main steps: target bombardment, target stripping, first Ge-G8 extraction, Ge-68 wash, second Ga-68 extraction, pH adjustment, and dispense

The key element of the finished product radionuclide generator, germanium-68, is the radioactive parent radionuclide which provides, by its radioactive decay, the daughter radionuclide, gallium-68, which will be used in radiopharmacy and nuclear medicine departments. This key element, germanium-68, is generated at huge particle accelerator facilities by shooting accelerated protons on stable gallium-69 or gallium-71 targets using the nuclear reactions.

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 active substance manufactured by the first manufacturer is packaged in borosilicate glass vials sealed with a fluoropolymer coated 4432/50 grey chlorobutyl septum and an aluminium seal which complies with Commission Regulation (EU) 10/2011, as amended.

The active substance manufactured by the second manufacturer is packaged in borosilicate glass vial with a coated flat-face butyl rubber stopper and aluminium seal which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for: appearance (visual), radionuclidic identity (gamma ray spectroscopy), chloride content (in-house), radionuclidic purity (gamma ray spectroscopy), chemical purity (ICP-MS analysis).

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 on 3 commercial batches per manufacturing site of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 commercial scale batches of active substance from the second manufacturer stored in the intended commercial package for up to 6 months under long term (25°C/60% RH) and accelerated conditions (40°C/75% RH) stored at upright and inverted orientation is provided.

The following parameters were tested: appearance, radionuclidic purity, radioactive concentration, specific activity, metallics, radiochemical purity, chloride concentration, nitrate concentration, fluoride concentration, pH, residual solvents (heptane) and adsorption. The analytical methods used were the same as for release and were stability indicating.

All results for testing performed met pre-determined acceptance criteria.

The stability results indicate that the active substance manufactured by the second manufacturer is sufficiently stable. The stability results justify the proposed retest period of 6 months at 25°C/60% RH, stored upright in the proposed container.

Stability data from 5 commercial scale batches of the active substance from the first manufacturer stored in the commercial packaging at room temperature and ambient humidity were tested for stability for up 180 days post product calibration date were provided.

The following parameters were tested: appearance, normality, radiochemical purity, radiochemical identity, activity concentration, radionuclidic purity, chemical purity, specific activity. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the second manufacturer is sufficiently stable. The stability results justify the proposed retest period of 6 months post reference date at 20 - 25°C in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The radionuclide generator is presented as a case with two handles and an inlet and an outlet port.
The radionuclide generator provides after elution a sterile gallium (^{68}Ga) chloride solution for radiolabelling. The solution is clear and colourless.

The qualitative and quantitative composition includes germanium-68 chloride/gallium-68 chloride as active substance and titanium dioxide, sterile 0.1 M Hydrochloric acid as excipients.

Ther finished product is a radionuclide generator containing ^{68}Ge as mother nuclide which decays to the daughter nuclide ^{68}Ga. The germanium (^{68}Ge)/gallium (^{68}Ga) radionuclide generator is a system for the elution of gallium (^{68}Ga) chloride solution for radiolabelling in compliance with Ph. Eur. monograph 2464. This solution is eluted from a TiO_2 column adsorbent on which the mother nuclide germanium (^{68}Ge) chloride, parent of gallium (^{68}Ga) chloride is fixed. The system is shielded for radiation.

The objective was to develop a germanium (^{68}Ge)/gallium (^{68}Ga) radionuclide generator system which includes chromatographic column for selective separation of parent ^{68}Ge and daughter ^{68}Ga, to obtain a sterile solution of gallium (^{68}Ga) chloride for radiolabelling of 'cold' non – radioactive chemical precursors.

The excipients are 0.1 M hydrochloric acid and titanium dioxide. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There is 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 developed to provide gallium (^{68}Ga) chloride solution according to current edition of the Ph. Eur. Gallium (68Ga) Chloride Solution for Radiolabeling, monograph no 2464.

The most challenging issue in the development of a generator system is to develop a reliable separation system to frequently isolate the desired daughter radionuclide (gallium-68) from the long living parent radionuclide (germanium-68) in high radionuclide purity. For a germanium-68 / gallium-68 radionuclide generator it is crucial that the parent radionuclide (germanium-68) is nearly completely fixed on the solid phase material of the chromatographic column while the daughter radionuclide (gallium-68) can be eluted in a good yield.

Different stationary and mobile phases of chromatographic systems were described with reference to literature data. The choice for stationary phase is titanium dioxide as an inert material that can easily be packed as stationary phase in columns. Tetravalent ions like $^{68}Ge^{4+}$ show good absorption to the titanium dioxide stationary phase, while bi- or trivalent ions like $^{68}Ga^{3+}$ do not, thereby fixing the parent radionuclide on the column while the daughter radionuclide can be eluted dissolved in the hydrochloric acid and can be diluted. The reliability of this chromatographic system was demonstrated.

In addition to the chemical identity of the stationary phase titanium dioxide, its particle size (meaning the surface of the titanium dioxide particles), it's crystal modification phases and its chemical surface activation in hydrochloric acid are relevant for the chromatographic suitability of the solid phase titanium dioxide.

For the performance of a chromatographic column, the choice of the stationary and mobile phase and the filling and preparation process of the column with the stationary and mobile phase are important. In the manufacturing process description, it is confirmed that 0.5 mol / L hydrochloric acid is used for the loading process of the germanium-68 solution. Depending on the chloride ion concentration in the loading solution, different chloro – germanium complex ions are possible in the solution. The sterilisation of germanium-68

chloride loading solution is achieved through filtration using a filter made of cellulose acetate membrane. A filter validation study has been conducted for this process, which includes a bacterial challenge test, chemical compatibility test, and leachable test to ensure the effectiveness and safety of the filtration method. It is reasonable that the loaded generator column is not finally sterilised by heat considering the risk of contamination with the full load of the parent radionuclide and its volatility. Therefore, the sterile filtration of the loading solution has been justified.

The core of the generator is its chromatographic column made of PEEK filled with the stationary phase made of titan dioxide on which the parent radionuclide germanium-68 is fixed. The PEEK column is the primary packaging material. The PEEK of the column is specified as food grade which complies with the requirements of the FDA for Poly(aryletherketone) resins. The O-rings, frits and pipes are made of plastic materials as fluorinated rubber, polyether ether ketone (PEEK) and polyethylene (PE). The primary packaging complies with USP and ISO requirements.

The radiation shield and the generators outside body are declared as secondary packaging.

Manufacture of the product and process controls

The manufacturing process consists of 10 main steps: assembly of sterile two-piece radiation shield, shield holder and column, column conditioning and filtration, transferring ^{68}Ge bulk into the hot cell and preparation of loading solution, loading the activity into the column, rinse of the column and waste measurement, removal of the lines, assembly of shield and body, generator elution and quality control analysis. The sterilisation of the cold prepared titanium dioxide column with γ-radiation is a standard process.

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 control), elution yield (measurement with dose calibrator), radioactivity value (measurement with dose calibrator), identification A (gamma-ray spectrometer), identification B (measurement with dose calibrator), identification C (measurement with pH paper), identification D (measurement with dose calibrator), identification E (visual control), iron (ICP-MS), zinc (ICP-MS), radionuclidic purity (gamma-ray spectrometer), sterility (direct inoculation), and bacterial endotoxin (a kinetic chromogenic method).

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

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. To evaluate the presence of iron, aluminium, zinc, copper, lead and titanium impurities, studies have been conducted. The metallic impurities required to be controlled in Ph. Eur. 2464 monograph, Fe and Zn, were added to the release specifications. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) 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 1 commercial scale batch per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 9 commercial scale batches of the finished product stored for up to 13 months under long term conditions (25ºC / 60% RH), for up to 13 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) 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.

Because the highest strength radionuclide generator (3.70 GBq starting activity) is capable to provide even after one year enough gallium (^{68}Ga) chloride solution for radiolabelling to radiolabel kits there is still an ongoing shelf – life study scheduled for 19 months for this radionuclide generator at long term conditions (25°C±2°C, 60%RH±5%RH).

Samples were tested for appearance, elution yield, iron, zinc, radionuclidic purity, sterility, and bacterial endotoxins. The analytical procedures used are stability indicating.

The stability behaviour of the rare and very uncommon pharmaceutical form "radionuclide generator" differs fundamental from the standard pharmaceutical forms.

For a safe use of the eluate gallium (^{68}Ga) solution for radiolabelling its radionuclide purity and its sterility are relevant and should be assured during the complete shelf-life period. For radionuclide purity first it must be assured that the parent radionuclide stays fixed on the column matrix during all elution rhythms over the self-life.

