Amsterdam, 12 October 2023
EMA/247635/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

GeGant

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

Procedure No. EMEA/H/C/5165

Note

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

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1. CHMP recommendation

Based on the review of the data and the applicant's response to the Day120 list of questions and of the data on quality, safety, efficacy, the application for GeGant in the following claimed indication:

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

The eluate (gallium (^{68}Ga) chloride solution) from the radionuclide generator GeGant (1000 MBq, 2000 MBq and 4000 MBq) is indicated for in vitro labelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such eluate to be used for positron emission tomography (PET) imaging."

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

1.1. Questions to be posed to additional experts

None

1.2. Inspection issues

1.2.1. GMP inspection(s)

A request for GMP inspection (manufacturing authorisation / GMP – certificate) has been adopted for the finished product manufacturer and to the manufacturer proposed for the sterilisation process of the sterile hydrochloric acid used as mobile phase (elution solution) as part of the finished product radionuclide generator in order to verify the GMP compliance status. The outcome of this/these inspection(s) is required for the Committee to complete its examination of the application and will be needed by Day 181.

1.2.2. GCP inspection(s)

Not applicable as no clinical studies have been submitted.

1.2.3. New active substance status

Not applicable.

1.3. Additional data exclusivity / marketing protection

Not applicable

1.4. Similarity with authorised orphan medicinal products

Not applicable.

1.5. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

This is a centralised application for a (68Ge)germanium/(68Ga)gallium radionuclide generator (invented name GeGant) which is not intended for direct use in patients. The generator provides the radionuclide precursor gallium (68Ga) chloride solution, that is utilized for in vitro labelling of various kits for radiopharmaceutical preparation developed and approved for radiolabelling with such solution to be used for positron emission tomography (PET) imaging.

Thus, no indication in specific condition is claimed by the applicant. The disease or condition, for diagnosing of which the eluate will be applied is dependent on the carrier molecules to be labelled with the PET – radionuclide (68Ga)gallium and cannot be specified for the product under evaluation.

As the product under evaluation is a radionuclide generator, focus of its evaluation lies on the quality and assessment of pharmacokinetics, pharmacodynamics, dosimetry, efficacy and safety in the usual sense is not possible and does not apply. The same applies to the eluate as well, that is also not intended for direct use in patients.

The applicant has submitted an overview including large number of published literature describing various applications of (68Ga)gallium-labelled carrier referring to the rules defined in the Directive 2003/63, Annex I on radionuclide precursors:

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

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

Overall, 275 publications have been presented to substantiate the claim of clinical utility of 68Ga-labelled somatostatin analogues in the diagnostics of neuroendocrine tumours (NETs) and meningiomas, and 68Ga-PSMA tracer of prostate-specific membrane antigen (PSMA) in the detection of prostate cancer. Majority of the tracers is currently under investigation. The somatostatin analogue DOTATOC (edotreotid) is the single 68Ga-carrier molecule that has gained marketing authorisation in Europe. In 2016, the medicinal product SomaKit TOC (Marketing authorisation holder: Advanced Accelerator Applications, France) was licenced via the centralised procedure (EMEA/H/C/004140) in the diagnostics of gastro-enteropancreatic neuroendocrine tumours (GEP-NET) after labelling with 68Ga and a ready-to-use preparation of 68Ga-labelled DOTATOC (brand name: TOCscan®/Sogacin®, previously: IASOtoc®; Marketing Authorisation Holder: ITM Medical Isotopes GmbH) was authorised in 2016 via a decentralized mutual recognition procedure (procedure number: FR/H/0611/001/MR) in France, Austria and Germany in the diagnostics of NETs and meningioma.

It has been noted during the review that the submitted pre-clinical and clinical dossier contains data covered by data exclusivity. Such data were removed from the assessment. A major objection has been raised requesting submission of an updated dossier, which was provided by the applicant.

2.2. About the product

The (^{68}Ge)germanium/(^{68}Ga)gallium- radionuclide generator (proposed name: GeGant 1-4 GBq radionuclide generator, also named as GeGant in this document) provides with gallium (^{68}Ga) a positron emitter in the chemical form gallium (68Ga) chloride solution for radiolabelling which can be used as a radionuclide precursor suitable to radiolabel in an in-vitro radiolabelling reaction dedicated

substances as for e. g. kits for radiopharmaceutical preparation to obtain after a manufacturing step a tool for positron emission tomography (PET).

Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals, ATC code: V09X.

Gallium (^{68}Ga) chloride solution for radiolabelling is not intended to be administered directly to the patient. It is intended for the in-vitro radiolabelling of specific carrier molecules, which have been specifically developed and authorised for radiolabelling with (^{68}Ga)Gallium. These carrier molecules determine the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the labelled molecule and the diagnostic indication it should be used in.

The ^{68}Ge/^{68}Ga-generator contains germanium ($_{68}$Ge) as mother nuclide, which decays to the daughter nuclide gallium (^{68}Ga)Gallium by electron capture with a half-life of 270.95 days. (^{68}Ga3+)Gallium is eluted from the generator with 4 mL of 0.05 N hydrochloric acid (= "elution") and a solution of Gallium (^{68}Ga) in 0.05 N hydrochloric acid is obtained. (^{68}Ga)Gallium decays to stable (^{68}Zn)Zinc with a half-life of 67.71 min.

Physical characteristics of both mother and daughter nuclides are summarised in Table 1.

Table 1 Physical characteristics of germanium (^{68}Ge) and gallium (^{68}Ga)

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

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

The eluted gallium (^{68}Ga) chloride solution complies with the Ph. Eur. monograph 2464 "Gallium (^{68}Ga) chloride solution for radiolabelling".

By the decay of 250 MBq (^{68}Ga)Gallium (the highest dose commonly used in imaging applications), approximately 0.1 ng Zn is created. Together with the metal (Zn or Fe) contamination (< 10 µg/GBq Zn or Fe, or < 2.5 µg/250 MBq calculated for the highest commonly used dose), the amount of additional Zn exposure through the eluate injection is far below the levels of absorbed zinc as a trace element (estimated to be 1.4 mg/day for men and 1.0 mg/day for women by EFSA based on WHO data).

The total radioactivity due to (^{68}Ge)Germanium ("breakthrough") and gamma-ray-emitting impurities is not more than 0.001%, in accordance with the EMA guideline on core SmPC and Package Leaflet for ^{68}Ge/^{68}Ga) generators and Ph. Eur. Monograph no. 2464.

2.3. The development programme/compliance with guidance/scientific advice

No clinical studies have been presented, as these are not applicable. The application for marketing authorisation relies upon well-established medicinal use supported by scientific literature.

To comply with the rules defined in the Directive 2003/63, Annex I on radionuclide precursors the applicant has submitted 275 publications to support the claim of clinical utility for ^{68}GaCl3.

The product has not been granted eligibility for PRIME.

Scientific advice has been sought at the European Medicines Agency (EMA) to discuss several questions. No clinical questions have been addressed. A pre-submission meeting was held on 31.03.2021. No clinical issues have been discussed either.

The SmPC/PL for this product has been written in accordance with the EMA Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals (EMA/CHMP/167834/2011) and Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator (EMA/CHMP/337681/2016). In view to individual product related quality items which cannot be described by the core SmPC because they depend on the individual radionuclide generator as for e. g. the instructions for use especially in part 6 and 12 of the SmPC some points for clarification are identified.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

For the manufacturer responsible for finished product manufacturing and release testing of the radionuclide generator no-current valid GMP – certificate is presented. According to the letter dated 18 May 2021 send by the applicant to EMA the applicant knows this deficiency and is in contact with the GMP authorities to schedule an inspection of this manufacturer. However for the moment it is fact that for this manufacturer no current valid GMP – certification exists. As a current valid GMP-certification of a manufacturer is essential, this item is rated as a Major Objection.

The manufacturer of the sterile 0.05 mol / L hydrochloric acid used as mobile phase of the chromatographic system radionuclide generator to eluate the desired sterile [^{68}Ga]Gallium chloride solution for radiolabelling no current valid GMP – certification exists for the sterilisation process of the hydrochloric acid as part of the finished product manufacturing process. As a current valid GMP-certification of a manufacturer is essential, this item is rated as a Major Objection.

GCP

Not applicable as no clinical studies have been conducted.

GLP

Not applicable as no non-clinical studies have been conducted.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

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

This marketing authorisation application (MAA) has been submitted through the Centralised Procedure for Human Medicinal Products in accordance with Regulation (EC) No.726/2004, Article 3(2)a, optional scope since "the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community". Eligibility to apply for a Marketing Authorisation via the Centralised route was confirmed by the European Medicines Agency in September 2018. It is, however, noted that the active substances of GeGant (^{68}Ge)Germanium / (^{68}Ga)Gallium radionuclide generator, (^{68}Ge) Germanium chloride and (^{68}Ga)Gallium chloride, cannot be qualified as new active substance as similar active substances have been previously authorised in the European Union (e.g., GalliaPharm by Eckert & Ziegler Radiopharma GmbH, Germany; decentralised procedure DK/H/2294/001/DC and GalliAd, 0.74-1.85 GBq, radionuclide generator by IRE-Elit, Belgium; authorised via a decentralised procedure DK/H/2690/001/DC). Thus, in view of the CHMP criteria for Article 3(2)a is not fulfilled.

Proof of well-established use and similarity to other radionuclide generators

The applicant has submitted module 1.5.1 to substantiate the claim of well-established use and additional data on request.

