Risk management plan
GalliaPharm 1.11 – 3.70 GBq radionuclide generator

Active substance(s) (INN or common name):	Germanium (^{68}Ge) chloride, Gallium (^{68}Ga) chloride
Pharmaco-therapeutic group (ATC Code):	V09X
Name of Marketing Authorisation Holder or Applicant:	Eckert & Ziegler Radiopharma GmbH
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	GalliaPharm

Data lock point for this RMP 31/07/2022 Version number 01

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Germanium ([^{68}Ge] chloride, Gallium ([^{68}Ga] chloride
Pharmacotherapeutic group(s) (ATC Code)	V09X
Marketing Authorisation Holder	Eckert & Ziegler Radiopharma GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	GalliaPharm
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: GalliaPharm is a $^{68}Ge/^{68}Ga$ radionuclide generator. The eluate of the generator is never administered directly to humans. Instead, the generator is a source for gallium (^{68}Ga) chloride solution intended for *in vitro* radiolabelling of medicinal products, which are used for positron emission tomography (PET) imaging.
	Summary of mode of action: The mother nuclide ^{68}Ge decays to ^{68}Ga by electron capture with a half-life of 270.95 days. The daughter nuclide ^{68}Ga decays to stable ^{68}Zn by positron emission with a half-life of 67.71 min.
	The radionuclide generator is a system for the elution of gallium (^{68}Ga) chloride solution for radiolabelling. This solution is eluted from a titanium dioxide column on which the mother nuclide germanium (^{68}Ge), parent of gallium (^{68}Ga) is fixed.
eCTD link to the Product Information	The proposed summary of product characteristics, package leaflet inner, and outer labelling are included within Module 1.3.1 of the initial marketing authorization application.

Indication(s) in the EEA Proposed	This medicinal product is not intended for direct use in patients. The eluate from the generator (gallium (^{68}Ga) chloride solution) is indicated for *in vitro* radiolabelling of specific carrier molecules, developed and approved for radiolabelling with such solution, to be used for positron emission tomography (PET) imaging.
Dosage in the EEA Proposed	The quantity of the eluate (gallium (^{68}Ga) chloride solution) required for radiolabelling and the quantity of ^{68}Ga-radiolabelled medicinal product that is subsequently administered will depend on the medicinal product (carrier molecule) that is radiolabelled and its intended use. Refer to the summary of product characteristics/package leaflet of the particular medicinal product to be radiolabelled.
Pharmaceutical form(s) and strengths	Radionuclide generator, 1.11 – 3.70 GBq
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication: *in vitro* radiolabelling of specific carrier molecules, developed and approved for radiolabelling with such solution, to be used for PET imaging

Incidence: Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor and thus only incidence of the indications for the radiolabelled medicinal products are relevant.

Prevalence: Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor and thus only prevalence of the indications for the radiolabelled medicinal product are relevant.

Demographics of the population in the authorised age, gender, racial and/or ethnic origin and risk factors for the disease: Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients. Relevant population will be determined by the radiolabelled medicinal product.

The main existing treatment options: Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients. Available diagnostics/ treatment options will be determined by the radiolabelled medicinal product.

Natural history of the indicated condition in the population, including mortality and morbidity: Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor. Only radiolabelled medicinal products will have characterizable indications with regard to the population.

Important co-morbidities:

Not applicable as ^{68}Ga chloride is a radiopharmaceutical precursor and is not intended to be administered directly to the patients.