For bracketing in the stability studies the applicant used the smallest strength (0.74 GBq) and the highest strength (3.70 GBq) together with a strength in the middle between both (1.85 GBq). This approach is acceptable considering that the construction of the generator is always the same and the chemical substance amount of the radionuclide germanium-68 which is fixed on the chromatographic column is even in the highest strength low and does not overstrain the binding capacity of the stationary phase titanium dioxide. Stability data available for 12 months available for the 3.70 GBq radionuclide generator justify an extrapolation of the stability to 18 months for the 3.70 GBq radionuclide generator.

In-use period of generator batches is not a part of the stability studies. During stability study, the generators are stored ready to elute with the lines and connections are assembled. Since this condition also represents the use of the generator by the user, there is no need to perform additional in-use stability study.

It is demonstrated that the radionuclide generator delivers the desired eluate gallium (^{68}Ga) solution for radiolabelling in compliance with its specification at the long-term storage temperature C and at accelerated conditions.

The stability studies of the eluent (sterile 0.1 M hydrochloric acid) are defined and conducted according to ICH guidelines. Within Q1D Bracketing and Matrixing based approach, several samples were analysed, and test periods were evaluated according to the risk assessment.

Stability data from 3 commercial scale batches of the eluent stored for up to 13 months under long term conditions (25ºC / 60% RH), for up to 6 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed polypropylene bags.

Samples were tested for appearance, assay, metallic purity, sterility, water loss and bacterial endotoxins. The analytical procedures used are stability indicating.

It has been determined that all the of stability analyses conducted according to validated test methods are within specified specification limits. In consequence of the stability study performed for the eluent is 12 months when stored in its original packaging.

To assess the maximum number of elutions during the product's intended shelf-life, a stability study was conducted using a single generator. The selected generator was eluted twice daily under routine conditions, and the elution yield was monitored throughout the study period. In parallel, full quality control testing was performed monthly on the same generator to evaluate product quality and generator performance over time. This approach enabled the assessment of generator suitability under high-frequency elution conditions, simulating extended clinical use. This approach enabled the assessment of generator suitability under high-frequency elution conditions, simulating extended clinical use. Regarding multiple daily elutions, as stated in the SmPC, a minimum waiting period of 7 hours between two elutions is recommended to ensure optimal generator yield. Accordingly, the maximum number of elutions is in line with this recommendation.

Based on available stability data, the proposed shelf-life of the generator is defined as 12 months from the calibration date for strengths 0.74 GBq, 1.11 GBq, 1.48 GBq, 1.85 GBq, 2.22 GBq, 2.59 GBq, 2.96 GBq, 3.33 GBq and 18 months from the calibration date for strength 3.70 GBq as stated in the SmPC (section 6.3) is acceptable.

Based on the available stability data, the proposed shelf life of the sterile hydrochloric acid solution for elution is defined as 12 months when stored in its original packaging as stated in the SmPC (section 6.3) is acceptable.

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. 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. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The eluate of the Ge-68/Ga-68 generator is Ga-68 chloride ($^{68}GaCl_3$). This medicinal product is not intended for direct use in patients. It is intended for *in vitro* radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide for diagnostic purposes. No natural physiological function is known for the element gallium.

This application procedure was submitted according to Article 10a well-established use application. In line with this type of application, the applicant did not submit own non-clinical studies. The non-clinical data presented was based entirely on published literature.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

No non-clinical pharmacology studies with the eluate of the Ge-68/Ga-68 generator were submitted. ^{68}Ga chloride is not administered to humans directly. Therefore, no studies related to the pharmacodynamic drug interactions with $^{68}GaCl_3$ have been identified to date. Nevertheless, the applicant provided an overview of effects of ^{68}Ga chloride observed in the past, including antitumor activity, cytotoxicity and interference with physiological iron binding systems within the body (Collery et al. 1984; 1989; 2002; 2012). Gallium interferes in the blood with iron. However, gallium cannot be reduced to a divalent state unlike Fe(III). Nonradioactive gallium binds avidly to both metal binding sites on transferrin, but with much less affinity than ferric iron. Under physiological conditions, only about one-third of circulating transferrin is occupied by iron; hence, the metal-binding sites of the remaining transferrin molecules are available to bind and transport gallium as transferrin-gallium complexes. With higher levels of gallium in the circulation, transferrin binding is exceeded, and gallium may likely circulate as gallate, $Ga(OH)_4$.

2.5.2.2. Secondary pharmacodynamic studies

Not applicable.

2.5.2.3. Safety pharmacology programme

No data provided.

2.5.2.4. Pharmacodynamic drug interactions

No studies related to the pharmacodynamic drug interactions with $^{68}GaCl_3$ have been identified to date.

2.5.3. Pharmacokinetics

Although the ^{68}Ga chloride solution is not intended for direct use in patients, its pharmacokinetic properties were investigated in a few animal studies which started as early as 1951 using the non-radioactive form (King et al., 1951).

Absorption

Elemental Ga is insoluble in water and is therefore poorly absorbed in mammals. Gallium chloride undergoes hydrolysis and becomes colloidal in biological tissues. The gastrointestinal absorption of orally administered cationic gallium salts in mammals is less than 1% for physiological doses due to the hydrolysis of the Ga^{+3} salts to insoluble and unabsorbable gallium hydroxide $Ga(OH)_3$ (Gray et al., 2013; National Center for Biotechnology Information, 2024).

In a comparative study, Bernstein et al., using the data from a single oral dose of 800 mg Ga chloride (317 mg Ga) administered to cancer patients, reported that gallium chloride was absorbed very poorly when orally administered, due in part to hydrolysis that produces low-solubility polymerised gallium oxide hydroxides in the gastrointestinal fluids (Bernstein et al., 2000).

Parenterally injected gallium chloride is excreted mainly in the urine; only about 7.8% of a dose of gallium trichloride is excreted in the feces (Bernstein et al., 2000).

In an absorption, distribution and excretion study, Sprague-Dawley rats were intravenously (IV) injected with ^{68}Ga chloride and maximum plasma concentration was observed at 5 minutes after injection and were 3.5% of injected activity/g in males and 5.1% in females. The biological half-life was estimated as 188 hours in male and 254 hours in female rats, which was much longer than the physical half-life of ^{68}Ga (Autio et al., 2015).

This finding was not in accordance with an early study where biological half-life was calculated as 21 hours after IV injection of $^{68}GaCl_3$. This value can be considered as more reliable since the samples were taken at 6, 12, 24, 48 and 96 hours after injection (Brucer et al., 1953). However, taking into account that most of the ^{68}Ga activity would decay to nonradioactive ^{68}Zn within 5 half-lives (about 6 hours), biological half-life can be assumed to be equal to physical half-life (68 hours).

Following inhalation of gallium trichloride aerosols containing 0.125 - 0.25 mg Ga/L, gallium is retained in the alveoli and not absorbed (Ivanoff et al., 2012).

Gallium metal is insoluble in water and, therefore, not readily absorbed through the skin. The generator eluate $^{68}GaCl_3$ is known to cause local venous irritation, in case of accidental administration of the eluate, due to the high acidity, but there are no reports of absorption of gallium through the skin.

Biodistribution

The eluate of the Ge-68/Ga-68 generator, ^{68}Ga chloride, is not intended to be administered to the body without conjugation to a carrier molecule. The metabolism of the final radiolabelled medicinal product will depend on the carrier molecule to be labelled.

Lendvai and coworkers studied the biodistribution of $^{68}GaCl_3$ in rats and reported that it was retained almost in all organs, the maximum being in blood and minimum in the brain. Bone marrow and lung were the second and third after blood. Whole body autoradiography was performed in some animals and the most pronounced uptake was observed in the liver and spleen one hour after the $^{68}GaCl_3$ injection. Radioactivity in the lung was also considerable. Uptake in the kidney, bone marrow, lymph nodes and vessels, and skin was much lower but well above the background (Lendvai et al., 2005).

In their study to check the ability of ^{68}Ga chloride for imaging the experimentally created vaginal infection in mice, Nanni and coworkers also followed some healthy animals by PET imaging. The tracer showed localisation mainly in the vascular compartment and only minimal uptake was noticed in the liver one hour after injection. No activity was present in the urinary tract, bladder or in the bowel. Later images showed that excretion was solely by the kidneys and there was no significant hepatic elimination of the tracer (Nanni et al., 2009).