Proof of use of these substances in PET diagnostics for more than 10 years has been provided, primarily evidenced by the fact, that the first recommendations by the European Association of nuclear Medicine (EANM; Virgolini et al.) to use ^{68}Ga-labeled DOTA-conjugates in the diagnostics of neuroendocrine tumors originate (NETs) from as early as 2010.

In total, more than 280 clinical studies and case reports are referenced in the present clinical overview reporting the clinical use of ^{68}Ga-labelled tracer molecules in diagnostic PET imaging. Since 2001, about 160 studies were conducted in the EU comprising about 16,000 patients as summarised in the table below.

Table 2 Clinical investigations on the diagnostic utility of ^{68}Ga-labelled tracer molecules (EU)

^{68}Ga-tracer-complex	**Diagnostic use**	**First described in the EU**	**Number of clinical studies in the EU (case reports)**	**Number of patients in EU studies**
^{68}Ga-DOTATOC	NETs	2003	37 (8)	1,543
	Meningiomas	2001	8 (1)	198
^{68}Ga-DOTANOC	NETs	2005	27 (2)	4,237
^{68}Ga-DOTATATE	NETs	2006	36 (1)	1,895
	Meningiomas	2015	6 (2)	461
^{68}Ga-PSMA	Prostate cancer	2012	51 (2)	8,421

Different EU member states (13) were involved in clinical investigations on the diagnostic utility of the ^{68}Ga-labelled tracer molecules DOTATOC, DOTANOC, DOTATATE and PSMA in patients with NETs, meningiomas or prostate cancer.

Most of the studies were done in Germany, followed by Italy and UK (EU member state at time of study conduct). In total, 13 different EU member states could be identified as summarised in Table below.

Table 3 Number of clinical investigations on the diagnostic utility of 68Ga-labelled tracer molecules per EU country

Country	DE	IT	UK*	AT	FR	SE	BE	DK	NL	PL	PT	IR	LV
No. of studies/case reports published from 2001 to 2021	98	23	18	13	6	5	3	3	3	3	3	1	1

* EU member state at time of study conduct

Thus, most of the studies were done in Germany, followed by Italy, UK (EU member state at time of study conduct), and Austria. Furthermore, the results of various systematic reviews and meta-analyses are presented in the present dossier.

Outside the EU, more than 100 clinical studies comprising about 9,000 patients were conducted as summarised below.

Table 4 Clinical investigations on the diagnostic utility of ^{68}Ga-labelled tracer molecules (non-EU)

^{68}Ga-tracer-complex	Diagnostic use	First described outside the EU	Number of clinical studies outside the EU (case reports)	Number of patients in non-EU studies
^{68}Ga-DOTATOC	NETs	2001	5 (1)	100
^{68}Ga-DOTANOC	NETs	2005	12 (6)	563
^{68}Ga-DOTATATE	NETs	2012	36 (7)	2,222
	Meningiomas	2016	1 (1)	21
^{68}Ga-PSMA	Prostate cancer	2015	38 (1)	6,167

Furthermore, the results of various systematic reviews and meta-analyses are presented in the present dossier.

According to published clinical studies referenced in the present clinical overview, ^{68}Ga-labelled DOTATOC, DOTANOC, DOTATATE and PSMA were applied to about 20,000 patients between 2001 and 2021 worldwide. In these clinical studies, patients suspected of NETs, meningioma or prostate cancer, respectively, were enrolled. As several national and international guidelines exist for the use of ^{68}Ga-labelled tracers in cancer diagnostics in daily clinical practice and several medicinal products containing the radionuclide Gallium-^{68} are already authorised in the Community and worldwide, it can be assumed that a substantial number of patients have been exposed to ^{68}Ga-labelled tracers, also outside published clinical studies.

Increasing and continuous scientific interest in ^{68}GaCl3 is apparent from the figure below, that displays numbers of scientific publications per year over a period of 21 years. The numbers are based on the search "gallium AND 68" in the PubMed database.

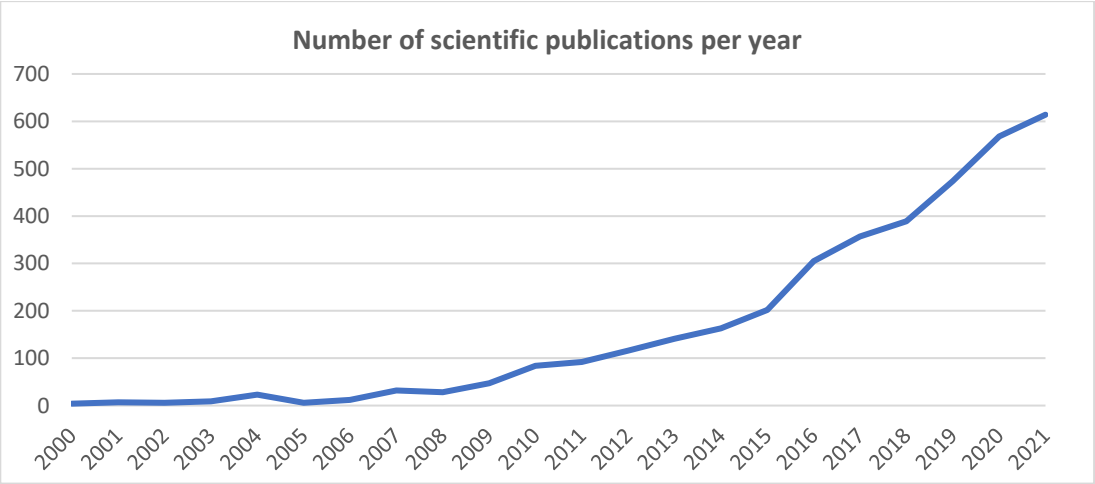

Figure 1 Number of clinical investigations on the diagnostic utility of 68Ga-labelled tracer molecules

Based on the available data well-established use in the context of the Annex I of Directive 2001/83/EC is considered proven.

Radionuclide generators similar to GeGant have been in use over 15 years. Ga-^{68} preparations are obtained in dilute hydrochloric acid solution (i.e., 0.05M HCl) and in small volume of 4 mL. Obtained Ga-^{68} preparations comply with the Ph.Eur. monograph no. 2464 "gallium (^{68}Ga) chloride solution for radiolabelling" and can be directly used for radiolabelling of peptides. This monograph has been issued and is valid for more than 10 years as well. It is assumed that large part of the presented published evidence to substanciate clinical utility has been generated with use of the radionuclide generators similar to GeGant (including the handling and maintaining procedures). Consequently, bridging to the products used in the published studies can be considered established.

PRIME

Not requested.

Accelerated assessment

Not requested.

Conditional marketing authorisation

Not applicable.

Marketing authorisation under exceptional circumstances

Not applicable.

Biosimilarity

Not applicable.

Additional data exclusivity/ marketing protection

Not applicable.

New active substance status

The radionuclide Generator GeGant, (^{68}Ge)Germanium / (^{68}Ga)Gallium radionuclide generator delivering the eluate (^{68}Ga)Gallium chloride for radiolabelling as a radionuclide precursor contains the same active substances which have been authorised before in the European Union (e.g., GalliaPharm by Eckert & Ziegler Radiopharma GmbH, Germany; authorised via DK/H/2294/001/DC and GalliAd, by IRE-Elit, Belgium authorised via DK/H/2690/001/DC). Consequently, these substances are not considered new substances. The applicant agrees with this assessment and intends to withdraw the NAS claim, which had been submitted by mistake.

Orphan designation

Not Applicable.

Similarity with orphan medicinal products

Not applicable.

Derogation(s) from orphan market exclusivity

Not applicable.

Information on paediatric requirements

Not applicable as per Article 9 of the Regulation (EC) 1901/2006 ("Paediatric Regulation").

3. Scientific overview and discussion

3.1. Quality aspects

A radionuclide generator contains two active substances, the mother radionuclide in this case Germanium – ^{68} fixed on the generator column and its daughter radionuclide Gallium - 68 which can be eluted with sterile 0.05 M hydrochloric acid and is intended to be used for radiolabelling.

The desired main property of Germanium-^{68} and Gallium-^{68} is their radioactive character. Germanium-^{68} with its physical half-life of 271 days delivers for a long shelf-life duration the for radiolabelling desired PET-radioisotope Gallium-^{68} with its physical half life of only 68 minutes which decays by positron emission into the non-radioactive stable zinc isotope Zn-^{68}. This characteristic makes the pair Germanium-^{68} / Gallium-^{68} suitable to be used as radionuclide generator.

Chemical form

Germanium-^{68} and Gallium-^{68} are solved in hydrochloric acid. In the radionuclide generator the Germanium-^{68} is fixed on the chromatographic column in the solid phase of the generator system and the by radioactive decay of Germanium-^{68} obtained Gallium-^{68} is solved in diluted hydrochloric acid which eluates as mobile phase in the chromatographic system the Gallium-^{68} from the radionuclidegenerator column.

In the past for the description of the active substances of the Germanium / Gallium radionuclide generator the names [^{68}Ge]Germanium tetrachloride or Tetrachloro[^{68}Ge]german for the mother nuclide and [^{68}Ga]Gallium chloride for the daughter nuclide have been established but it should be aware that the metal cations are solved in aqueous hydrochloric acid and are not isolated as a salt. In

the generator column the mother nuclide Germanium-^{68} will be bounded with the column matrix as solid phase which consist of an excipient.