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

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity of ionic gallium, germanium, and zinc: The eluate produced from the generator, consisting of ^{68}Ga chloride in sterile ultrapure 0.1 mol/l hydrochloric acid is intended for the *in vitro* radiolabelling of medicinal products (carrier molecules) and will not be administered directly to patients. Carrier molecules for radiolabelling are always designed for efficient and stable radiolabelling with ^{68}Ga chloride. Otherwise, such carrier molecules cannot be used for PET. Complexing of ^{68}Ga with carrier molecules via their chelating moieties is therefore irreversible and no free ^{68}Ga is administered or released. A nonclinical distribution study was carried out in rats to obtain extrapolated human dosimetry data after direct, i.e., imitating an accidental, intravenous administration of ^{68}Ga chloride. The study showed that most ^{68}Ga is contained in the blood and urine with some uptake in the lungs, spleen, and bone. However, due to the short half-life of ^{68}Ga, with almost complete decay to inactive ^{68}Zn within 6 h, any exposure to gallium is very transient. The study also demonstrated that the breakthrough of < 0.001% ^{68}Ge (i.e., proportion of activity that is due to ^{68}Ge in the total activity of the eluate), specified for the generator, does not lead to ^{68}Ge accumulation in any particular organ. With regard to the element ^{68}Zn, the decay of 250 MBq ^{68}Ga (which is in the highest dose commonly used) produces only approximately 0.1 ng Zn. This amount is negligible, considering the maximum permitted Zn contamination in the eluate of < 10 µg/GBq according to the European Pharmacopeia (Ph. Eur.) monograph 2464 "Gallium (^{68}Ga) chloride solution for radiolabelling".	Overall, based on the known toxic effects of ionic gallium, germanium, and zinc in animals and on the dosimetry data of gallium and germanium obtained in rats, the generator can be considered safe to use with no toxicity to be expected from the amounts needed for diagnostic imaging. A potential safety concern with accidental direct eluate administration would however remain local tissue damage possible due to the highly acidic ultrapure 0.1 mol/l hydrochloric acid used as eluant, see details in Module SVII.
Safety pharmacology: Since ^{68}Ga chloride solution is not intended to be administered directly to the patient, no safety pharmacology testing was carried out by Eckert & Ziegler Radiopharma GmbH. However, a published scientific work investigated the effects of ^{68}Ga chloride in cardiac cells derived from 2-4 days old new-born rats. There was a slight and transient decrease in the beat rate after 15 min of exposure to ^{68}Ga chloride at	No pharmacodynamic effects are to be expected for the use of gallium (^{68}Ga) chloride solution due to quick decay of ^{68}Ga to zinc. Even with accidental direct injection of the eluate theoretically containing up to 3.70 GBq ^{68}Ga, the total amount of ^{68}Ga

Key Safety findings (from non- clinical studies)	Relevance to human usage
all concentrations tested (0.5, 2 and 8 mg/l of Ga^{3+}), but it was concluded that ^{68}Ga chloride might have a protective rather than a deleterious cardiac effect, based on an observed decrease in malondialdehyde production following oxidative stress, an increase in glycogen stores in normal oxygen concentrations together with maintenance of ATP concentrations, and the lack of any chronotropic effects. Other results of the study with hearts from rats treated for 3 wks with ^{68}Ga chloride at 50 mg/kg/day showed no abnormalities, but contractile abnormalities were observed in animals treated with 200 mg/kg/day. These concentrations and doses greatly exceed any potential exposure with ^{68}Ga from the generator, even in the case of massive overdose.	would not exceed 2.4 ng, which is well below the mg/kg doses at which secondary pharmacodynamic effects could be expected based on the literature.
Radiation effects: In the organ distribution study in rats carried out by the applicant, the highest exposure, apart from that seen in the blood/plasma and urine, was observed in the liver, lung, spleen, and bones. In female rats, relatively high activities were also seen in the ovaries and uterus, but the exposure was still low in absolute terms (1.1-1.3 % of the injected amount per gram, 1 h after injection). The impact of the dosimetry from the ^{68}Ge breakthrough after injection of gallium (^{68}Ga) chloride was thus negligible in rats, with no retention seen in any particular organ.	The animal data showed that there is no radiation safety concern to be expected after accidental injection of ^{68}Ga chloride from the generator. For the intended use of the generator eluate, the pharmacokinetics of radiolabelled medicinal products will be rather of clinical importance than the pharmacokinetics of free ^{68}Ga.

Note: for detailed references to the literature and dosimetry study report, see CTD module 2.4.

Part II: Module SIII - Clinical trial exposure

Gallium (^{68}Ga) chloride is not directly administered to patients, and therefore no clinical studies can be carried out with the active substance of the generator alone.