Ujula and coworkers injected 16 ± 3 MBq of ^{68}Ga chloride as a bolus IV via a tail vein to rats with subcutaneous human pancreatic adenocarcinoma xenografts. Samples of blood, tumour, liver, lung, muscle, and skin were excised, weighed, and measured for total radioactivity. PET images of the animals were taken. It was observed that radioactivity was rapidly localised in the tumour and declined with a plateau 10 minutes after injection and the excess of radioactivity was distributed into heart, liver, and urinary bladder. The authors reminded that at least some of the ^{68}Ga is hydrolysed in vivo in the form of a soluble anion, gallate, $^{68}Ga(OH)_4^-$, and/ or insoluble neutral hydroxide colloids, $^{68}Ga(OH)_3$ and the ^{68}Ga radioactivity can migrate in the blood circulation as free $^{68}Ga^{3+}$ or $^{68}Ga^{3+}$ bound to transferrin, ferritin, or lactoferrin after rapid intravenous administration to the vascular system (Ujula et al., 2010).

Velikyan and coworkers investigated the biodistribution of $^{68}GaCl_3$ by injecting as a bolus IV to healthy male rats. Samples from blood and various organs were collected and weighed at 75 min post injection. Radioactivity uptake was the highest in blood and almost evenly distributed in most of the organs (Velikyan et al., 2012).

The absorption, distribution and excretion of radioactivity after a single intravenous injection of $^{68}GaCl_3$ diluted with phosphate-buffered saline to Sprague-Dawley rats, were assessed by Autio et al. The radioactivity of excised organs was measured at various time intervals after injection. Additionally, female and male rats were imaged by PET for in vivo visualisation of biodistribution. Maximum plasma concentration was observed at 5 minutes after injection but was cleared relatively slowly from blood circulation and excreted into the urine, with some retention in the liver and spleen. Interestingly, it was observed that ^{68}Ga radioactivity in female genital organs, i.e., the uterus and ovaries, was considerable higher compared with male genitals so were the plasma values (Autio et al., 2015).

Steinberg and coworkers injected $^{68}GaCl_3$ to female nude mice bearing HT-1080 xenograft tumour to image the vasculature. A dynamic PET/CT scan showed that the largest amount of radioactivity was in the blood followed by the liver and spleen. Tumour and intestinal uptake were relatively low with negligible uptake in the brain. Clearance was through the renal system (Steinberg et al., 2014).

Excretion

The ^{68}Ga chloride solution is not intended for direct use in patients. The uptake and excretion of the radiolabelled medicinal product will depend on the carrier molecule to be labelled. Many studies reported that unbound ^{68}Ga was excreted mainly through the urine. However, in the clinical use of ^{68}Ga-labelled radiopharmaceuticals, the excretion will depend on the carrier molecule to be radiolabelled.

Biodistribution of Possible Germanium-68 Impurity in the Eluate

The ^{68}Ge content in the ^{68}Ga-containing eluate is limited in the EP monograph to 0.001% of the total radioactivity. However, this limit was not based on experimental data and did not reflect the actual biodistribution pattern. Additionally, a hypothetical assumption of total accumulation of ^{68}Ge(IV) radioactivity in the bone marrow with an infinite retention, was made for the calculation (Decristoforo et al., 2012).

2.5.4. Toxicology

^{68}Ga chloride, as eluted from the generator, is not intended for direct use in patients. It is intended for *in vitro* radiolabelling of various carrier molecules prior to administration. The amount of the eluate required for radiolabelling and the radioactivity of ^{68}Ga-labelled medicinal product that will be administered to humans will depend on the radiopharmaceutical and its intended use. The amount of gallium in the final radiopharmaceutical that will be administered will be extremely low (a few ng), and therefore no toxicity due to this amount is expected. The toxicological properties of the ^{68}Ga-labelled medicinal products will be determined by the nature of the carrier molecule. Additionally, as a diagnostic agent, a $^{68}GaCl_3$ labelled product will be administered to patients only once or a few times in his/her lifetime.

The eluate of a commonly used 1.85 GBq generator will contain a potential maximum of 1.2 ng of gallium. Accidental injection of the entire eluate would therefore result in a maximum single intravenous dose of 20 pg ^{68}Ga/kg in a 60 kg person. Due to the short half-life of ^{68}Ga, with almost complete decay to stable ^{68}Zn within 6 hours, no toxic effects are to be expected from the free ^{68}Ga after an inadvertent administration of the eluate.

The resulting 1.2 ng zinc is far below what is allowed to be administered on a daily basis as a metal residue in medicinal drug products. According to the ICH Guideline, zinc is classified as a class-3 metal which suggests minimal safety concern (ICH guideline Q3D (R2) on elemental impurities-Step 5. EMA/CHMP/ICH/ 353369/ 2013 Committee for Medicinal Products for Human Use. 02 May 2022). The permitted daily exposure (PDE) for zinc is given as 1300 µg/day.

2.5.4.1. Single dose toxicity

Table 3. Summary of single dose toxicity studies with Ga chloride

Study	Species	LD_{50} [mg/kg]	LD_{10} [mg/kg]
Brucer et al., 1953	Rats	220	
	Dogs	18.2	
Dudley and Levine 1949	Rats	46	
	Rabbits	43	

Collery at al., 2002	Mice (tumour bearing)		150

Published studies in humans performed by Shealy and coworkers in 1964 (8.5 -89.2 mg/kg bw.) and Collery and coworkers in 1989 (800 mg) showed no significant single dose toxicity in humans (Shealy et al., 1964; Collery et al., 1989). At dosages of 8.5 mg/kg to 89.2 mg/kg gallium chloride skin rash, nausea and anorexia have been observed. In another study reported by Collery and coworkers in 2002 oral doses of 100 and 1400 mg/day have been applied without signs of major toxicity (Collery et al., 2002).

2.5.4.2. Repeat dose toxicity

Table 4. Summary of repeated dose toxicity studies

Study	**Species**	**Substance / dose [mg/kg]) / route**	**Duration**	**Main findings**
Collery et al., 2002	Mice	Ga chloride 200-400 Oral	20-40 Days	None
	Rats			
	Dogs	Ga chloride 10 Oral	2 to 13 Months	None
	Dogs	(likely) Ga chloride 20, 40, 60 (likely) oral	6 Months	Findings in lungs

Table 3: Summary of repeated dose toxicity studies with other Ga salts

Study	**Species**	**Substance / Dose [mg/kg] mode of administration**	**Duration**	**Main findings**
Hart et al., 1971	Mice	Ga nitrate Various doses intraperitoneal	10 Days (+ 30 days follow up)	LD_{50} 80 mg/kg/day
	Rats			LD_{50} 67.5 mg/kg/day
Newman et al., 1979	Rats	Ga nitrate 100	6 Days	Renal findings, which seemed to be related to the

		intraperitoneal		precipitation of Ga in a complex with calcium and phosphate, which occluded the tubular lumen

2.5.4.3. Genotoxicity

No mutagenicity studies are available.

2.5.4.4. Carcinogenicity

No studies were conducted.

2.5.4.5. Reproductive and developmental toxicity

Ferm and Carpenter carried out a reproductive toxicity study in hamsters with indium nitrate, germanium trioxide, and gallium sulphate. They injected IV increasing amounts of each agent into pregnant hamsters on Day 8 of gestation. The embryos were examined for gross congenital malformation. Only a few malformations were noted with anhydrous $Ga^2(SO_4)^3$ indicating that it did not induce any serious teratogenic threat in the form and dose used in this experiment which was as high as 40 mg/kg (Ferm et al., 1970).

Gómez and coworkers intraperitoneally injected gallium nitrate to pregnant Swiss Mice at 12.5, 25, 50, and 100 mg/kg/day doses on Days 6, 8, 10, 12, and 14 of gestation. Embryo/fetal toxicity was evaluated. No significant increase in the incidence of malformations was observed at 12.5, 25, or 50 mg/kg. It was concluded that gallium nitrate administration during the period of organogenesis resulted in fetal growth retardation in mice. The no-observable-adverse-effect level (NOAEL) for both maternal and developmental toxicity of gallium nitrate was <12.5 mg/kg (Gómez et al., 1992).

2.5.4.6. Toxicokinetic data

Not applicable.

2.5.4.7. Local tolerance

Not applicable.

2.5.4.8. Other toxicity studies

Not applicable

2.5.5. Ecotoxicity/environmental risk assessment

GalenVita will be used for *in vitro* labelling of various kits for radiopharmaceutical preparations which are used and administered only by authorised personnel 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_Rev. 1- corr.2).

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

2.5.6. Discussion on non-clinical aspects

This application procedure was submitted according to Article 10a well-established use application. In line with this type of application procedure, the applicant did not submit own non-clinical studies. The non-clinical overview (eCTD module 2.4) was based entirely on published literature (104 references, published up to 2022), which is considered appropriate. The ^{68}Ga solution eluted from the Ge-68/Ga-68 generator under review complies with the Pharm. Eur. Monograph 2464/gallium (^{68}Ga) chloride solution for radiolabelling and the respective European core SmPC (Autio et al., 2015).