The applicant informed in the initial submission by the headline "Justification of starting material", citation:

"*The starting material Germanium (^{68}Ge)(IV) hydrochloric acid aqueous solution is a commercially available product. Considering a simple chemical structure of the active substance (a tetrachloride salt dissolved in hydrochloric acid) the proposed starting material is considered acceptable*."

and defines as active substances manufacturing process only a chromatic purification process of Germanium (^{68}Ge) (IV) hydrochloric acid aqueous solution.

The justification of the applicant, citation: "*Considering a simple chemical structure of the active substance (a tetrachloride salt dissolved in hydrochloric acid) the proposed starting material is considered acceptable*." completely ignored the radioactive character of the active substance meaning its nuclear physical and nuclear chemical manufacturing and isolation process which is essential for the quality of the radionuclide germanium-^{68} in the chemical form Germanium (^{68}Ge) (IV) hydrochloric acid aqueous solution.

The guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) demands for the description of the manufacturing of the radionuclide the following information, citation page 5 of the guideline:

"*Manufacture (3.2.S.2) Manufacturer(s) (3.2.S.2.1)*

For radionuclides this should include the source of any irradiation target materials and site(s) at which irradiation occurs.

Description of Manufacturing Process and Process Controls (3.2.S.2.2)

For radioactive components, a full description is required of the production process of the radionuclide (isolation or manufacturing of the radioactive starting material).

Control of Materials (3.2.S.2.3) Requirements for the target material (specifications and control methods) should be described. Manufacturing Process Development

(3.2.S.2.6) For radionuclides this should include nuclear transformation, including unwanted transformations that may occur under the irradiation conditions used due to isotopic impurities present in the target material; irradiation conditions, including effect of variations on nuclear reactions; description and validation of separation processes; influence of geometry of the target chamber and its material."

In the response the applicant added for the first time in this application a complete ASMF from the ASMF holder which describe the necessary information in view to the nuclear physical and radiochemical manufacturing of the active substance germanium-^{68} as the parent radionuclide.

Because the ASMF was submitted last year as an EU – ASMF which was assessed and accepted last year the with the response submitted ASMF was not assessed again in this procedure but reference to the previous EU – ASMF – AR is made.

Because of the recently in the last year accepted EU – ASMF for the active substance and parent radionuclide Germanium-^{68} solved in hydrochloric acid no major objection in view to the active substance Germanium – ^{68} remain.

Also because of the introduction of the ASMF most of the other concerns in the active substance part are solved and only one minor other concern remain dealing with the test on identity of the Germanium-^{68} by gamma – spectroscopy used as control method by the finished product manufacturer which is not covered by the ASMF but could be solved without any effort.

The quality of the second active substance, the daughter radionuclide Gallium-^{68} solved in 0.05 M hydrochloric acid which is eluted from the chromatographic system radionuclide generator to be used for radiolabelling is in conformity with its pharmacopoeia monograph and its quality depends on the performance of the radionuclide generator.

3.1.1. Finished Medicinal Product

A radionuclide generator is a non typical pharmaceutical form where only its sterile eluate is dedicated to be used as a radionuclide precursor for radiolabelling, in this case the daughter radionuclide gallium-^{68} solved in 0.05 M hydrochloric acid, meaning that the radionuclide generator and its eluate is not dedicated for direct patient use.

The radionuclide generator GeGant where the mother nuclide germanium 68 is fixed on a chromatographic column is a system for elution of gallium (^{68}Ga) chloride solution for radiolabelling, which is not suitable for direct use in patients but for radiolabelling of substances dedicated for diagnostic use in Positron Emission Tomography (PET). Gallium-^{68} which is permanently generated by the radioactive decay of its mother radionuclide Germanium 68 is separated in a radionuclide generator from its mother nuclide using a chromatic column with the stationary phase where the mother nuclide Germanium 68 sticks on the column but the desired daughter radionuclide Gallium-^{68} can be eluted from the column with diluted sterile 0.05 M hydrochloric acid as mobile phase.

The eluted sterile gallium (^{68}Ga) chloride solution which comply with the Ph. Eur. monograph 2464 "Gallium (^{68}Ga) chloride solution for radiolabelling" is the radioactive starting material to radiolabel substances which can be formulated into radiopharmaceuticals for direct patient use. Typically the gallium (^{68}Ga) chloride solution is dedicated to be combined *in-vitro* in the nuclear medicine department with a kit for radiopharmaceutical preparation delivering the ready for patient use injection.

The advantage of a radionuclide generator is that with its current supply of a radionuclide a nuclear medicine department obtain a permanent source of radioactivity used for daily on site manufacturing of radiopharmaceuticals.

The core part of the radionuclide generator GeGant is its chromatographic column on which the mother radionuclide Germanium-^{68} is fixed. The mobile phase of the chromatographic system is the sterile 0.05 mol / L hydrochloric acid providing a sterile (^{68}Ga]Gallium chloride solution for radiolabelling.

For the manufacturer responsible for the finished product manufacturing and release testing no valid GMP – certification is submitted yet. Because till today no GMP – certification of the manufacturer is presented by the applicant manufacturing of the radionuclide generator in conformity with the GMP – rules is not proven and therefore without a declaration of a manufacturer who possess a manufacturing authorisation / GMP certification for the manufacturing of the radionuclide generator this issue is a major objection which exclude a recommendation for the issue of a marketing authorisation.

Because of the characteristic of the pharmaceutical form radionuclide generator as column chromatographic system the hydrochloride acid as the sterile mobile chromatographic phase is the second essential part of the finished product and chromatographic system GeGant which needs to be separately stored from the stationary phase of the chromatographic system and will be consumed in the daily use of the radionuclide generator.

Manufacturing steps with the hydrochloric acid dedicated for the finished product radionuclide generator GeGant as filling, sterilisation and for the finished product GeGant dedicated labelling of the packaging material vials are typical finished product manufacturing steps which should be done in the frame of a manufacturing authorisation or GMP-certificate. The manufacturer possess a manufacturing authorisation covering the sterile production of small liquid volumes.

A second major objection which is still not solved in the drug substance part is raised in view to a nitrosamine risk evaluation. The applicant provides only a declaration that no nitrosamine risk exist but a risk evaluation concerning the presence of nitrosamine and applying the principles outlined in the notice "Information on nitrosamines for marketing authorization holders" has to be updated.

The manufacturing process of the generator as finished product start with the manufacturing of the column stationary phase. Both preparation processes with the non radioactive stationary phase and the radioactive loading process with the mother radionuclide are challenging processes needing much experience because these are the key manufacturing processes of a chromatographic based radionuclide generator.

the Germnaium-^{68} loaded generator column closed at their inlet and outlet ports is sterilized according pharmacopeia standards. After the sterilization process the loaded column is packed into a radiation shielding . The housing contain the inlet and outlet port of the generator column, where the user will connect the tubes necessary for elution.

Because of the complexity of the manufacturing process each generator is one batch which is eluted with sterile 0.05 M hydrochloric acid and the sterile eluate is tested for generator release in conformity to the pharmacopeia monograph "gallium (^{68}Ga) chloride for radiolabeling" and on sterility.

For the sterile 0.05 M hydrochloric acid used for elution of the radionuclide generator a separate product part is submitted describing the manufacturing process as sterile solution using sterilization according the standard methods of the pharmacopeia.

For radiopharmaceuticals the SmPC contains in its part 12 "*Instructions for preparations of radiopharmaceuticals*" descriptions for the user how to work with the radionuclide generator "GeGant".

3.1.2. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Beside the remaining major objections in the finished product part which belong to missing manufacturing authorisation / GMP – certification of the manufacturer and the nitrosamine risk assessment still 9 other concerns remain in all fields of the description of the drug product and one other concern in the drug substance part.

Because of remaining major objections in quality a recommendation for the issue of a marketing authorization is excluded for the moment.

3.2. Non clinical aspects

3.2.1. Pharmacology

$^{68}GaCl_3$, the eluate of the ^{68}Ge/^{68}Ga-generator, is clinically used in PET diagnostic imaging already for decades. ^{68}Ga-chloride is not intended to be administered directly to the patient. The ^{68}Ga-chloride eluted from the ^{68}Ge/^{68}Ga-generator will be used to label selected carrier molecules which are not matter of this Marketing Authorisation procedure and which will determine the specific pharmacodynamic effects of the ^{68}Ga-labelled complex.

No clinically relevant amounts of dissociated (free and hence potentially pharmacologically active) $^{68}Ga^{3+}$ are administered with correct use. $^{68}Ga^{3+}$ decays almost completely to zinc within 6 hours. A full eluate of the ^{68}Ge/^{68}Ga-generator with a potential maximum strength of 4000 MBq of ^{68}Ga contains 2.7 ng gallium, an amount which is well below the doses (in mg/kg) at which secondary pharmacodynamic effects of gallium might be observed.

3.2.2. Pharmacokinetics

The eluate produced from the $^{68}Ge/^{68}Ga$-generator, consisting of $^{68}GaCl_3$ in 0.05 N hydrochloric acid is intended for the *in vitro* radiolabelling of medicinal products and will not be administered directly to the patient. Therefore, the pharmacokinetics of the radioactivity contained in the eluate produced from the $^{68}Ge/^{68}Ga$-generator will depend on the pharmacokinetics of the carrier molecule.

The pharmacokinetics (absorption, distribution, excretion) of unbound $^{68}Ga^{3+}$ is well known and had been investigated in detail in the past. The organ with the highest effective dose was calculated to be the thyroid. Due to the persistence and circulation of radioactivity in blood, the radiation dose was also relatively high for the heart wall and the lungs.