[redacted]

Part II: Module SIV - Populations not studied in clinical trials

Publications on the use of any ^{68}Ga-radiolabelled compounds in the paediatric population are very scarce. Since ^{68}Ga chloride is not directly administered to patients, a product-specific PIP-waiver was granted.

Part II: Module SV - Post-authorisation experience

The generator from Eckert & Ziegler Radiopharma GmbH is currently authorized as medicinal product under the trade name GalliaPharm for the *in vitro* radiolabelling of specific carrier molecules in 16 European Union/European Economic Area countries (via the decentralised authorization procedure [DCP] DK/H/2294), United Kingdom, Canada, and Brazil (marketing authorization holder is a local company). Furthermore, GalliaPharm is registered as an active pharmaceutical ingredient in the United States.

A limited number of safety reports has been collected for medicinal products radiolabelled with the eluate of GalliaPharm in the scope of routine pharmacovigilance activities for the current marketing authorizations of the generator. All reports are considered as rather specific for particular radiolabelled medicinal products, and no safety concern directly related to the generator or its eluate has been detected so far.

As GalliaPharm (i.e., its eluate) is only used for *in vitro* radiolabelling of specific carrier molecules which have been specifically developed and authorised for radiolabelling with this radionuclide to be used for diagnostic imaging with PET, a discussion on the on-label and off-label use for certain medical conditions is not of relevance for this product.

SV.1 Post-authorisation exposure

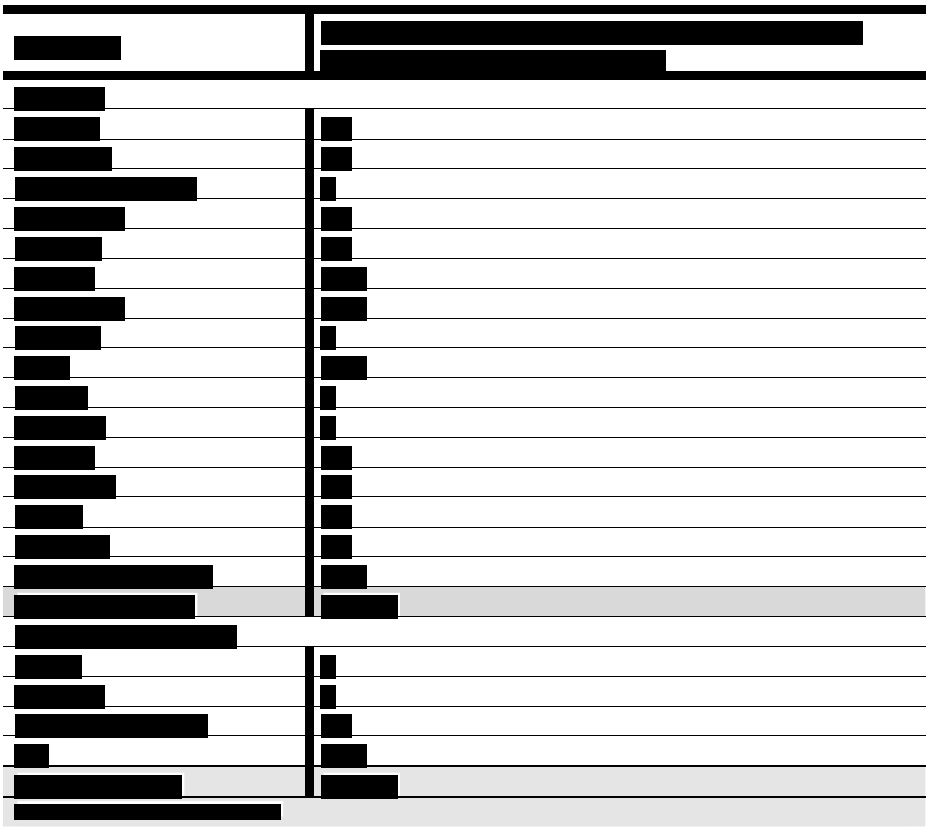
SV.1.1 Method used to calculate exposure

Since GalliaPharm is not intended for direct administration to patients and is used only to obtain the eluate gallium (^{68}Ga) chloride solution for *in vitro* radiolabelling, the exact number of patients which were exposed to diagnostic procedures with substances radiolabelled by the eluate is not available to the applicant.