Pharmacodynamics

The labelling of specific molecules by ^{68}Ga chloride is an established diagnostic concept for decades, which is recognised by the European core summary of product characteristics and package leaflet for (68Ge/68Ga) generator and the Pharm. Eur. Monograph. Non-clinical studies investigating pharmacodynamic effects of ^{68}Ga chloride have neither been submitted nor are considered necessary. An overview of available literature is thus acceptable. Since ^{68}Ga chloride is not intended for direct interactions with the body, primary and secondary pharmacodynamic studies would be of low relevance. The applicant does not comment on safety pharmacology aspects following the recommendation of the respective guideline (S7A/CPMP/ICH/539/00). However, considering that the use of similar generators generating ^{68}Ga chloride is already established for decades and the low ^{68}Ga chloride dose given to the patient, relevant effects are not anticipated, and further actions are not required.

Pharmacokinetics

No studies investigating the pharmacokinetics of ^{68}Ga chloride have been submitted and none are required. Instead, published evidence were submitted. Although ^{68}Ga chloride solution is not intended for direct use in patients, its pharmacokinetic properties had been investigated in some animal studies in the past. However, the main determinant of pharmacokinetics in clinical use is the molecule to be labelled. The finally labelled (conjugated) product is not subject of the marketing authorisation application procedure under review.

The assessment of the contribution by unbound ^{68}Ga to the radiation dose following the administration of ^{68}Ga-labelled radiopharmaceutical or of the radiation dose resulting from an inadvertent intravenous injection of gallium (^{68}Ga) chloride solution is based on biodistribution studies in rats. The studies showed the highest radioactivity in the blood, with a slow clearance from blood by urinary excretion. Studies investigating distribution into organs showed inconsistent results. In the study of Velikyan et al. evenly distribution was found, whereas in other studies retention in liver, spleen and female genital organs could be shown.

Toxicology

No studies investigating the toxicity of ^{68}Ga chloride have been submitted. Instead published evidence was submitted. ^{68}Ga chloride, as eluted from the generator, is not intended for direct use in patients. It is used for *in vitro* radiolabelling of various carrier molecules prior to administration. The amount of the eluate required for radiolabelling and the radioactivity of ^{68}Ga-labelled medicinal product that will be administered to humans

will depend on the radiopharmaceutical and its intended use. The amount of gallium in the final radiopharmaceutical to be administered will be extremely low (a few ng) that no toxicity due to this amount is expected. The toxicological properties of the ^{68}Ga-labelled medicinal products will be determined by the nature of the carrier molecule.

No toxicological effect due to stable ^{68}Zn in the ^{68}Ga-conjugated radiopharmaceuticals is expected.

Concerning reproductive toxicity, it is agreed to that radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Therefore, only essential investigations should be carried out during pregnancy, when the benefit clearly outweighs the risk incurred by the mother and fetus. When administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether she is pregnant or not.

Administering a radiopharmaceutical to a breast-feeding mother needs special consideration. If the investigation could be delayed until the mother has ceased breast-feeding, waiting until then should be reasonable. Otherwise, breast-feeding should be interrupted and the expressed feeds discarded for a defined period depending on the radiopharmaceutical used. Further information concerning the use of a ^{68}Ga-labelled medicinal product in pregnancy and breastfeeding should be specified in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

ERA

^{68}Gallium chloride is an inorganic salt which is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

GalenVita is composed of the long half-life parent radionuclide germanium-68 (271 days) and the daughter radionuclide gallium-68 (68 minutes) on a matrix with an elution solution of 0.1 N HCl. The eluate is in gallium-68 chloride ($^{68}GaCl_3$) form. $^{68}GaCl_3$ is a radiopharmaceutical precursor and is not intended to be administered directly to the patient. It is used for *in vitro* radiolabelling of carrier molecules which have been specifically developed for radiolabelling with this radionuclide for diagnostic purposes. The diagnostic concept is established and further studies investigating ^{68}Ga chloride are not considered necessary and none have been submitted.

No toxicological effect due to stable ^{68}Zn in the ^{68}Ga-conjugated radiopharmaceuticals is expected.

The published literature provided by the applicant in support of the GalenVita MAA, based on the Article 10a (well-established use), is considered acceptable.

2.6. Clinical aspects

2.6.1. Introduction

The clinical data package is limited to published efficacy and safety data from the studies evaluating ^{68}Ga-labelled carrier molecules. Dosimetry for the case that $^{68}GaCl_3$ is unintentionally injected to patients has been calculated and included in the SmPC.

GCP aspects

No clinical studies were performed by the applicant.

2.6.2. Clinical pharmacology

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. Therefore, the pharmacokinetic properties of ^{68}Ga-labelled radiopharmaceuticals will depend on the nature of carrier molecules to be radiolabelled.

2.6.2.1. Pharmacokinetics

Distribution and dosimetry

For the event of an accidental administration of the $^{68}GaCl_3$ eluate directly to patients, human dosimetry has been estimated based on animal biodistribution data. A study by Autio et al, 2015 was considered for sourcing the information on dosimetry of $^{68}GaCl_3$ in 21 male and 21 female Sprague-Dawley rats. The study reported biodistribution as % of injected activity per gram of tissue for individual organs. Time points for measurements were 5 minutes, 30 minutes, 60 minutes, 120 minutes and 180 minutes. Data on organ weights are also reported in the study.

This data was used to calculate the organ activity as suggested by Bagheri, 2023:

$$A(t) = \frac{\%IA/g(t)\ x\ organ\ weight(g)}{100} \cdot Ao\ x\ e^{-\lambda t}$$

Where:

%IA/g = percent of injected activity per gram of tissue (at time t)

A_0 = injected activity (47 MBq per animal)

λ = decay constant for ^{68}Ga

t = time (5 minutes = 0.083h)

The decay constant was calculated as $\lambda = \frac{ln\,2}{t_{1/2}}$ = 0.6135

The half-life ($t_{1/2}$) for ^{68}Ga is 68 minutes (1.13 hours).

The time-integrated activity was further calculated as follows according to Schmitt, 2003 and Hindorf, 2014 considering study duration when selecting integration period (10x$t_{1/2}$ or 11.3h):

$$\tilde{A} = \int_0^{10t1/2} A(t)dt$$

The obtained time-integrated activities were extrapolated to humans using the following equation (Schmitt 2003):

$$\tilde{A}h = \tilde{A}a\ x\ (\frac{Oh}{BWh})/(\frac{Oa}{BWa})$$

Where:

Ãh = time-integrated activity in human

Ãa = time-integrated activity in animal

Oh = organ weight in human

Oa = organ weight in animal

BWh = body weight in human

BWa = body weight in animal

The time-integrated activity coefficients (TIACs; ã) were calculated by dividing the Ã with A_0.

Scaling to children

In order to obtain the absorbed doses in children as well, scaling of TIACs was performed using the formula:

$$ãc = ãa\ x\ (\frac{Oc}{BWc})/(\frac{Oa}{BWa})$$

Where:

ãc = time-integrated activity coefficient in child

ãa = time-integrated activity coefficient in adult

Oc = organ weight in child (average of M and F)

Oa = organ weight in adult

BWc = body weight in child (average of M and F)

BWa = body weight in adult

Body and organ weights were taken from the ICRP 89 publication (Table 2.8) and sex averaged TIAC's are calculated as shown in the table below:

Table 5. Sex-averaged TIACs

TIAC	Newborn	1 Y	5 Y	10 Y	15 Y
Liver	0.98095896	0.8715443	0.792313	0.68502062	0.62997364
Heart (wall)	0.07258524	0.06351209	0.0568266	0.05557308	0.05244117
Lung (w blood)	0.29428967	0.25750347	0.27105628	0.26823278	0.25986588
Salivary glands (all)	0.01512302	0.02117223	0.01578631	0.01212992	0.01076417
Pancreas	0.01066777	0.01244573	0.01146317	0.01166787	0.01198901
Spleen	0.04589599	0.04903625	0.0444975	0.04227263	0.04033351
Urinary bladder	0.00856942	0.00674842	0.0035518	0.005858	0.00515934
Adrenals (2)	0.027436	0.00640173	0.00421167	0.00350095	0.00278975

Kidneys (2)	0.17788547	0.17432776	0.14418085	0.14008481	0.11195361
Brain	0.21391153	0.18717259	0.12910243	0.08065661	0.04916557

Table 6. Sex-averaged organ doses (mSv/MBq) for the adults and individual paediatric phantoms*