Due to the low breakthrough concentration of ^{68}Ge (NMT 0.001% in line with Ph. Eur. monograph 2464) leading to an overall low exposure to ^{68}Ge, and due to the rapid clearance of ^{68}Ge with a half-life of 36 min without retention in bone, the potential maximal breakthrough concentration of ^{68}Ge does not significantly contribute to the overall radiation exposure, which would result from an accidental injection of the $^{68}Ge/^{68}Ga$-generator eluate.

3.2.3. Toxicology

The eluate produced from the $^{68}Ge/^{68}Ga$-generator, consisting of $^{68}GaCl_3$ in 0.05 N hydrochloric acid is intended for the *in vitro* radiolabelling of medicinal products and will not be administered directly to the patient.

Complexing with the most commonly used chelating agent, DOTA, is irreversible [Riss et al.] and no free $^{68}Ga^{3+}$ is administered or released. However, due to the short half-life of $^{68}Ga^{3+}$, with almost complete decay to inactive ^{68}zinc within 6 h, any exposure to gallium is short-lived. Published data also shows that the breakthrough of < 0.001% ^{68}Ge specified for the $^{68}Ge/^{68}Ga$-generator does not lead to accumulation in any particular organ.

With regard to the element ^{68}Zn, the decay of 250 MBq $^{68}Ga^{3+}$ (which is in the highest dose commonly used in the clinics) produces only approximately 0.1 ng Zn. This, together with the Zn contamination of the eluate of < 10 µg/GBq is far below the requirements for absorbed zinc as trace element, which were estimated to be 1.4 mg/day for men and 1.0 mg/day for women [EFSA, 2014].

Overall, the safety of $^{68}Ge/^{68}Ga$-generator eluate is determined by the safety and distribution of the selected ligand to be used for *in vitro* labelling. The respective ligand determines the distribution due to its respective targeting moiety, and this distribution determines the organ exposure and radiation exposure of respective tissues.

The toxicity which may arise from any free ^{68}gallium or ^{68}germanium, or from any zinc generated from the decay of these isotopes, can be expected to not contribute significantly to the overall toxicity, since the exposure with these elements is in the ng-range. In addition, the acute toxicity of gallium and germanium is low moderate, with a NOAEL of gallium in dogs of 5 mg/kg, and single dose LD50 values for germanium being in the g/kg range. The compounds are not genotoxic and were not shown to have any reproduction toxicity potential.

The $^{68}Ge/^{68}Ga$-generator is intended to be eluted with 4 mL of 0.05 N hydrochloric acid. Local irritation was only observed following administration of highly concentrated or highly acidic solutions.

3.2.4. Ecotoxicity/environmental risk assessment

GeGant is a ^{68}Germanium / ^{68}Gallium chloride radionuclide generator to be used for *in vitro* labelling of various kits for radiopharmaceutical preparations which are used and administered only by authorised

personal in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to national regulations on radioactive materials. Additionally, ^{68}Gallium chloride is an inorganic salt for which neither an ERA nor PBT screening are required according to the Guideline on the Environmental risk assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00_corr2).

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

3.2.5. Discussion on non-clinical aspects

$^{68}GaCl_3$, the eluate of the ^{68}Ge/^{68}Ga-generator, is not intended to be administered directly to the patient. The ^{68}Ga-chloride eluted from the ^{68}Ge/^{68}Ga-generator will be used to label selected carrier molecules which are not matter of this Marketing Authorisation procedure and which will determine the specific pharmacodynamic effects of the ^{68}Ga-labelled complex.

No clinically relevant amounts of dissociated (free and hence potentially pharmacologically active) $^{68}Ga^{3+}$ are administered with correct use. $^{68}Ga^{3+}$ decays almost completely to zinc within 6 hours. A full eluate of the ^{68}Ge/^{68}Ga-generator is well below the doses (in mg/kg) at which pharmacodynamic effects of gallium might be observed.

The pharmacokinetics (absorption, distribution, excretion) of unbound $^{68}Ga^{3+}$ is well known and had been investigated in detail in the past. The organ with the highest effective dose was calculated to be the thyroid. Due to the persistence and circulation of radioactivity in blood, the radiation dose was also relatively high for the heart wall and the lungs [1].

Due to the low breakthrough concentration of ^{68}Ge (NMT 0.001% in line with Ph. Eur. monograph 2464) leading to an overall low exposure to ^{68}Ge, and due to the rapid clearance of ^{68}Ge with a half-life of 36 min without retention in bone, the potential maximal breakthrough concentration of ^{68}Ge does not significantly contribute to the overall radiation exposure, which would result from an accidental injection of the ^{68}Ge/^{68}Ga-generator eluate.

The eluate produced from the ^{68}Ge/^{68}Ga-generator, consisting of $^{68}GaCl_3$ in 0.05 N hydrochloric acid is intended for the in vitro radiolabelling of medicinal products and will not be administered directly to the patient. With regard to the element ^{68}Zn, the decay of 250 MBq $^{68}Ga^{3+}$ (which is in the highest dose commonly used in the clinics) produces only approximately 0.1 ng Zn. From toxicological point of view no concerns are raised regarding the medicinal product in the intended clinical use.

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

3.2.6. Conclusion on non-clinical aspects

$^{68}GaCl_3$, the eluate of the ^{68}Ge/^{68}Ga-generator, is not intended to be administered directly to the patient. The ^{68}Ga-chloride eluted from the ^{68}Ge/^{68}Ga-generator will be used to label selected carrier molecules which are not matter of this Marketing Authorisation procedure. The pharmacodynamics, kinetic and toxicity of the $^{68}GaCl_3$ eluate are well known. SmPC and PL are in line with the "Guideline on core SmPC and Package Leaflet for (^{68}Ge/^{68}Ga) generator" (EMA/CHMP/337681/2016). There are no objections against Marketing Authorisation from the non-clinical point of view.

3.3. Clinical aspects

GeGant is a radionuclide generator and not intended for direct use in patients. Consequently, no clinical data are available and characterisation of pharmacokinetics, pharmacodynamics, efficacy and safety in the traditional sense is not applicable. Technical functioning of the product and the quality of the

produced eluate are the main aspects of the assessment and the focus in this regards lies in the quality assessment, that is presented in the quality assessment report and Section 3.1 of this document.

As $^{68}GaCl^3$ is also not used directly in patients, but only for labelling of the carrier molecules, no clinical data are available, which is acceptable. Clinical characteristics of ^{68}Ga-labelled tracers are fully dependent on the specific features of these carrier molecules and are not relevant within the context of this Application.

3.3.1. Radiation dosimetry

The applicant presented dosimetry data for three substances: (1) $^{68}GaCl_3$ in case the generator eluate is accidentally intravenously administered to a patient; (2) $^{68}GeCl_4$ to consider the contamination ($\leq$ 0.001 %) of the generator eluate with the mother nuclide ^{68}Ge; and (3) ^{68}Ga-citrate, since, according to the core SmPC of ^{68}Ge/^{68}Ga-generator(s), the data for ^{68}Ga-citrate may be used to estimate the organ doses and the effective dose resulting from an application of the unbound $^{68}Ga_{3+}$ from the eluate, even though these data were obtained using a different salt.

As the main publication on the pre-clinical biodistribution and dosimetry study with $^{68}GaCl_3$ submitted falls under data exclusivity, this has not been considered in this assessment. Data on the radiation dose to patients of gallium (^{68}Ga) citrate are from ICPR 53.

The tables with absorbed dose coefficients and the effective dose coefficients for $^{68}GaCl_3$ and ^{68}Ga-citrate for different age groups presented in the SmPC by the applicant are listed below.

Table 5 Absorbed dose per unit activity administered –inadvertent administration in women

	Absorbed dose per administered unit of activity (mGy/MBq)					
Organ	**Adult (57 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adrenals	0.0114	0.0112	0.0164	0.0238	0.0403	0.0782
Brain	0.0180	0.0159	0.0176	0.0206	0.0292	0.0667
Breasts	0.0059	0.0058	0.0110	0.0163	0.0269	0.0545
Gallbladder Wall	0.0096	0.0092	0.0127	0.0201	0.0390	0.0750
Lower large intestine Wall	0.0032	0.0032	0.0050	0.0077	0.0133	0.0292
Small Intestine	0.0039	0.0039	0.0062	0.0099	0.0178	0.0376
Stomach Wall	0.0057	0.0056	0.0088	0.0133	0.0250	0.0502
Upper large intestine Wall	0.0040	0.0039	0.0067	0.0104	0.0199	0.0425
Heart Wall	0.1740	0.1940	0.3010	0.4830	0.8730	1.7200
Kidneys	0.0385	0.0421	0.0600	0.0888	0.1600	0.4150
Liver	0.0972	0.0974	0.1480	0.2200	0.4270	0.9890
Lungs	0.1860	0.2240	0.3190	0.4930	0.9840	2.7100
Muscle	0.0073	0.0076	0.0131	0.0319	0.0622	0.0954
Ovaries	0.0188	0.0203	0.0566	0.0988	0.2250	0.4590
Pancreas	0.0187	0.0218	0.0406	0.0547	0.1120	0.3400
Red Marrow	0.0225	0.0256	0.0415	0.0777	0.1770	0.5710
Osteogenic Cells	0.1160	0.1140	0.1840	0.3100	0.7350	2.3500
Skin	0.0029	0.0029	0.0044	0.0067	0.0122	0.0271
Spleen	0.0055	0.0056	0.0086	0.0130	0.0238	0.0492
Thymus	0.0100	0.0102	0.0133	0.0190	0.0297	0.0570
Thyroid	0.2210	0.2980	0.4600	1.0200	1.9300	2.6300
Urinary Bladder Wall	0.0023	0.0022	0.0038	0.0063	0.0110	0.0222
Uterus	0.0792	0.0802	1.3400	2.0300	3.6900	1.4700
Total Body	0.0177	0.0178	0.0289	0.0468	0.0920	0.2340
Effective Dose (mSv/MBq)	0.0483	0.0574	0.1230	0.2090	0.4100	0.7170