To nevertheless provide a rough estimate of exposed patients, following assumptions are taken into consideration: shelf-life of 1 year, 230 working days, 4–7 hours waiting period between the eluates (according to the SmPC) leading to 1–2 eluates daily (1.5 eluates as approximation) and 1 patient per eluate. Based on this assumptions, 345 patients can be presumably treated with each generator.

SV.1.2 Exposure

According to the sales volumes, a total of 1,643 GalliaPharm radionuclide generators were sold since the first national marketing authorisation in September 2014 until the DLP of this RMP. In accordance with the calculation method described above, this would correspond to a total exposure of 566,835 patients.



No data are available regarding the use of GalliaPharm in special patient populations. Therefore, the patient exposure for these groups of patients cannot be estimated.

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

As the distribution of this radioactive medicinal product is strictly regulated and it may be purchased only by the authorized medical facilities, where it is also handled exclusively by trained and duly authorized personnel, there is no feasible risk of misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

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

1) Accidental direct use in patients

Although numerous warnings are included in SmPC and labelling to prevent accidental direct use in humans, occurrence of such events due to human error cannot be ruled out completely.

There is a potential for adverse reactions upon the direct use of the eluate as it may lead to venous irritation and tissue necrosis due to low hydrochloric acid pH in the eluate (CTD module 2.4.4.8). No toxicity has been described for free ^{68}Ga at the quantities contained in the eluate (CTD modules 2.4.3.4, 2.4.4.2, and 2.6). Hence, no toxic effects are to be expected from free ^{68}Ga after an inadvertent administration of the eluate. The administered free ^{68}Ga decays almost completely to inactive ^{68}Zn within a short time (97 % are decayed in 6 hours). During this time, ^{68}Ga is mainly concentrated in the blood/plasma (likely bound to transferrin) and in the urine. The patient should be hydrated to increase the excretion of the ^{68}Ga. Forced diuresis as well as frequent bladder voiding are recommended.

Information regarding this risk, in particular in form of instructions, warnings and a contraindication are included in the SmPC. In addition, radiopharmaceuticals are used only by nuclear medicine specialists who are experienced and qualified by training in appropriate employment of such products. Therefore, human errors leading to the direct administration of the eluate are considered very improbable. In line with this, since the first decentralized marketing authorization for GalliaPharm in September 2014 and until the DLP of this RMP, the applicant received no reports on direct use of the eluate in patients. Hence, no further risk minimization activities are currently warranted for this risk, and it will not be listed as a potential important risk in this RMP. Nevertheless, it will be further monitored and discussed as a potential safety concern in periodic safety update reports (PSURs) for GalliaPharm.

2) Sterility of the eluate

Based on the half-life of ^{68}Ge, the ^{68}Ge/^{68}Ga-generator has a potential useful life of 18 months. During this time, the sterility of the eluate has to be maintained. The generator is manufactured under aseptic conditions and the environment inside the generator - acidic pH (0.5 -2) and gamma radiation - are not favourable for the growth of microorganisms. With the use of sterile ultrapure 0.1 mol/l hydrochloric acid, the acidic pH is maintained throughout the shelf-life of the generator. The antimicrobial effect was verified by a bacterial challenge test, which has proven that the survival of microorganisms inside the generator column is highly unlikely. Moreover, the endotoxin levels were thereby found to be reliably below the detection limit, probably due to depyrogenation potential of the hydrochloric acid. In line with this, in all stability studies performed so far under routine conditions of use (for up to 18 months) with regular testing of eluates for sterility and endotoxins, no microbial contamination (non-sterility) or elevated endotoxin levels have ever been detected in the eluates.