	Adult (sex-averaged mean; 66.5 kg)	**Newborn (sex-averaged mean; 3.5 kg)**	**1 year (sex-averaged mean; 10 kg)**	**5 years (sex-averaged mean; 19 kg)**	**10 years (sex-averaged mean; 32 kg)**	**15 years (sex-averaged mean; 54.5 kg)**
Target Organ						
Adipose tissue	0.00287	0.03231	0.0224	0.01245	0.00775	0.00574
Adrenals	0.1017	0.1915	0.298	0.212	0.154	0.104
Bone - endosteal cells	0.00255	0.015385	0.0138	0.00788	0.00448	0.00223
Bone marrow - red (active)	0.00666	0.01736	0.014	0.008045	0.00606	0.00382
Brain	0.001775	0.00546	0.00367	0.002625	0.0023	0.00176
Breast tissue	0.0066	0.023425	0.0192	0.0134	0.0074	0.00617
Bronchial basal cells	0.1795	0.558	0.566	0.279	0.161	0.0996
Bronchial secretory cells	0.178	0.558	0.566	0.279	0.161	0.0996
Bronchiolar secretory cells	0.128	0.951	0.749	0.3395	0.213	0.118
Colon - ICRP133	0.00406	0.02103	0.0145	0.00767	0.00481	0.00315
Colon - left	0.003085	0.015445	0.01475	0.00717	0.005	0.00331
Colon - rectosigmoid	0.000445	0.0094435	0.00519	0.00264	0.00145	0.000801
Colon - right	0.007055	0.032735	0.0198	0.0111	0.00652	0.00436
Oesophagus	0.0176	0.11515	0.0529	0.0331	0.0252	0.0123
ET1 airway basal cells **	0.000678	0.004958	0.00292	0.001555	0.00103	0.00066
ET2 airway basal cells **	0.00186	0.00597	0.003765	0.00227	0.00158	0.001

Extrathoracic region - ICRP133	0.00181	0.00591	0.003735	0.00224	0.00156	0.00099
Eye lens	0.000549	0.0034865	0.001995	0.001185	0.000849	0.000525
Gallbladder wall	0.0678	0.1046	0.11	0.0589	0.046	0.0312
Heart wall	0.07835	0.56285	0.406	0.224	0.144	0.0855
Kidneys	0.1345	0.9025	0.603	0.343	0.213	0.146
Liver	0.159	0.943	0.762	0.423	0.291	0.187
Lung - ICRP133	0.1195	0.9365	0.746	0.3375	0.212	0.118
Lungs (AI) ***	0.1195	0.9365	0.7465	0.3375	0.213	0.118
Lymph nodes - extrathoracic	0.00285	0.01346	0.00707	0.00816	0.00546	0.00297
Lymph nodes - systemic	0.00977	0.020955	0.0159	0.00769	0.00458	0.00407
Lymph nodes - thoracic	0.03845	0.07775	0.0881	0.0439	0.0218	0.014
Lymphatic nodes - ICRP133	0.01159	0.02367	0.0212	0.0108	0.00611	0.00481
Muscle	0.002255	0.017715	0.0104	0.005835	0.00377	0.00208
Oral mucosa	0.001435	0.010455	0.00499	0.002915	0.0019	0.00261
Ovaries	0.0002015	0.0004445	0.0031	0.001405	0.00128	0
Pancreas	0.04975	0.3539	0.237	0.137	0.0843	0.0463
Pituitary gland	0.0011265	0.005065	0.00318	0.00206	0.00155	0.00111
Prostate	0.000107	0.00393	0.001605	0.00061	0	0.000336
Salivary glands	0.04985	0.2879	0.154	0.107	0.0838	0.0548
Skin	0.00143	0.008715	0.006615	0.003555	0.00217	0.00138
Small intestine	0.005345	0.02588	0.0183	0.009135	0.00631	0.0048
Spleen	0.01675	0.0862	0.0656	0.0355	0.0222	0.0131
Stomach	0.0172	0.0567	0.06025	0.0222	0.0172	0.0102
Testes	0.00002715	0.0025	0.001105	0.0004425	0	0.000321
Thymus	0.01097	0.09225	0.0609	0.023	0.0223	0.0113
Thyroid	0.00475	0.019675	0.03605	0.01	0.00582	0.00437
Tongue	0.001655	0.01293	0.00845	0.00445	0.00322	0.00227

Tonsils	0.0012425	0.010885	0.006625	0.005035	0.0037	0.00234
Ureters	0.005975	0.051525	0.0399	0.0218	0.00821	0.00551
Urinary bladder wall	0.0003935	0.0063605	0.0048	0.00204	0.000927	0.000667
Uterus	0.0002055	0.000391	0.002715	0.00138	0.00117	0
Whole body target	0.0123	0.1041	0.0731	0.039	0.0239	0.014
Effective whole-body dose (mSv/MBq)	0.0335	0.3295	0.149	0.07435	0.04815	0.0312
ICRP 103 effective dose (mSv/MBq)	0.035	0.329	0.149	0.0743	0.0482	0.0312

*The calculation was performed using the software MIRDCalc

** ET1 extrathoracic region 1 (anterior nasal passage); ET2 extrathoracic region 2 (posterior nasal passage, oral cavity, pharynx and larynx)

*** AI alveolar region

The sex-averaged effective dose for adults is 0.035 mSv/MBq. Following accidental administration of 250 MBq of $^{68}GaCl_3$, the effective dose is 8.75 mSv in adults.

Effective doses from an accidental injection of a typical radiopharmaceutical activity of 3.76 MBq/kg BW in paediatric patients are as follows: 4.336 mSv in newborn, 5.602 mSv in 1 year, 5.312 mSv in 5 years, 5.793 mSv in 10 years, 6.394 mSv in 15 years.

2.6.2.2. Pharmacodynamics

The pharmacodynamic properties of ^{68}Ga-labelled radiopharmaceutical prepared by radiolabelling with the radionuclide generator eluate prior to administration will be dependent on the nature of the medicinal product (carrier molecule) to be labelled.

Mechanism of action

^{68}Ga is a positron emitter. The molecules marked with ^{68}Ga can be utilised in diagnostic imaging with PET.

2.6.3. Discussion on clinical pharmacology

GalenVita produces $^{68}GaCl_3$ that is intended for *in vitro* radiolabelling of kits for radiopharmaceutical preparation and will not be administered directly to a patient. Therefore, no clinical data are available for $^{68}GaCl_3$. This is acceptable.

Pharmacokinetic properties of ^{68}Ga-labelled molecules will depend on the characteristics of these molecules and is to be presented in the respective marketing authorisation procedures.

Conduct of a dedicated dosimetry study does not apply to the product under evaluation. However, for the event of accidental administration of $^{68}GaCl_3$ (the eluate) directly in patients, dosimetry tables have been

included in the proposed SmPC. The dosimetry information is based on a non-clinical study in rats by Autio et al., 2015. Non-clinical data collected in this study were used to calculate dosimetry in humans.

Upon request, the applicant provided the equation and supporting documentation for scaling Time-Integrated Activity Coefficients (TIACs) from adults to paediatric populations using an allometric approach. Reference masses for paediatric individuals were selected in accordance with ICRP Publication 89 (Table 2.8, pp. 18–19). The applicant's methodology relies on organ-to-body weight ratios, as described by Cicone et al., 2022, rather than using absolute organ and body weights, which exhibit substantial variability across age groups. Consequently, paediatric dosimetry was derived based on these organ-to-body weight ratios.

Alternative and widely accepted approaches for dosimetry estimation, such as direct scaling from adult models to paediatric phantoms or direct calculation using validated software like OLINDA or IDAC-Dose (in their appropriate versions), were not considered by the applicant.

The applicant has transitioned from IDAC-Dose version 2.1 to MIRDCalc software, because of the lack of paediatric data in IDAC-Dose 2.1. The applicant has committed to update dosimetry calculation with IDAC Dose 2.2 when software is available by the end of year 2025 **(REC)**. This is agreed.

As ^{68}Ga is a positron emitter, the molecules marked with ^{68}Ga can be utilised in diagnostic imaging with PET. Since the product under evaluation is a generator, its mode of functioning is the matter of the quality assessment and is being addressed in the quality assessment report respectively. No further information on PD has been provided, which is accepted.

2.6.4. Conclusions on clinical pharmacology

No clinical studies have been conducted, neither are these required. Information on the applied methodology to calculate dosimetry in humans and the respective non-clinical study in rats have been presented, as well as the estimated maximum radiation exposure in the case of erroneous injection of full amount of the produced eluate.

2.6.5. Clinical utility

In total, >50 publications were submitted describing use of ^{68}Ga-marked carrier molecules – DOTA-TOC (edotreotide), DOTA-NOC, DOTA-TATE and PSMA - in the indications of neuroendocrine tumours (NETs), meningiomas and prostate cancer (PCa).