Table 6 Absorbed dose per unit activity administered – inadvertent administration in men

	Absorbed dose per administered unit of activity (mGy/MBq)					
Organ	**Adult (70 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adrenals	0.0093	0.0112	0.0165	0.0235	0.0377	0.0749
Brain	0.0134	0.0137	0.0148	0.0170	0.0241	0.0563
Breasts	0.0062	0.0074	0.0142	0.0213	0.0350	0.0725
Gallbladder Wall	0.0081	0.0096	0.0137	0.0213	0.0409	0.0803
Lower large intestine Wall	0.0015	0.0020	0.0031	0.0051	0.0091	0.0204
Small Intestine	0.0022	0.0029	0.0048	0.0080	0.0146	0.0309
Stomach Wall	0.0048	0.0066	0.0099	0.0153	0.0287	0.0560
Upper large intestine Wall	0.0027	0.0033	0.0058	0.0094	0.0182	0.0385
Heart Wall	0.3030	0.3930	0.6110	0.9830	1.7800	3.4900
Kidneys	0.0198	0.0241	0.0345	0.0510	0.0911	0.2310
Liver	0.0766	0.1030	0.1570	0.2330	0.4500	1.0400
Lungs	0.1340	0.2000	0.2850	0.4390	0.8720	2.3800
Muscle	0.0051	0.0074	0.0129	0.0326	0.0636	0.0961
Pancreas	0.0187	0.0257	0.0480	0.0646	0.1310	0.4030
Red Marrow	0.0138	0.0154	0.0243	0.0441	0.0980	0.3110
Osteogenic Cells	0.0431	0.0558	0.0901	0.1510	0.3560	1.1300
Skin	0.0020	0.0024	0.0036	0.0057	0.0103	0.0232
Spleen	0.0041	0.0056	0.0084	0.0130	0.0227	0.0469
Testes	0.0011	0.0018	0.0075	0.0094	0.0138	0.0239
Thymus	0.0139	0.0158	0.0194	0.0276	0.0417	0.0794
Thyroid	0.1980	0.3250	0.5020	1.1200	2.1100	2.8800
Urinary Bladder Wall	0.0011	0.0013	0.0022	0.0039	0.0070	0.0152
Total Body	0.0115	0.0147	0.0237	0.0383	0.0748	0.1900
Effective Dose (mSv/MBq)	0.0338	0.0506	0.0756	0.1340	0.2600	0.5550

The effective dose resulting from an accidental intravenously injected activity of 250 MBq of $^{68}GaCl_3$ is 12.1 mSv for a 57-kg female adult and 8.45 mSv for a 70-kg male adult.

Table 7 Absorbed dose per unit activity inadvertent administration of gallium (^{68}Ga) citrate

	Absorbed dose per administered unit of activity (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.034	0.044	0.064	0.088	0.140
Bone surface	0.037	0.048	0.080	0.140	0.310
Breast	0.014	0.014	0.023	0.037	0.074
Lower large intestine Wall	0.018	0.022	0.036	0.059	0.110
Small Intestine	0.064	0.080	0.140	0.230	0.450
Stomach Wall	0.014	0.017	0.027	0.044	0.084
Upper large intestine Wall	0.053	0.064	0.110	0.180	0.360
Kidneys	0.026	0.032	0.046	0.068	0.120
Liver	0.027	0.035	0.053	0.079	0.150
Lungs	0.013	0.016	0.025	0.041	0.080
Pancreas	0.014	0.018	0.029	0.047	0.089
Red Marrow	0.046	0.064	0.110	0.210	0.450
Spleen	0.036	0.051	0.080	0.130	0.240
Testes	0.013	0.015	0.024	0.039	0.077
Thyroid	0.012	0.015	0.025	0.042	0.081
Urinary Bladder Wall	0.014	0.016	0.026	0.044	0.081
Other tissue	0.013	0.015	0.025	0.041	0.080
Effective Dose (mSv/MBq)	0.027	0.034	0.056	0.095	0.190

The results of two studies investigating the biodistribution of $^{68}GeCl_4$ are reported in the application: (1) Sabbioni et al. (DOI: 10.1002/jat.1469) and (2) Velikyan et al. (Am J Nucl Med Mol Imaging. 2013; 3(2): 154–165). The first study evaluated the biodistribution of $^{68}GeCl_4$ in rats after an intraperitoneal injection. No scaling to humans and no dosimetry were done by Sabbioni et al. Velikyan et al. studied the biodistribution of $^{68}GeCl_4$ in rats after an injection in the tail vein. The uptake of $^{68}GeCl_4$ in various organs and tissues of rats as a function of time (up to 168 h post-injection) was evaluated and the number of decays (or time-integrated activity coefficients (TIACs)) were computed. The obtained TIACs for rats were extrapolated to humans and subsequently used for dose calculations using the software OLINDA/EXM version 1.1. Dose coefficients for organ absorbed doses and the effective dose are not given in a table in the application. However, the dose coefficients for the effective dose and the absorbed dose to kidneys and osteogenic cells are given in the text of the application. The effective dose coefficient amounted to 1.55·10-2 mSv/MBq as adopted from Velikyan et al. Kidneys were found to be an organ receiving the highest dose with the absorbed dose coefficients of 18.5·10-2 mGy/MBq and 17.1·10-2 mGy/MBq for adult female and adult male, respectively. Based on the obtained dose coefficients for the effective dose and the absorbed organ doses after an injection of the compound $^{68}GeCl_4$, Velikyan et al. concluded that the limit of the eluate contamination with nuclide ^{68}Ge currently recommended by the Ph.Eur. monograph (<0.001 %) could be substantially increased.

Discussion on biodistribution and dosimetry

The biodistribution and the dosimetry of ^{68}Ga-labelled medicinal products has no direct relevance for this application. Hence, it is acceptable that only $^{68}GaCl_3$, $^{68}GeCl_4$ and the free $^{68}Ga_3$+ are the subjects for dosimetry in this application.

To estimate the organ absorbed doses and the effective dose after an accidental intravenous administration of the eluate $^{68}GaCl_3$, the applicant provided one publication describing a pre-clinical study

in rats with administration of $^{68}GaCl_3$. The data collected in this study, however, are considered protected by data exclusivity (see above). Consequently, the publication has not been considered in this assessment. No other data have been submitted.

The dosimetry data as presented in the proposed SmPC for $^{68}GaCl_3$ and ^{68}Ga-labelled citrate are identical to those reported in the EMA guideline on Core SmPC and package leaflet for ^{68}Ge/^{68}Ga-generator(s). The Core SmPC provides no further information regarding the calculations for $^{68}GaCl_3$ done and the formalism used for the estimation of the effective dose coefficients. Thus, no further assessment of the dosimetry of the compound $^{68}GaCl_3$ is possible. However, the presented dosimetry is endorsed, as in line with the above guideline.

Effective dose resulting from an accidental use of $^{68}GaCl_3$ has been estimated for the intravenously injected activity of 250 MBq (the activity commonly applied) is higher than the effective doses reached when ^{68}Ga-labelled carrier molecules are used for diagnostic purposes (see section 3.3.5).

An issue of an accidental intake of $^{68}GaCl_3$ by personnel (via e.g. inhalation, ingestion or other incorporation ways) was not addressed. However, these represent non-product-specific generic risks, are subjects of the occupational radiation protection and are considered less relevant in the frame of the clinical radiation protection of patients. Thus, no additional information is being requested.

The dosimetry for $^{68}GeCl_4$ can be considered acceptable, although it cannot be verified.

3.3.2. Clinical utility

Subject of this MAA is a radionuclide generator and assessment of efficacy does not apply in this case. Technical features and quality of the product has been discussed in the quality dossier and quality assessment report.

The eluate of the proposed medicinal product ^{68}Ge/^{68}Ga-generator is a radiopharmaceutical precursor and not intended for direct use in patients either. In accordance with Annex I, Part III, Section 2.2 of Directive 2001/83/EC, as amended, stating *"[…] information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented"*, the applicant has submitted published clinical data to support the claim of clinical utility.

In total, 275 publications (including clinical studies and case reports) were submitted describing use of ^{68}Ga-marked carrier molecules - DOTATOC, DOTANOC, DOTATATE and PSMA - in the indications of NETs, meningiomas and prostate cancer.

Table 8 Summary of the publications supporting the clinical utility of ^{68}Ga-marked molecules

^{68}Ga-tracer-complex	**Diagnostic use**	**First described**	**Number of published clinical studies included (single case reports)**	**Total number of patients enrolled**
^{68}Ga-DOTATOC	NETs	2001	52 (9)	1.702
	Meningiomas	2001	9 (1)	198
^{68}Ga-DOTANOC	NETs	2005	48 (8)	4.910
^{68}Ga-DOTATATE	NETs	2006	80 (8)	4.420
	Meningiomas	2015	10 (3)	482
^{68}Ga-PSMA	Prostate cancer	2012	76 (3)	12.585

Additionally, systematic reviews and meta-analyses have been presented.

As mentioned above, some of these publications have not been considered in this assessment.