The proposed SmPC clearly states that aseptic working techniques must be maintained during the assembly process, during the exchange of the container with sterile ultrapure 0.1 mol/l hydrochloric acid, and while eluting the generator. In general, only authorised persons in designated clinical settings shall receive, use, and administer radiopharmaceuticals. No reports on microbial

contamination or non-sterility of generator eluates have been received since 2014 when the first national marketing authorization approval of the DCP was issued for GalliaPharm.

All in all, it is highly unlikely that the eluate sterility can be compromised during the routine, SmPC-compliant use of the radionuclide generator. Therefore, this risk is currently not considered as important and will not be listed as such in this RMP. Nevertheless, it will be further monitored and discussed as a potential safety concern in PSURs for GalliaPharm.

3) Presence of elemental impurities in the eluate

Toxicology from elemental impurities is a common safety concern for medicinal products. However, in case of GalliaPharm, any considerable levels of elemental impurities are avoided by the use of highly pure materials for the manufacturing (including the eluent solution) and by the nature of the manufacturing process itself. The only elemental impurities specified in the Ph. Eur. monograph 2464 "Gallium (^{68}Ga) chloride solution for radiolabelling", zinc and iron, are controlled for release of each radionuclide generator assuring adherence to the monograph limits for these metals. In conclusion, the risk of elemental impurities is not considered important for GalliaPharm and does not require any surveillance or risk minimization measures.

4) Use of the incorrect solution to produce the eluate

GalliaPharm is eluted with sterile ultrapure 0.1 mol/l hydrochloric acid supplied with the generator. Section 12 of the SmPC contains a statement that only sterile ultrapure 0.1 mol/l hydrochloric acid provided by the marketing authorization holder should be used for elutions. At least one container is delivered with each GalliaPharm and more containers can be purchased from the marketing authorization holder as consumable. Each container with the eluent is clearly labelled as solution for elution for the radionuclide generator and the SmPC contains detailed instructions how the container should be connected to the generator and exchanged. This information makes accidental coupling with a wrong container highly unlikely, especially as the GalliaPharm is used only by well-trained and authorized nuclear medicine specialists. Moreover, once connected, a hydrochloric acid container remains attached to the generator until it is empty, which further reduces the probability of using a wrong eluent by accident.

Another aspect to be pointed out is that the sterile ultrapure 0.1 mol/l hydrochloric acid is delivered in polypropylene bags or bottles, which are unique, rather uncommon packaging materials for such solutions and thereby contribute to avoidance of mix-ups with other comparable (i.e., hydrochloric acid-containing) solutions. Although similar containers are often used as packaging material for medically utilized, abundantly available in hospitals liquids like, for instance, sodium chloride for infusions, such liquids are not capable to elute ^{68}Ga from a GalliaPharm. In this case, missing activity (missing ^{68}Ga) would be quickly noticed during a quality control step of the radiolabelling procedure, so that a potential yet very unlikely mix-up involving that kind of wrong eluents would have no clinical consequences.

Taken together, the risk of using a wrong eluent solution is not considered to require specific surveillance or risk minimization activities and will not be listed as important in this RMP.

5) Occupational and inadvertent exposure to radiation

All radiopharmaceuticals pose a potential danger of inadvertent, in particular occupational, exposure to radioactivity. In case of GalliaPharm, the inadvertent radiation from the radionuclide generator itself is prevented by its built-in appropriately designed and reliable shielding. Moreover, specialized medical facilities which work with such products usually have additional radiation-protective measures in place in accordance with their inter-institutional as well as national regulations. The SmPC of GalliaPharm (provided with each generator) contains instructions for use that should assure appropriate handling of the generator and thereby minimize the risk of any events causing inadvertent exposure to radiation for the involved personnel. Since generally only well-trained, authorized nuclear medicine specialists operate GalliaPharm, including preparation and administration to patients of ^{68}Ga-labelled radiopharmaceuticals, any unintended radiation incidents are considered highly unlikely to occur.

Possible occupational exposure to the radiation of ^{68}Ga eluted from GalliaPharm generator will always depend on the protective measures routinely applied at a medical facility and on the specific handling procedure of each carrier molecule to be radiolabelled. Specific protection measures can be also imposed by the manufacturers of the carrier molecules.