Selected publications are being presented below:

<u>Ga-68 labelled Somatostatin Derivatives – Neuroendocrine and other types of tumours</u>

Neuroendocrine tumours are rare and have a heterogeneous nature, with possibility of multiple and variable anatomic sites of the primary tumour. Most differentiated NETs overexpress somatostatin receptors (SSTRs). There are five subtypes of SSTRs (SSTR1 to SSTR5) present naturally in the body. SSTR-2 receptor-mediated action inhibits hormone release and also causes anti-proliferation, whereas stimulation of SSTR-2 and 3 causes apoptosis, which forms the basis of the use of (non-radioactive) octreotide in the treatment of NETs. The development of novel somatostatin analogues for labelling with Ga-68 and also with therapeutic radionuclides like Lu-177, Y-90 and Ac-225 has enabled highly specific targeting of NETs for theranostics. The common Ga-68 radiopharmaceuticals used in the clinical setting, are Ga-68 DOTA-D-Phe1-Tyr3-octreotide

(DOTATOC), Ga-68 DOTA-1-Nal3-octreotide (DOTANOC) and Ga-68 DOTA-D-Phe1-Tyr3-Thr8-octreotide (DOTATATE).

These ^{68}Ga-labeled Positron Emission Tomography (PET) tracers are used in diagnosis of NETs (mostly gastroenteropancreatic neuroendocrine tumours (GEP-NETs), but also in nonfunctioning pituitary NETs, paragangliomas, head and neck paragangliomas, pheochromocytomas, medullary thyroid carcinomas, Merkel cell carcinomas, pulmonary carcinomas and meningiomas) with improved sensitivity and specificity compared to other imaging modalities, as well as the ability to detect small and functional tumours. In the recent years, it is recommended as the first choice, for PET/CT imaging of most NETs, by international guidelines (Quak et al., 2023, Singh et al., 2018, Taieb et al., 2019, Ambrosini et al., 2021).

In a meta-analysis by Graham et al., 2017, ^{68}Ga-DOTATOC was found to be useful for evaluating the presence and extent of disease, for staging and restaging and for assisting in treatment decision making for patients with NET. This meta-analysis showed a pooled sensitivity for detection of NETS of 92% and specificity of 82%. The sensitivity of ^{68}Ga-DOTATOC PET was definitely better than 111In-octreotide single photon emission computed tomography (SPECT) imaging.

In a recent study by Bonazzi et al., 2024, data on the real-life use of and indications for ^{68}Ga-DOTANOC PET/CT were collected from 2000 NET patients imaged in a single centre. The main point raised by the investigators was that: although generally described as rare tumours, prevalence of NENs was increasing due to improvements in imaging techniques, a deeper clinical awareness, and the introduction of novel and efficient treatment strategies. The most common indications for ^{68}Ga-DOTANOC PET/CT scanning were staging, therapy assessment, follow-up, and suspected NET. The results of this study, with high number of patients, revealed that most scans were performed in GEP and lung NETs but also in less common tumour sites. A high positivity rate was determined across all indications. The detection rate was higher in scans performed for staging, Peptide Receptor Radionuclide Therapy (PRRT) selection, and treatment response assessment.

A comparison study between Ga-68 DOTANOC PET/CT and conventional imaging (computed tomography (CT) and endoscopic ultrasound) in patients with pathologically confirmed NETs, by Ambrosini et al., 2010 showed superiority of Ga-68 DOTANOC PET/CT over conventional techniques and it either affected stage or caused a therapy modification in more than half the patients, thus confirming the clinical role of Ga-68 DOTANOC PET in the management of NETs.

Ambrosini et al., 2012 (N= 1239 patients) showed good sensitivity (92%) and specificity (98%) of ^{68}Ga-DOTA-NOC PET/CT for the detection of NET.

Haidar et al., 2017 (N = 445 patients) reported sensitivity, specificity, negative-predictive value, and positive-predictive value of ^{68}Ga-DOTA-NOC PET/CT of 87.1, 97.7, 79.6, and 98.7%, respectively.

Yang et al., 2014 carried out a systematic review of published data (10 studies comprising a total of 416 patients) regarding the diagnostic role of Ga-68 DOTATOC and Ga-68 DOTATATE PET in NETs. The statistical analysis of collected data demonstrated high sensitivity and specificity for both agents, with Ga-68 DOTATATE being slightly more sensitive and specific compared to Ga-68 DOTATOC.

Galldiks et al., 2023 performed a recent review and stated that ^{68}Ga-labeled tracers DOTATATE and DOTATOC were the most common clinically applied tracers in patients with meningioma. These tracers provided an improved lesion contrast relative to the background due to a negligible uptake in both osseus structures and the unaffected brain parenchyma, thus improving the clinical management of patients with meningioma.

A study by Nyuyki et al., 2010, for the evaluation of ^{68}Ga-DOTATOC PET in definition of gross tumour volume in meningioma, led to changes in tumour volume compared to CT and Magnetic Resonance Imaging (MRI) in 72% of patients and delivered additional information for stereotactic radiotherapy.

In two comparative studies (Kunz et al., 2017 and Rachinger et al., 2015) with neuropathological validation of imaging findings, Ga-68 DOTATATE PET allowed a more precise delineation of meningioma extent compared to contrast-enhanced MRI. It has been demonstrated that SSTR PET added essential clinical information for the differentiation of meningioma relapse from posttreatment-related changes (e.g., scars related to prior treatment) which usually present equivocal radiologic findings on contrast-enhanced MRI. Ga-68 DOTATATE PET had superior sensitivity compared to conventional MRI (90% vs. 79%).

Ga-68-labelled Prostate-specific membrane antigen (PSMA) ligands – prostate cancer (primary staging and diagnosis of recurrence)

PSMA is a type II integral membrane glycoprotein, that is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands. It is upregulated in human prostatic carcinoma cells, both in density (100-1000 times) and activity (8-10 times) compared to benign prostatic tissue (Ho et al., 2020, Simon et al., 2022, Write et al., 1995).

PSMA is a well-established target for diagnostic and potential therapeutic applications. Its enzyme activity allows for development of specific inhibitors and their internalisation after ligand binding that leads to enhanced tumour uptake and retention. Ga-68 labelled PSMA tracers are such ligands.

^{68}Ga-PSMA-11 is successfully used in primary PCa imaging, diagnosis of recurrent PCa and PCa metastases and diagnostic strategies and patient management and decision making.

A meta-analysis by Hope et al., 2019 assessed the accuracy of ^{68}Ga-PSMA PET/CT for the detection of prostate cancer compared to histopathology at initial staging and recurrence. A sensitivity and specificity of 0.74 and 0.96, respectively were demonstrated at initial staging. A total of 256 patients with biochemical recurrence were enrolled across 15 studies, of which 233 were reported as true positive lesions. The positive predictive value was 0.99, the detection rate was 0.63 with a PSA<2.0 and 0.94 with a PSA>2.0. These results led the authors to conclude that ^{68}Ga-PSMA-11 performed well for the localisation of metastatic prostate cancer at both initial staging and at biochemical recurrence.

In the context of biochemical recurrence of prostate cancer, a prospective, multicentre study with 635 patients and blinded readings, reported an overall detection rate of 75%. This detection rate was closely linked to Prostate-Specific Antigen (PSA) levels, ranging from 37% for PSA <0.5 ng/mL to 97% for PSA ≥5 ng/mL. The study found a positive predictive value of 84% when ^{68}Ga-PSMA-11 PET/CT findings were confirmed by histopathology, which increased to 92% when a composite reference standard, including histopathology and other imaging modalities, was used for verification (Fendler et al., 2019).

In a recent review by Purysko et al., 2024, to assess the sensitivity and specificity of Ga-68 PSMA-11 PET for prostate imaging and clinical use for patient management, 75 studies in >5000 men with prostate cancer were evaluated. A sensitivity ≥80% and a specificity ≥90% was reported for primary staging and for biochemical recurrence. Ga-68 PSMA-11 PET led to a change in clinical management in 19% to 52% of patients with primary prostate cancer and 16% to 75% of patients with biochemical recurrence.

There are various studies reviewing the influence of Ga-68 PSMA PET imaging on patient management and decision-making. These studies revealed that change in planned management was observed reaching levels of >50% in some settings (Ekmekcioglu et al., 2021, Emmett et al., 2020, Roach et al., 2018, Sonni et al., 2020).