Clinical utility of ^{68}Ga-DOTA conjugates in the diagnostic of neuroendocrine tumours (NETs) and meningiomas – main data

DOTATOC (edotreotid) has already been licensed EU-wide for labelling with ^{68}Ga under the trade name of SomaKit TOC via a centralised procedure (EU/1/16/1141/001; in 2016) "for Positron Emission Tomography (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."

Further, **^{68}Ga-labelled DOTATOC** (edotreotid), as ready-to-use preparation, has been authorized since 2016 in France, Austria and Germany under the product names, Sogacin® and TOCscan® via a decentralized mutual recognition procedure (FR/H/0611/001) "for imaging in patients undergoing oncologic diagnostic procedures describing functions or diseases where enhanced somatostatin receptors expression of specific organs or tissues is the diagnostic target.

The following indications have been particularly documented:

- detection of the primary occult neuroendocrine tumour when a metastasis of neuroendocrine tumour has been demonstrated or when the serum concentration of a specific marker is increased,

- characterisation of bronchial mass as neuroendocrine tumour when other diagnostic modalities have not been conclusive,

- characterisation, initial staging, detection in case of biochemical recurrence and restaging of neuroendocrine tumours of the foregut, including in the thymus or the bronchi,

- characterisation, initial staging, detection in case of biochemical recurrence and restaging of neuroendocrine tumours of the midgut, when 6-fluoro-(18F)-L-dihydroxyphenylalanine is not available or when PET with 6-fluoro-(18F)-L-dihydroxyphenylalanine is non-conclusive,

- as an adjunct to anatomic imaging in pre-therapeutic evaluation of meningeoma.

Tumours which do not bear somatostatin receptors will not be visualised with Sogacin."

The largest studies evaluating diagnostic performance of **^{68}Ga-DOTANOC** PET in the diagnostics of **NETs** were conducted by Ambrosini et al., 2012b (n=1239), Sharma et al., 2005 (n=141), and Haidar et al., 2017 (n=445).

Sensitivity and specificities within the range of 85.7% and 92.4%% and specificities of 79.1% and 98.3% were reported in these larger studies.

Impact of **^{68}Ga-DOTANOC** on **patient management** was investigated in the meta-analysis by Barrio et al., that included 3 studies in patients with **NETs** (n=218) and showed change in disease management in 16-36% of patients.

Relatively large studies evaluating diagnostic performance of **^{68}Ga-DOTATATE PET** in NETs and utilizing blinded image interpretation by independent readers (n=2) were conducted by Sadowski et al., 2015 (n=131) in the patients with suspected or confirmed tumour and Haug et al., 2013 (n=63) in the patients with suspected recurrence or as a routine follow-up.

Sensitivity of ^{68}Ga-DOTATATE PET/CT tested against histopathology reached 63.7%, which was better than anatomic imaging (38.9%, respectively). Diagnostic accuracy of the test in detection of recurrent tumour was reported in >80% of cases.

Considerable impact on **patient management**/decision-making estimated as 20-71% based on the 8 clinical studies in **NETs** diagnostics was reported in one meta-analysis (Barrio et al., 2011).

^{68}Ga-DOTATATE was investigated in 2015 by Rachinger et al., in the diagnosis of **meningiomas** in the adult patients with either **parasagittal or skull-base tumours**. ^{68}Ga-DOTATATE PET imaging revealed a median SUVmax of 6.6 (range 0.1-106.6) and significant correlation between SUVmax and histopathology could be found. Additional meningiomas in nine patients were detected. The authors concluded that ^{68}Ga-DOTATATE PET has significant impact on the diagnosis and management of meningiomas, particularly with tumours in complex locations or at recurrent stage.

Kunz et al., (2017) compared **^{68}Ga-DOTATATE** PET/CT with contrast-enhanced (CE) MRI. Patients with trans-osseous extension of meningioma (n=67) showed significantly larger lesions and significantly higher tracer uptake values than patients with extra-osseous meningiomas (n=15). ^{68}Ga-DOTATATE PET/CT showed a higher sensitivity (98.5% vs. 53.7%) compared to CE-MRI while maintaining high specificity (86.7% vs. 93.3%) in the detection of osseous involvement ($p<0.001$). The authors therefore concluded that ^{68}Ga-DOTATATE PET/CT improves the detection of trans-osseous extension of intracranial **meningiomas** compared to CE-MRI.

Clinical utility of ^{68}Ga-PSMA (prostate-specific membrane antigen) in the diagnostics of prostate cancer

Eiber et al,. published the results of a more comprehensive retrospective study in 248 patients with **recurrent prostate cancer** after radical prostatectomy. Two-hundred-twenty-two patients (89.5%) showed one or more areas suggestive for recurrent prostate cancer. Mean prostate specific antigen (PSA) was significantly lower in patients with negative **^{68}Ga-PSMA-11** ligand PET/CT results than in patients with positive results ($p=0.0080$). The detection efficacy of ^{68}Ga-PSMA-11 PET/CT was 96.8% (120/124) for a PSA value of ≥2 ng/mL, 93.0% (67/72) for a PSA value of 1 to <2 ng/mL, 72.7% (24/33) for a PSA value of 0.5 to <1 ng/mL, and 57.9% (11/19) for a PSA value of 0.2 to <0.5 ng/mL. In total, in only 37.1% (92/248) of patients a comprehensive standard of reference (histopathology, decrease of PSA level after targeted radiation therapy, or undisputable follow-up/other imaging methods) was available. In all of these cases, concordant results in correlation with the findings derived from ^{68}Ga-PSMA ligand PET/CT were present.

Meta-analyses by Eyben et al., 2016 (15 studies and 1256 patients), Perera et al., 2016 (16 studies and 1.309 patients), Perera et al., 2019 (37 articles including 4,790 patients), Wu et al., 2019 (13 studies comprising 1,597 patients), Satapathy et al., 2020 (7 studies and 389 patients), and Peng et al., 2020 (10 studies comprising 701 patients) showed moderate to high levels of diagnostic performance in primary cancer detection, staging and diagnosis of recurrence.

3.3.3. Discussion on clinical utility

As the product under evaluation is not directly used in patients, no specific indication has been targeted. Proposed indication, as per submitted SmPC is

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

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

This wording is in line with the EMA "Guideline on Core SmPC and Package Leaflet for ^{68}Ge/^{68}Ga-generator" (EMA/CHMP/337681/2016). The proposed wording of the indication and the absence of clinical data for GeGant is, therefore, endorsed.

The applicant has submitted evidence to substantiate the clinical utility of $^{68}GaCl_3$ following the rule defined in the Directive 2001/83:

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

Large number of publications (including clinical studies and case reports) has been submitted describing use of ^{68}Ga-marked DOTATOC, DOTANOC, DOTATATE and PSMA in the indications of NETs, meningiomas and prostate cancer diagnostics. Additionally, systematic reviews and meta-analyses have been presented.

It has been noted, that the provided clinical dossier contained data, which may be subject to data exclusivity (Reference is made to the marketing authorisations of GalliaPharm by Eckert & Ziegler Radiopharma GmbH (Berlin, Germany; DK/H/2294/001/DC), GalliAd, 0.74-1.85 GBq, radionuclide generator, IRE-Elit (DK/H/2690/001/DC)). Consequently, these data were reviewed, but not considered in the assessment. Respectively, the submitted number of the publications and number of patients does not reflect the analysed data set.

Based on the available evidence the following can be summarized:

DOTATOC (edotreotid) has already been licensed EU-wide for labelling with ^{68}Ga under the trade name of SomaKit TOC via a centralised procedure (EU/1/16/1141/001; in 2016) PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated GEP-NETs. Further, ^{68}Ga-labelled DOTATOC (edotreotid) as ready-to-use preparation under the product names Sogacin® and TOCscan® has been authorized since 2016 in France, Austria and Germany (FR/H/0611/001) for imaging of NETs and meningiomas.

Notably, the marketing authorization holder of Sogacin/TOCscan seems to be same as the applicant of the current MAA. Thus, diagnostic efficacy and clinical benefits in the diagnostics of NETs and meningiomas for ^{68}Ga-laballed DOTATOC have already been proven, which substantiates the clinical utility of ^{68}Ga and ^{68}GaCl3, and is considered sufficient for the Application under evaluation, so that in fact no further proof is required.

For the remaining DOTA conjugates, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE limited evidence in diagnostic of NETs was submitted describing high levels of sensitivity and specificity and considerable impact on patient management (about 1/5 to 1/3 of the tested population for ^{68}Ga-DOTANOC and 1/3-2/3 for ^{68}Ga-DOTATATE in NETs), suggestive of relevant role of these substances in the NETs diagnostics.

Notably, in the 2016 FDA approved DOTATATE under the trade name NETSPOT (by Advanced Accelerator Applications USA Inc.) for PET detection of rare somatostatin receptor positive NETs in adults and paediatric patients after marking with ^{68}Ga (https://www.fda.gov/news-events/press-announcements/fda-approves-new-diagnostic-imaging-agent-detect-rare-neuroendocrine-tumors). NETSPOT was granted Priority Review and orphan drug designations by the FDA.

The presented studies with ^{68}Ga-DOTATATE in the diagnostics of meningiomas can be considered a PD studies. These studies provide very limited evidence of clinical utility of the ^{68}Ga-DOTATATE in the diagnostics of meningiomas.

Obvious limitations of the presented studies for all DOTA conjugates are e.g., open-label retrospective design, small size and inadequate control in the majority of the cases, unclear blinding and reading procedures, which render the data some uncertainty.