Given the above, short half-life of ^{68}Ga and predominantly single-dose administration of the low activities of the currently known ^{68}Ga-labelled radiopharmaceuticals, the overall risk due to inadvertent or occupational exposure to radiation is considered negligible and is not included as important in this RMP.

6) Carcinogenicity and hereditary effects

Carcinogenic and hereditary toxicity induced by radioactivity is a potential risk associated with the use of radiopharmaceuticals. The information on this risk is included in the section 4.8 of the GalliaPharm SmPC, whereas section 4.4 contains a precaution regarding individual benefit/risk justification urging to use the lowest reasonable radioactivity dose for diagnostic procedures. However, as the eluate of GalliaPharm is not administered to patients directly, carcinogenic, mutagenic, or genotoxic effects are always dependent on the particular carrier molecule to be radiolabelled and its intended use considering that the radioactivity dose, the distribution, excretion, and retention of the radioactivity in the body are specific for each radiolabelled pharmaceutical. Therefore, the risk of such adverse effects can be established, and assessed from the perspective of the required mitigation measures only for kits for radiolabelling (by their developers), but not for GalliaPharm itself. Taking into account also the short half-life of ^{68}Ga and that the currently known ^{68}Ga-labelled radiopharmaceuticals are only administered as single doses with rather low activities, this risk is not regarded as an important safety concern for GalliaPharm in the scope of this RMP.

7) Stability of the chelates

^{68}Ga cannot be covalently bound to ligands like peptides used as targeting carrier molecules for PET procedures. Therefore, such carrier molecules are equipped with so-called bifunctional chelators allowing stable coupling of ^{68}Ga (i.e., radiolabelling) immediately before the labelled radiopharmaceutical is administered to patients. The ^{68}Ga-chelator complexes must have sufficiently high, durable *in vivo* and *in vitro* stability implying high thermodynamic stability and kinetic inertness, adequate resistance to hydrolysis as well as competitive resistance to transferrin, which would otherwise seize ^{68}Ga from the chelate [1, 2]. The commonly used, well-studied bifunctional ^{68}Ga chelators, the macrocyclic chelator 1,4,7,10-tetraazacyclododecane-N,N`,N",N"`-tetraacetic acid (DOTA; e.g., used in the approved in the EU/EEA product "SomaKIT TOC") as well as the acyclic

chelator N,N'-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid (HBED-CC; e.g., used in the approved in the EU/EEA "LOCAMETZ") form especially stable complexes with ^{68}Ga and other radioligands [1], [2], [3], [4]. Of note, any chelators not capable to provide sufficient radiolabelling stability would likely strongly hamper PET imaging efficiency of the concerned tracer, which per se prevents utilization of such chelators in clinical practice. Moreover, the companies developing kits for radiolabelling with ^{68}Ga have to assure the reliability of chelation for their carrier molecules. All in all, chelate stability is not considered as an important risk for GalliaPharm and therefore is not included as an important safety concern for GalliaPharm in the scope of this RMP.

8) Toxicity of Zinc (generated by decay of ^{68}Ga)

Zinc (^{68}Zn) is the decay product of ^{68}Ga. Hence, patients treated with ^{68}Ga-labelled radiopharmaceuticals are exposed to this heavy metal. However, the decay of 0.25 GBq ^{68}Ga (which is roughly the highest commonly used dose) produces only approx. 0.1 ng zinc and even the theoretical maximum of 3.7 GBq which could be obtained with the radionuclide generator of the highest strength would yield only approx. 1.5 ng. These values (i.e., 0.4 ng/GBq) are much lower than the limit established for zinc in the Ph. Eur. monograph 2464 "Gallium (^{68}Ga) chloride solution for radiolabelling", which is 10 µg/GBq. Notably, the dietary recommendations for zinc intake are still several-fold higher (approx. 6 – 13 mg/day) [5] and therefore substantially outweigh possible zinc amounts arising from ^{68}Ga. Thus, zinc toxicity is not considered as important risk for GalliaPharm and does not require any specific pharmacovigilance or risk minimization activities.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Following important potential risks are included in the list of safety concerns:

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

This risk has been defined as potential in the RMP of this medicinal product currently authorized via the DCP DK/H/2294 (stated there as "Elevated ^{68}Ge-breakthrough"). It is based on considerations arising from the specific properties and specific modalities of the use of the generator. Even though the pharmacovigilance activities of the applicant have not revealed any incidents confirming this risk so far (with already applied routine risk minimisation measures), it is included in this new RMP for the centralized procedure due to a potential impact on the benefit-risk profile of the product.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

None.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risks:

There are no important identified risks.

Important Potential Risks:

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

Potential mechanisms:

A small amount of ^{68}Ge is washed out from the column with each generator elution, which is called ^{68}Ge breakthrough. It is expressed as percentage of radioactivity from ^{68}Ge in the total radioactivity eluted from the column, corrected for decay. ^{68}Ge breakthrough in eluates of GalliaPharm is not more than 0.001 % of the eluted radioactivity and thus, is in line with the requirement of the Ph. Eur. monograph 2494 specifying this maximum breakthrough level considered as safe. However, the breakthrough can theoretically increase above 0.001 % if the generator is not eluted for several days.

Evidence source(s) and strength of evidence:

Rare quality complaints reporting elevated ^{68}Ge breakthrough levels in eluates received so far were either not confirmed during the complaint investigation or were a result of a handling error by the complaining user (i.e., with setting up the generator or determination of breakthrough) and could be readily resolved. Hence, no confirmed reports of elevated ^{68}Ge breakthrough have ever been received for regular, routine use of generators. The applicant has also not received to date any adverse event reports pointing to the elevated ^{68}Ge breakthrough as their root cause. Nevertheless, there is a clear potential for radiation-induced adverse events in a hypothetical case of excessive ^{68}Ge amount in an eluate, given the relatively long half-life of this radionuclide (270.95 days), which justifies special attention to this risk.

Characterisation of the risk:

Expectedly, due to adherence to Ph. Eur. recommendation, rat data from the dosimetry study performed by the applicant with direct injection of the eluate indicated no safety concerns with specified breakthrough limit of 0.001 % (CTD modules 2.4.3.4, 2.4.4.2, 2.6.4, 2.6.5, and [6]). Notably, the maximum human effective radiation dose from this ^{68}Ge level is 2.500-3.000 times lower than the permitted effective doses ranges (starting at 0.1 mSv) that are currently recommended by the International Commission on Radiological Protection for use in healthy volunteers for biomedical research [7]. No significant ^{68}Ge accumulation was observed in any organ including bone marrow.

In a different dosimetry study in rats, in which $^{68}GeCl_4$ was administered intravenously, ^{68}Ge elimination rate was shown to be fast, with a half-life of 36±5 min and no selective bone uptake [6].

Higher ^{68}Ge content in the eluate and therefore higher resulting doses of ionizing radiation could, however, bear a potential risk for adverse reactions in patients. ^{68}Ge breakthrough can exceed the limit of 0.001 % only if the generator is not eluted for several days. Hence, if the generator has not been used for 96 hours or more, it should be pre-eluted with 10 ml of sterile ultrapure 0.1 mol/l hydrochloric acid at least 7 hours prior to the intended use (the time between the pre-elution and the elution for radiolabelling can be reduced if the intended radiolabelling procedure does not require maximum achievable eluate activity). When this instruction is followed, the breakthrough constantly remains below 0.001 % in eluates obtained for radiolabelling during the entire shelf-life of the generator. As the proposed SmPC clearly states this pre-elution requirement, the risk of elevated ^{68}Ge levels in eluates is estimated as very low.

Although no confirmed cases of elevated ^{68}Ge breakthrough with regular use of generators (or potentially related adverse events) have been reported to the applicant to date for the nationally authorised GalliaPharm, the applicant does not possess sufficient information to completely refute

this potential risk / safety concern, hence, it shall be inherited for the centralized marketing authorization of the product.