Pozdnyakov et al., 2022 conducted a meta-analysis, on patient management and decision-making, with a total of 34 studies in 3680 men. The impact of Ga-68 PSMA-PET on patient management and outcomes, including PSA response, and intermediate and long-term outcome measures were assessed. At least one outcome measure was reported, in 27 studies with 2639 men reported on and had follow-up data. PSMA-PET was positive in 2508/3680 (68.2%). The pooled proportion of change in management after PSMA-PET was 56.4%. A decrease in serum PSA was documented in 72.4% of men, and complete biochemical response at a median follow-up of 8.1 and 11 months, respectively. PSMA PET was positive in more than 2/3 of men with biochemical recurrence and impacts patient management in more than half of the men. Biochemical Recurrence-Free Survival (BRFS) after PET-directed management was 60% at a median of 20 months after salvage therapy, and complete biochemical response could be achieved in up to a quarter of men.

Other ligands in the experimental phase of development

Additionally, several other ^{68}Ga imaging agents with new biological targets demonstrated promising preclinical and clinical outcomes. Fibroblast activation proteins (FAPs) are overexpressed in a variety of tumours. C-X-C chemokine receptor type 4 (CXCR4) is overexpressed in numerous tumour types and plays a critical role in tumour growth and invasiveness, as well as metastasis. Gastrin-releasing peptide receptors are overexpressed in breast and lung cancers in addition to prostate cancers. Other promising areas of application of Ga-68 based radiopharmaceuticals are, but not limited to, neurotensin and exendin-4 in pancreatic cancers, integrin receptor targeting RGD for angiogenesis imaging, human epidermal growth factor receptor 2 (HER2) in breast cancer and carcinoembryonic antigen (CEA) for colorectal cancers (Davey et al., 2022, Gao et al., 2024, Lepareur et al., 2022, Meisenheimer et al., 2021, Pomykala et al., 2023).

Kits for radiopharmaceutical preparation approved for ^{68}Ga-labelling

Dotatoc (edotreotide) labelled 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:

"This medicinal product is for diagnostic use only. 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 Dotatoc for intravenous use (brand name: TOCscan®/Sogacin®, previously: IASOtoc®; Marketing Authorisation Holder: ITM Medical Isotopes GmbH) was authorised in 2016 via a decentralised mutual recognition procedure (procedure number: FR/H/0611/001/MR) in France, Austria and Germany.

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:

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

- Primary staging of patients with high-risk PCa prior to primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,

• Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated (see section 4.4)."

Several other gozetotide-containing products to be labelled with ^{68}Ga have also been approved via decentralised procedures.

2.6.6. Discussion on clinical utility

As GalenVita and its eluate gallium (^{68}Ga) chloride solution are not intended for direct use in patients, no specific condition has been targeted as part of the indication, and no clinical data have been provided, which is acceptable.

The proposed indication, as per submitted SmPC is:

> "This radionuclide generator is not intended for direct use in patients.
> The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalenVita 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."

This wording is generally in line with the EMA "Guideline on Core SmPC and Package Leaflet for ^{68}Ge/^{68}Ga-generator" (EMA/CHMP/337681/2016).

In accordance with Annex I, Part III, Section 2.2 of Directive 2001/83/EC, as amended, for radionuclide precursors used for *in vitro* radiolabelling "[…] information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented". In this sense, the information provided by the Applicant demonstrates the clinical utility of the eluate $^{68}GaCl_3$ obtained from GalenVita when is used to prepare available molecules authorised for radiolabelling with $^{68}GaCl_3$. This is agreed.

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

Diagnostics of

- 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: DOTATOC, DOTATATE, DOTANOC and PSMA-11.

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

Place in diagnostic imaging and positive benefit-risk ratio has been established for ^{68}Ga-DOTA-TOC (edotreotide) and ^{68}Ga-PSMA-11 (gozetotide), and these two carrier molecules have gained marketing authorisation throughout the EU in the recent years.

- DOTATOC (edotreotide) was approved 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:

"This medicinal product is for diagnostic use only. 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"

- Gozetotide (PSMA-11), the substance that binds to the prostate specific membrane antigen (PSMA), was approved in the EU as a kit for radiopharmaceutical preparation under the trade name Locametz (Marketing authorisation holder: Novartis Europharm Limited) also via a centralised procedure (EMEA/H/C/005488) on 09.12.2022 in the indication:

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

- Primary staging of patients with high-risk PCa prior to primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,
- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated (see section 4.4)."

Besides the above centrally approved product containing edotreotide, a ready-to-use preparation of ^{68}Ga-labelled Dotatoc for intravenous use (brand name: TOCscan®/Sogacin®, previously: IASOtoc®; Marketing Authorisation Holder: ITM Medical Isotopes GmbH) was authorised in 2016 via a decentralised mutual recognition procedure (procedure number: FR/H/0611/001/MR) in France, Austria and Germany.

Along with Dota-noc and Dota-tate, additionally, several other ^{68}Ga imaging agents with new biological targets demonstrated promising preclinical and clinical outcomes: Fibroblast activation proteins (FAPs) are overexpressed in a variety of tumours; C-X-C chemokine receptor type 4 (CXCR4) is overexpressed in numerous tumour types and plays a critical role in tumour growth and invasiveness, as well as metastasis; Gastrin-releasing peptide receptors are overexpressed in breast and lung cancers in addition to prostate cancers. Other promising areas of application of Ga68 based radiopharmaceuticals are, but not limited to, neurotensin and exendin-4 in pancreatic cancers, integrin receptor targeting RGD for angiogenesis imaging, human epidermal growth factor receptor 2 (HER2) in breast cancer and carcinoembryonic antigen (CEA) for colorectal cancers (Davey et al., 2022, Gao et al., 2024, Lepareur et al., 2022, Meisenheimer et al., 2021, Pomykala et al., 2023).

2.6.7. Conclusions on the clinical utility

GalenVita is a radionuclide generator. Demonstration of the clinical utility of the generator and its eluate ($^{68}GaCl_3$) is expected. The presented evidence indicates that ^{68}Ga is broadly used for labelling purposes in PET diagnostics. Various products have been approved for labelling with ^{68}Ga, which further supports its clinical utility. The clinical utility of GalenVita and its eluate ($^{68}GaCl_3$) is considered sufficiently substantiated.

2.6.8. Clinical safety

Safety profile of the ^{68}Ga-labelled molecules will completely depend on the characteristics of these molecules.

The eluate of the generator (^{68}Ga- chloride) is not directly administered to patients. No detailed information is available about the eluate's toxicity and side effects in humans. The amount of gallium and germanium in the final radiopharmaceutical are expected to be in a microdose range.

Assuming the use of a standard generator of 1.85 GBq, the eluate will contain a potential maximum of 1.2 ng of gallium. Accidental injection of the entire eluate would result in a maximum single intravenous dose of 20 pg ^{68}Ga/kg in a 60 kg person.

Ga-68 decays almost completely to stable Zn-68 within 6 hours. The 1.2 ng ^{68}Ga in the eluate would decay to 1.2 ng zinc.

Detailed information on toxicity of gallium, germanium and the eluate is presented in the non-clinical section of this report.

68Ge-breakthrough

A major concern in terms of safety, and independent of the type of generator, is the long half-life of the parent ^{68}Ge of 271 days. Incidental spikes of ^{68}Ge higher than 0.01% of the eluate have been reported, when daily elution of the generator has not been possible (de Blois et al., 2011).

According to the Ph. Eur. Monograph for Ga-68 Chloride, the amount of Ge-68 allowed in the eluate is limited to 0.001 % of the total radioactivity, which means 18.5 kBq of ^{68}Ge breakthrough in the total Ga-68 elution activity of 1.85 GBq eluate. This amounts to 0.07 ng of germanium. SmPC includes detailed instructions on use and maintenance of GalenVita, as a preventive measure against ^{68}Ge breakthrough.

Sterility/risk of infections

The eluate $^{68}GaCl_3$ produced by the generator is sterile.

Radiation safety

In case of accidental administration, the effective dose from an accidental injection of a typical radiopharmaceutical activity of 250 MBq is 8.75 mSv in adults when applying the sex-averaged value of 0.035 mSv/MBq.

Effective doses from an accidental injection of a typical radiopharmaceutical activity of 3.76 MBq/kg BW in paediatric patients are as follows: 4.336 mSv in newborn, 5.602 mSv in 1 year, 5.312 mSv in 5 years, 5.793 mSv in 10 years, 6.394 mSv in 15-year-olds.

External radiation exposure

The average surface or contact radiation for the radionuclide generator is less than 0.09 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. 337 µSv/h. It is generally recommended that the radionuclide generator is stored within auxiliary shielding to minimise dose to operating personnel.

2.6.8.1. Patient exposure

Not applicable.