Overall, use of ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE in the diagnostics of NETs is recommended by a number of European and international scientific societies, such as EANM (Virgolini et al., 2010 and Bozkurt et al., 2017 – updated guideline), European Neuroendocrine Tumor Society

(ENETS) (Sandin et al., 2017) and European Society for medical Oncology (ESMO) (Pavel et al., 2020) for years. This further supports the clinical utility of the ^{68}Ga-marked DOTA-ligands and indicates their relevance in the diagnostic work-up of NETs.

For ^{68}Ga-PSMA more solid evidence suggestive of its clinical utility in diagnostics of prostate cancer is contained in the submitted 7 meta-analyses. Diagnostic performance of the substance in identification of the primary and recurrent tumour and staging have been tested and the presented data are encouraging.

It must be noted that ^{68}Ga-PSMA-11 PET has recently (in 2020) gained a marketing authorisation in the US for PET in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy, and/or with suspected recurrence based on elevated PSA level.

In the European members states, like in the case of DOTANOC and DOTATATE, no marketing authorisation has been granted yet and the substance is in the experimental stage of development. Nonetheless, the relevance of ^{68}Ga-marked PSMA in the diagnostic imaging of prostate cancer has been acknowledged by the European medical community. This is evidenced by a number of guidelines dedicated specifically to the PSMA PET, or recommending this imaging method in the diagnostics of prostate cancer. Namely, a Joint EANM (European Association of Nuclear Medicine) and SNMMI (Society of Nuclear medicine and Molecular Imaging) procedure guideline for prostate cancer imaging (Fendler et al., 2017), EANM standardized reporting guideline for PSMA-PET (Ceci et al., 2021). European Association of Urology (EAU) in the guideline on PCa recommend the use of PSMA-PET for biochemical recurrence after radical prostatectomy (PSA > 0.2 ng/mL), "namely if PSMA-PET scan is able to positively influence the subsequent treatment strategy" (Mottet et al., 2020). Also consensus paper from the Advanced Prostate Cancer Consensus Conference (APCCC, 2019; Gilessen et al., 2020) recommended use of PSMA ligands (e.g., marked with ^{68}Ga) in the diagnostics of prostate cancer prior to start of treatment.

In conclusion, the available evidence is sufficient to substantiate the claim of clinical utility of the ^{68}Ga-labelled substances and, consequently, of ^{68}Ga itself to support this application.

3.3.4. Conclusions on clinical utility

Overall, the presented evidence is considered sufficient to substantiate this MAA.

3.3.5. Clinical safety

No clinical data have been provided. Safety profile of the ^{68}Ga-labelled molecules will completely depend on the characteristics of these molecules and are irrelevant within the context of this Application. Only general safety considerations are specified in the "Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE" and the "Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-somatostatin receptor targeting peptides and 18F-DOPA" (Virgolini et al., 2010; Bozkurt et al., 2017). These safety considerations are also included in the "Guideline on core SmPC and Package Leaflet for ^{68}Ge/^{68}Ga-generator" (EMA/CHMP/337681/2016) and were considered in the submitted product information of GeGant.

The applicant has discussed specific issues, which may be potentially relevant in regards to safety, such as, unstable ^{68}Ga-ligand-complexes, accidental direct administration of the generator eluate and ^{68}Ga decay to Zinc. Further aspects, which may have relevance for safety, but are directly related with functioning of the generator are sterility of the eluate, radionuclidic purity, elemental impurities, bacterial endotoxins, ^{68}Ge breakthrough. All topics above are discussed in the quality and pre-clinical parts of this

report (sections 3.1 and 3.2). Accidental administration of $^{68}GaCl3$ is described in section 3.3.1 (Dosimetry).

Post marketing experience

Not applicable.

3.3.6. Discussion on clinical safety

As GeGant is a radionuclide generator its safety profile is completely dependent on its technical features and functioning. Thus, as long as the quality requirements and specifications are clearly defined and complied with, risks related to GeGant 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).

In order to minimize the above risks handling and maintenance procedures for GeGant (e.g., storage, instructions for preparation of the eluate) have been reflected in the SmPC in detail and can be regarded sufficient, as risk minimisation measure, as soon as the final wording is agreed upon. Generally, it must be noted, that in the case of possible ^{68}Ge breakthrough the amount of ^{68}Ge would need to exceed the allowed levels in the eluate more than 100 times, in order to reach harmful levels. Such degree of ^{68}Ge breakthrough is considered highly unlikely to happen in clinical practice, given the precise instructions of quality maintenance in the SmPC and the fact that the product will be utilized by well-trained personnel and in specialized clinical centers only.

In regards to the occupational hazards, routine measures of radiation protection apply. Information reflecting the risks of external radiation exposure (e.g., surface or contact radiation) have been adequately addressed in the SmPC. Which is endorsed.

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

The risk of direct application of the $^{68}GaCl_3$ eluate to patients has been addressed in the SmPC by presenting the respective dosimetry tables, which display the estimated absorbed and effective doses in the event that such inadvertent exposure takes place. The effective dose resulting from an accidental intravenously injected activity of 250 MBq is estimated as 12.1 mSv for a 57-kg female adult and 8.45 mSv for a 70-kg male adult. This exceeds the usual doses reached after administration of ^{68}Ga-marked carrier molecules (e.g. SomaKit: The effective dose resulting from the administration of an activity of 200 MBq to an adult weighing 70 kg is about 4.2 mSv). Adequate recommendations to increase hydration and voiding in order to reduce the dose/overdose have been included in section 4.9 of the SmPC to minimise the risk of radiation exposure to patients. The dosimetry tables and the above recommendations are in line with the information included in the guideline on Core SmPC and package leaflet for $^{68}Ge/^{68}Ga$ generators.

After the use of clinically recommended dose of 250 MBq ^{68}Ga, approximately 0.1 ng Zn is generated. This amount of Zn amounts to a fraction of the allowed daily nutritional intake of 1.0 and 1.4 mg Zn for women and men, respectively (please refer to the recommendations by EFSA Panel on Dietetic Products,

Nutrition and Allergies). This additional exposure to Zn can be considered clinically negligible, particularly in light of a single use of ^{68}Ga-labelled molecules for diagnostic purposes.

In summary, no major risks or concerns in terms of safety have been identified. Majority of the theoretical risks represent generic risks related to use of radionuclide products and have been addressed in the SmPC. Overall, the product can be considered to have favourable safety profile, provided that all quality requirements are fulfilled and adhered to. A request to search public databases (e.g., literature, other sources) on handling mistakes of the generators has been raised.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable

Additional safety data needed in the context of a conditional MA / MA under exceptional circumstances

Not applicable

3.3.7. Conclusion on clinical safety

In summary, no major risks or concerns in terms of safety have been identified. Majority of the theoretical risks represent generic risks related to use of radionuclide products and have been addressed in the SmPC. Overall, the product can be considered to have favourable safety profile, provided that all quality requirements are fulfilled and adhered to.

3.4. Risk Management Plan

The applicant submitted an updated RMP (version 03, DLP: 01.06.2022, date of final sign off: 12.09.2022), taking into account the questions raised as part of the D120 assessment.

3.4.1. Safety specification

Summary of safety concerns

The applicant identified the following safety concerns in the updated RMP:

Table SVIII.1: Summary of safety concerns

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

3.4.1.1. Discussion of the safety specification

In the updated RMP, "accidental direct use in patients" and "serious infections" were removed from the summary of safety concerns as requested. Generally, the applicant's proposal for the safety specification is adequate. However, the important potential risk regarding ^{68}Ge breakthrough was not reworded as recommended as the term "undetected" has not been included. Since preparation of the D120 LoQ it has also been noted that a further specification is reasonable by including the term "elevated":

"Long-term exposure to radiation (in case of *undetected* **elevated** ^{68}Ge breakthrough)".

The inclusion of the word "elevated" is reasonable since some ^{68}Ge breakthrough (up to the specified threshold of 0.001%) can be contained in the eluate. Only ^{68}Ge amounts exceeding this threshold level are considered associated with the risk.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification the rapporteur considers that the following issues should be addressed:

The important potential risk regarding ^{68}Ge breakthrough should be reworded as:

"Long-term exposure to radiation (in case of **undetected elevated** ^{68}Ge breakthrough)".

All relevant parts of the RMP should be updated accordingly.

3.4.2. Pharmacovigilance plan

3.4.2.1. Summary of additional PhV activities

Not applicable.

3.4.2.2. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term exposure to radiation (in case of ^{68}Ge breakthrough)	Routine risk communication: SmPC section 12 Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: • Use only by trained specialists • Sale limited to licenced nuclear medicine sites • Prescription only	

Part V "Risk minimisation measures" of the RMP has been updated in line with the amendments regarding the safety specification. Routine risk minimisation measures are considered sufficient to minimise the risks of the product.

However, recommendations in section 12 of the SmPC to avoid increased ^{68}Ge breakthrough should be included as "Routine risk minimisation activities recommending specific clinical measures to address the risk" in Part V, section V.1:

- After installation of the generator, the first five elutions should be discarded due to potentially increased ^{68}Ge breakthrough.
- To avoid increased ^{68}Ge breakthrough, the generator should be eluted at least once per working day.
- It is highly recommended to test the first eluates and the eluates obtained in routine use throughout the shelf-life of the generator for ^{68}Ge breakthrough in accordance with Ph. Eur. Monograph 2464.
- After an elution break for 30 days or more, the generator has to be rinsed with 5X4 mL elution medium 7-24 hours prior to the intended use to avoid elevated ^{68}Ge breakthrough levels.

The wording regarding the specific actions to be taken to avoid ^{68}Ge breakthrough in section V.1 should be aligned with the amended SmPC.