Risk factors and risk groups:

The risk is not linked to a special risk group and no promoting risk factors exist.

Preventability:

Radiopharmaceuticals are used only by nuclear medicine specialists who are qualified by training and experience. To keep the ^{68}Ge breakthrough low, the generator should be pre-eluted (at least 7 hours prior to the intended use requiring maximum achievable eluate activity) if not used for 96 hours or more. When this instruction is followed, the ^{68}Ge breakthrough should constantly remain below 0.001 % for the entire generator shelf-life of 18 months.

Impact on the risk-benefit balance of the product:

Potential adverse reactions would be related to the higher than necessary radiation exposure of the patients and would be therefore possibly of relevance for the risk-benefit balance of the product. However, based on the current knowledge about the product and already applied routine risk minimisation measures, this perspective is considered highly unlikely.

Public health impact:

No adverse reaction attributable to this risk have been received so far. Hence, no data for estimation of public health impact is available. However, this also indicates that no substantial impact is to be expected in the future.

SVII.3.2 Presentation of the missing information

There are no missing information topics.

Part II: Module SVIII - Summary of the safety concerns

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 undetected elevated ^{68}Ge-breakthrough)
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable. There are currently no planned or active follow-up questionnaires for safety concerns.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable. There are currently no planned or ongoing additional pharmacovigilance activities.

III.3 Summary Table of additional pharmacovigilance activities

Not applicable. There are currently no planned or ongoing additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorization efficacy studies planned with the GalliaPharm generator.

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

V.1 Routine Risk Minimisation Measures

Routine risk minimization measures previously established for nationally authorized GalliaPharm shall be maintained as specified below.

Table Part V.1: Description of routine risk minimisation measures by safety concern

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

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of 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 undetected elevated ^{68}Ge-breakthrough)	**Routine risk minimisation measures:** • Extensive information and instructions in SmPC section 12. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for GalliaPharm 1.11 – 3.70 GBq radionuclide generator

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

GalliaPharm's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how GalliaPharm should be used.

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

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

I. The medicine and what it is used for

GalliaPharm is authorised for *in vitro* radiolabelling of specific carrier molecules, which have been specifically developed and approved for radiolabelling with its eluate (gallium (^{68}Ga) chloride solution), to be used for diagnostic imaging with positron emission tomography (PET). This medicinal product is not intended for direct use in patients. Please refer to the information of the medicinal product that is to be radiolabelled with gallium (^{68}Ga) chloride.

The radionuclide generator contains germanium (^{68}Ge) as the mother nuclide which decays to the daughter nuclide gallium (^{68}Ga). Gallium (^{68}Ga) is eluted with sterile ultrapure 0.1 mol/l hydrochloric acid to obtain gallium (^{68}Ga) chloride applied for *in vitro* radiolabelling.

Further information about the evaluation of GalliaPharm’s benefits can be found in GalliaPharm’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/galliapharm)

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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

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

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)
Missing information	None

II.B Summary of important risks

Important potential risk: **• Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)**	
Evidence for linking the risk to the medicine	No confirmed reports of elevated ^{68}Ge breakthrough have ever been received for regular, routine use of GalliaPharm generators since 2014 when the first national marketing authorization approval for it was issued. No adverse event reports pointing to elevated breakthrough as their root cause were received either. Nevertheless, there is a clear potential for radiation-induced adverse events in a hypothetical 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-brekthrough in eluates (over the permitted level of 0.001 %), GalliaPharm should be pre-eluted 7 hours (or less if appropriate) prior to eluting for radiolabelling if it has not been used for a period of 96 hours. It is also recommended to test eluates for ^{68}Ge-brekthrough on a regular basis.

Risk factors and risk groups	The risk is not linked to a special risk group and no promoting risk factors exist.
Risk minimisation measures	Routine risk minimisation measures: • Extensive information and instructions in SmPC section 12 Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 Other studies in post-authorisation development plan

There are no studies required for GalliaPharm.

Part VII: Annexes

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable. There are no specific adverse event follow-up forms.

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable. This medicinal product has no additional risk minimisation measures.