2.6.8.2. Adverse events

Possible adverse reactions following the use of a ^{68}Ga-labelled radiopharmaceutical will be dependent on the specific kit for radiopharmaceutical preparation being used. Such information will be supplied in the Product Information of the kit for radiopharmaceutical preparation to be radiolabelled.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

Since the Ge-68/Ga-68 generator is eluted with dilute hydrochloric acid, accidental administration of the eluate may cause local venous irritation and, in case of paravenous injection, tissue necrosis. The catheter or affected area should be irrigated with isotonic saline solution to remove the local reaction. When ^{68}Ga is bound to the carrier molecule, no such local effect is expected.

2.6.8.3. Serious adverse event/deaths/other significant events

Not applicable.

2.6.8.4. Laboratory findings

Not applicable.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.9. Discontinuation due to adverse events

Not applicable.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety profile of this radionuclide generator is completely dependent on its technical features and functioning. Therefore, as long as the quality requirements and specifications are clearly defined and complied with, risks related to this product are considered very low.

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 to the hospital staff (exposure through surface, inhalation, etc.) or patients (e.g., through an accidental use of the eluate directly in the patients). ^{68}Ge breakthrough represents an important potential risk.

In order to minimise the above risks handling and maintenance procedures for the product have been reflected in the SmPC.

Information on the external radiation exposure and the potential risks to the personal has also been included in section 11 of the SmPC: "The average surface or contact radiation for the radionuclide generator is less than 0.09 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. 337 µSv/h. It is generally recommended that the radionuclide generator is stored within auxiliary shielding to minimise dose to operating personnel".

^{68}Ge breakthrough represents an important potential risk as it can lead to long-term exposure to radiation. Detailed instructions on how to keep the ^{68}Ge breakthrough low (<0.001 %) by eluting the generator regularly and how to test ^{68}Ge breakthrough, are included in section 4.4 and 12 of the SmPC. ^{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.

Based on the currently available dosimetry information, the estimated effective dose in the case of administration of the standard 250 MBq activity is 8.75 mSv. The following effective doses were calculated based on body-weight adjusted injected activities in paediatric patients: 4.336 mSv in newborn, 5.602 mSv in 1-year-olds, 5.312 mSv in 5-year-olds, 5.793 mSv in 10-year-olds, and 6.394 mSv in 15-year-olds.

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.

According to the ICH guideline on elemental impurities, zinc is classified as a class-3 metal, which suggests minimal safety concern. The permitted daily exposure (PDE) for zinc is specified as 1300 µg/day. Therefore, even in case of accidental administration of the whole volume of eluate from the generator, the amount of zinc received by the patient will be well below this limit. Therefore, no toxicologic effect due to Zn-68 is expected.

In summary, majority of the theoretical risks represent generic risks related to the use of radioactive products. General requirement that the product should be handled by a trained staff is included in the SmPC.

In general, the safety elements reflected in the SmPC and PL are in line with the EMA developed Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generators (EMA/CHMP/337681/2016).

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.

2.7. Risk management plan

2.7.1. Safety concerns

Table 7. 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

Not applicable.

2.7.3. Risk minimisation measures

Table 8. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breackthrough)	Routine risk minimisation measures: • Detailed instructions for use given 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 0.5 is acceptable.

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. 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 a $^{68}Ge/^{68}Ga$-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.

3.1.1. Disease or condition

The final agreed indication "This radionuclide generator is not intended for direct use in patients. The sterile eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GalenVita 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." - 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).

As neither the generator nor its eluate are directly used in patients, no specific condition is targeted. However, the key area of clinical utility for the eluate is diagnostic PET imaging of cancer (primarily NETs, mostly GEP-NETs, meningiomas and prostate cancer).

3.1.2. Available products and unmet medical need

Currently, two $^{68}Ge/^{68}Ga$ radionuclide generators, which are similar to the product under evaluation, have been approved in the EEA:

- GalliaPharm 1.11 - 3.70 GBq radionuclide generator (by Eckert & Ziegler Radiopharma GmbH, Germany via a centralised procedure: EMEA/H/C/006053) in August 2024.
- GalliAd, 0.74 - 1.85 GBq, radionuclide generator (by IRE-Elit, Belgium 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.

The following kits for radiopharmaceutical formulation to be labelled with ^{68}Ga have been approved in the EEA:

- In 2016 DOTATOC (edotreotide) 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 localizing primary tumours and their metastases.
- In 2022 Locametz (gozetotide - PSMA-11) (Marketing authorisation holder: Novartis Europharm Limited) 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).”*

Since at least two similar radionuclide generators are available on the market, the estimated unmet medical need is low. It is however considered that GalenVita will represent an adequate alternative to the authorised ^{68}Ge/^{68}Ga radionuclide generators.

3.1.3. Main clinical studies

No studies have been conducted. In line with the Annex 1 Part III of Directive 2001/83/EC, relevant information on the clinical utility of gallium (^{68}Ga) chloride solution as eluted from a ^{68}Ge/^{68}Ga radionuclide generator when attached to appropriate carrier molecules, has been provided.

An appropriate number of published articles and meta-analyses have been presented documenting a well-established use of ^{68}Ge/^{68}Ga radionuclide generator, mainly in diagnostics of neuroendocrine tumours, meningiomas and prostate cancer.

3.2. Favourable effects

GalenVita can provide a consistent supply of a high-quality precursor $^{68}GaCl_3$, without a need of a cyclotron facility, that can be further used for labelling of the licenced carrier molecules, e.g., edotreotide and gozetotide, to support the diagnostics of NETs, meningiomas 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 GalenVita.

Uncertainties and limitations about favourable effects will depend on the specific ^{68}Ga-labelled medicinal product prepared by radiolabelling with the gallium (^{68}Ga) chloride solution obtained from this generator.

3.4. Unfavourable effects

Potential unfavourable effects of the product are exposure to external radiation for health care professionals, excess radiation exposure of the patients (e.g., overdosing, or ^{68}Ge breakthrough), and general radiation-related risks for patients. These unfavourable effects may emerge through inadequate handling, maintenance, and use of the generator, or its eluate and are mostly generic in nature. These unfavourable effects can be addressed by following the rules and recommendations on handling and maintenance of the radionuclide generator and its eluate, and general rules of radiation protection, and are adequately reflected in the Product Information.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties related to the unfavourable effects of GalenVita.

Uncertainties and limitations about unfavourable effects will depend on the specific ^{68}Ga-labelled medicinal product prepared by radiolabelling with the gallium (^{68}Ga) chloride solution obtained from this generator.

3.6. Effects table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The ^{68}Ge/^{68}Ga generators demonstrate highly reproducible and robust performance in terms of elution yield, column matrix integrity, low metal and germanium impurities and no microbial contamination throughout the shelf life. ^{68}Ge/^{68}Ga generators are a common source of ^{68}Ga in the absence of a cyclotron facility, that is not always affordable for diagnostic sites. Given the short half-life of ^{68}Ga, its delivery from a nearby cyclotron facility may be challenging. An on-site ^{68}Ge/^{68}Ga generator, such as GalenVita, allows to obviate the need for a nearby cyclotron facility and development of highly efficient distribution networks. Thus, the product opens the opportunity of gallium-labelling on-site as required and without a need of a cyclotron facility. The product remains functional for 1 year and longer.

^{68}Ga based radiotracers play an increasingly important role in PET/CT diagnostics of oncological diseases. Their clinical utility in diagnosis of neuroendocrine tumours, meningiomas and prostate cancer has been shown in this application.

Overall, these favourable factors are regarded as highly important, as these contribute to optimisation of cancer diagnostics.

The unfavourable effects of the product relevant for medical personnel can be regarded as generic effects which are common for such products and are covered through routine radiation protection procedures and rules. Potential risks to the patients are radiation exposure and excess radiation exposure, e.g., through ^{68}Ge-breakthrough. These risks are currently regarded as low, as these can be minimised through general rules on radiation protection, quality control procedures and adequate instructions and training of the medical personnel.

3.7.2. Balance of benefits and risks

The clinical utility of the radionuclide generator and its eluate ($^{68}GaCl_3$) has been shown in this application. ^{68}Ga-labelled tracer molecules are used in diagnostic PET imaging for different types of tumours, such as neuroendocrine tumours, meningiomas and prostate cancer.

The key benefit of GalenVita is its ability to provide a consistent supply of ^{68}Ga directly at the site of its subsequent utilisation.

Risks related with GalenVita are dependent from 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 adequate instructions. These are sufficiently addressed in the Product

Information. Overall, as various types of radionuclide generator have been in use for decades and as GalenVita will only be used by well-trained staff in specialised facilities, probability of the above 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 GalenVita is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of GalenVita 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 GalenVita 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.