3.4.3.1. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Recommendations in the SmPC to avoid increased ^{68}Ge breakthrough should be provided in section V.1 regarding "Routine risk minimisation activities recommending specific clinical measures to address the risk".

3.4.4. Summary of the risk management plan

Part VI has generally been updated in line with the issues raised in other parts of the RMP. However, Part VI requires further revision.

Updated section II.B contains the following information for "Evidence for linking the risk to the medicine":

"When used according to these instructions, the ^{68}Ge breakthrough should stay below 0.001% for approximately 250 elutions or one year. The potential exposure from possible breakthrough of ^{68}Ge could be evaluated based on distribution data of ^{68}Ge. Animal data showed that there is no radiation safety concern to be expected after accidental injection of ^{68}GaCl3 from the ^{68}Ge/^{68}Ga-generator, even if a full eluate is administered, or in cases, where the labelling reaction was incomplete, resulting in administration of free ^{68}Ga3+ including the breakthrough content of ^{68}Ge. Due to the low breakthrough concentration of 68Ge leading to an overall low exposure to ^{68}Ge, and due to the rapid clearance of ^{68}Ge with a half-life of 36 min without retention in bone, the potential maximal breakthrough concentration of ^{68}Ge does not significantly contribute to the overall radiation exposure which would result from an accidental injection of the ^{68}Ge/^{68}Ga-generator eluate."

Updated information is not considered appropriate to describe the evidence linking ^{68}Ge breakthrough to the risk of long-term exposure to radiation. Part VI, section II.B should be further updated to adequately summarize information regarding "Evidence for linking the risk to the medicine" in line with recommendations in section 12 of the SmPC to avoid increased ^{68}Ge breakthrough:

"When used according to instructions, the ^{68}Ge breakthrough should stay below 0.001% for approximately 250 elutions or one year. However, there is a potential for radiation-induced adverse events in a case of excessive ^{68}Ge amount in an eluate, given the relatively long half-life of this radionuclide (270.95 days).

It is possible that free ^{68}Ge ions accumulate in the column inside of the radionuclide generator over time. Therefore, to avoid increased ^{68}Ge breakthrough in eluates (exceeding the permitted level of 0.001%), the generator should be eluted at least once per working day. In addition, the generator has to be rinsed with 5X4 mL elution medium 7-24 hours prior to the intended use after an elution break for 30 days or more. It is generally highly recommended to test eluates for ^{68}Ge breakthrough on a regular basis. Tests should be performed according to recent Ph. Eur. Monograph 2464."

Section SVII.3 "Evidence source(s) and strength of evidence" should be updated in accordance with Part VI, section II.B. The wording regarding the specific actions to be taken to avoid ^{68}Ge breakthrough in section SVII.3 and Part VI, II.B should be aligned with the amended SmPC.

3.4.5. PRAC outcome

During the October 2023 PRAC meeting, the PRAC supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report. The PRAC also supported the comments made in the PRAC AR on the list of safety concerns. In conclusion, the RMP for GeGant in the proposed indication could be considered acceptable provided that an update to RMP version 0.3 and satisfactory responses to the questions detailed in the joint CHMP-PRAC D180 List of outstanding issues are submitted.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.3 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 7.4.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The applicant/Proposed Future MAH has submitted a signed Summary of the applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File

fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

3.5.2. 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.

4. Significance/non-conformity of paediatric studies

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic context

5.1.1. Disease or condition

The subject of this centralised application is $^{68}Ge/^{68}Ga$-generator (proposed name: GeGant 1-4 GBq, radionuclide generator), a device that produces an eluate containing the active substance gallium (^{68}Ga) chloride ($^{68}GaCl_3$). $^{68}GaCl_3$ is a precursor, that is used for an *in-vitro* radiolabelling of specific carrier molecules, which are subsequently utilized in PET diagnostics.

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

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

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

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

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

5.1.2. Available therapies and unmet medical need

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

- In 2014, marketing authorisation has been granted in the EU for the $^{68}Ge/^{68}Ga$-generator GalliaPharm by Eckert & Ziegler Radiopharma GmbH (Berlin, Germany; DK/H/2294/001/DC; authorized in: AT, BE, CZ, DK, FI, FR, DE, ES, IE, IT, LV, NL, NO, PL, SE, SK).

- GalliAd, 0.74-1.85 GBq, radionuclide generator, IRE-Elit, Belgium has been authorised via a decentralised procedure (DK/H/2690/001/DC) in AT, BE, DE, DK, ES, FI, FR, IT, LU, NL, NO, and SE in 2018.

Further, in 2016 DOTATOC (edotreotide) was authorised with the brand name SomaKit TOC (Marketing authorisation holder: Advanced Accelerator Applications, France) via the centralised procedure (EMEA/H/C/004140) for radiolabelling with gallium (^{68}Ga) chloride solution and subsequent use for PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.

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

5.1.3. Main clinical studies

Not applicable

5.2. Favourable effects

GeGant is intended to provide a consistent supply of a high quality precursor containing $^{68}GaCl_3$, that can be further used for labelling of specific carrier molecules and subsequent PET diagnostics various types of cancer. GeGant will allow gallium-labelling on-site for diagnostic imaging as required and without a need of a cyclotron facility. The product is to function for a period of up-to a year.

5.3. Uncertainties and limitations about favourable effects

Currently, a number of objections, including major, have been raised in relation with the quality of GeGant. There is an uncertainty in respect to the adequacy of the technical characteristics of the product and quality control at this point in time, which create an uncertainty in regards to the favourable effects of the product.

5.4. Unfavourable effects

The key potential unfavourable effect of the product may be radiation exposure of the hospital/clinic staff. This is a generic risk, that is well-acknowledged and regulated by national rules and regulations on radiation protection.

Further, potential theoretical unfavourable effects relevant for patients are poor labelling of carrier molecules (e.g., because of presence of elemental impurities), increased exposure to ^{68}Ge (because of ^{68}Ge breakthrough), excess radiation exposure of the patients (e.g., direct accidental use of the eluate). These unfavourable effects may emerge through inadequate handling and maintenance of the product, or its eluate.

5.5. Uncertainties and limitations about unfavourable effects

As unfavourable effects are dependent on the technical factors mainly (definition of specifications and controls, technical functioning, stability testing, etc.), and as these are still under evaluation, there is an uncertainty which unfavourable effects and to which extent may emerge.

5.6. Effects table

Not applicable

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

^{68}Ga based radiotracers play an increasingly important role in PET/CT diagnostics of oncological diseases. Their clinical utility has been shown in this application. Common source of ^{68}Ga in the absence of ^{68}Ge/^{68}Ga generator is a cyclotron facility, that is not always affordable for diagnostic sites. Given the short half-life of ^{68}Ga, its delivery from nearby cyclotron facility may be challenging. An on-site ^{68}Ge/^{68}Ga generator, such as GeGant, allows to obviate the need for a nearby cyclotron facility and development of highly efficient distribution networks. This is especially important in the countries where no other ^{68}Ge/^{68}Ga generators have been licenced.

Thus, GeGant opens the opportunity of gallium-labelling on-site as required and without a need of a cyclotron facility. The product remains functional for up-to 1 year. Overall, these favourable factors are regarded as highly important, as these contribute to optimization of cancer diagnostics.

The unfavourable effects of GeGant relevant for medical personnel can be regarded as generic effects which are common for such products and are basically covered through routine radiation protection procedures and rules. Additional potential risks to the patients are currently regarded as low, as these can be minimised through quality control procedures and adequate instructions and training of the medical personnel.

5.7.2. Balance of benefits and risks

The key benefit of the ^{68}Ge/^{68}Ga radionuclide generator under evaluation is its ability to provide a consistent supply of ^{68}Ga directly at the site of its subsequent utilization. Usual source of ^{68}Ga in the absence of ^{68}Ge/^{68}Ga generator is a cyclotron facility, that is often not affordable for diagnostic facilities due to high costs. Also, delivery of ^{68}Ga from nearby cyclotron may be burdened with logistic challenges given the short half-life of gallium.

GeGant allows to obviate the need for a nearby cyclotron facility and development of highly efficient distribution networks. This is especially important in the countries where no other ^{68}Ge/^{68}Ga generators have been licenced and in light of the increasing utilization of ^{68}Ga-PET in the diagnostics of oncological diseases.

Risks related with GeGant 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 detailed information. These are currently under clarification. If not adequate, a risk of e.g., serious infection, excess radiation exposure, or inadequate performance of ^{68}Ga-labelled products may be the consequence.

More relevant theoretical safety risk, not related to the quality of the product is the risk that $^{68}GaCl_3$ is applied by mistake directly in patients. To reflect the consequences of such inadvertent exposure, dosimetry table has been included in the product information and recommendations on patient management are being given. These are considered adequate.

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

Overall, as various types of radionuclide generator have been in use for decades and as the generator under evaluation will only be used by well-trained staff in a specialized facilities, probability of the above risks is considered as very low. However, major concerns have been raised from the side of quality and the GMP conformity of the manufacturers have not yet been assured. These may have an impact on the benefit-risks balance.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable

Conditional marketing authorisation

Not applicable

Marketing authorisation under exceptional circumstances

Not applicable

5.8. Conclusions

In quality major objections have been raised because GMP conformity of the manufacturers have not yet been assured. Therefore, final conclusion on overall B/R of GeGant radionuclide generator cannot be drawn and is, therefore, negative at this point in time. The proposed indication is accepted.

6. Biosimilarity assessment

Not applicable.