EU Risk Management Plan

for

GalenVita 0.74 –3.70 GBq, radionuclide generator

(*Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride)*

RMP version to be assessed as part of this application:

RMP Version number: 0.5

Data lock point for this RMP: 09-SEP-2024

Date of final sign-off: 06-NOV-2025

Rationale for submitting an updated RMP: Initial version for MA submission

Summary of significant changes in this RMP:

- Update of the product strength

Other RMP versions under evaluation: None

QPPV name: Dr. Rabea Herz, SCRATCH Pharmacovigilance GmbH & Co. KG

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Germanium (^{68}Ge) (mother nuclide) Gallium (^{68}Ga) (daughter nuclide)
Pharmacotherapeutic group(s) (ATC Code)	Other diagnostic radiopharmaceuticals (V09X)
Marketing Authorisation Holder	Curium Romania SRL
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	GalenVita 0.74 –3.70 GBq, radionuclide generator
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Radiopharmaceutical
	Summary of mode of action: The pharmacodynamic properties of ^{68}Ga-labelled radiopharmaceutical prepared by radiolabelling with the generator eluate prior to administration will be dependent on the nature of the carrier molecule to be labelled.
	Important information about its composition: The radionuclide generator contains germanium (^{68}Ge) as mother nuclide which decays to the daughter nuclide gallium (^{68}Ga). The germanium (^{68}Ge) used for the production of the *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator is no carrier added. The total radioactivity due to germanium (^{68}Ge) and gamma-ray-emitting impurities is not more than 0.001%. The *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride* 0.74 –3.70 GBq radionuclide generator is a system for the elution of gallium (^{68}Ga) chloride solution for radiolabelling in accordance with Ph. Eur. 2464. This solution is eluted from a column on which the mother nuclide germanium (^{68}Ge), parent of gallium (^{68}Ga), is fixed. The system is shielded. 4 ml of the eluate from the radionuclide generator with highest strength (3.70 GBq) contains a potential maximum of 3700 MBq of ^{68}Ga and 37.0 kBq of ^{68}Ge (0.001 % breakthrough in the eluate). This corresponds to 2.4 ng of gallium and 0.14 ng of germanium. The quantity of gallium (^{68}Ga) chloride solution for radiolabelling Ph. Eur. that may be eluted from the radionuclide generator is dependent on the quantity of germanium (^{68}Ge) present on the date/time of elution, the volume of eluent used (typically 4 ml) and the lapsed time since the previous elution. If mother and daughter nuclides are in equilibrium, more than 60 % of the present gallium (^{68}Ga) activity can be eluted.
Hyperlink to the Product Information	eCTD Module 1.3.1

Indication(s) in the EEA	Current: Not applicable
	Proposed (if applicable): 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 specific carrier molecules developed and approved for radiolabelling with such solution to be used for positron emission tomography (PET) imaging.
Dosage in the EEA	Current: Not applicable.
	Proposed (if applicable): The quantity of the eluate gallium (^{68}Ga) chloride solution required for radiolabelling and the quantity of ^{68}Ga-labelled medicinal product that is subsequently administered will depend on the medicinal product that is radiolabelled and its intended use.
Pharmaceutical form(s) and strengths	Current (if applicable): Not applicable.
	Proposed (if applicable): 0.74 –3.70 GBq radionuclide generator
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Not applicable, as this RMP is related to an Article 10(a) of Directive 2001/83/EC application for *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator.

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

Not applicable, as this RMP is related to an Article 10(a) of Directive 2001/83/EC application for *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator.

Part II: Module SIII - Clinical trial exposure

Not applicable, as this RMP is related to an Article 10(a) of Directive 2001/83/EC application for *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator.

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

Not applicable, as this RMP is related to an Article 10(a) of Directive 2001/83/EC application for *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator.

Part II: Module SV – Post-authorisation experience

Not applicable, as this RMP is related to an Article 10(a) of Directive 2001/83/EC application for *Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride*, 0.74 –3.70 GBq, radionuclide generator.

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

Potential for misuse for illegal purposes

Germanium (^{68}Ge) chloride and Gallium (^{68}Ga) chloride do not have any potential for misuse for illegal purposes, e.g. as a recreational drug or to facilitate assault. Therefore, this risk is not considered in the risk minimisation plan.

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

GalenVita 0.74 –3.70 GBq, radionuclide generator is not intended for 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. Direct use of the eluate may lead to venous irritation or tissue necrosis in case of paravenous injection due to low hydrochloric

acid pH in the eluate. No toxic effects are to be expected from the free ^{68}Ga after an inadvertent administration of the eluate. The administered free ^{68}Ga decays almost completely to stable ^{68}Zn within a short time (97 % are decayed in 6 hours). During this time, ^{68}Ga is mainly concentrated in the blood/plasma (bound to transferrin) and in the urine.

Warnings regarding this risk are clearly stated in the SmPC in several sections (4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.9 Overdose). Additional advice is given in case direct use has nevertheless occurred. The catheter or affected area should be irrigated with isotonic saline solution. Additionally, the patient should be hydrated to increase the excretion of the ^{68}Ga and forced diuresis as well as frequent bladder voiding is recommended (SmPC 4.9 Overdose).

Finally, 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. Hence, no further risk minimisation 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) GalenVita 0.74 –3.70 GBq, radionuclide generator.

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 1 year from calibration date. 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 and gamma radiation - are not favourable for the growth of microorganisms. Therefore, survival of microorganisms inside the generator column is highly unlikely. The ^{68}Ge/^{68}Ga-generator is supplied with 250 ml of sterile 0.1 mol/l hydrochloric acid.

The proposed SmPC clearly states that aseptic working techniques must be maintained during the assembly process, during the exchange of the container with hydrochloric acid, and while eluting the generator. In general, only authorised persons in designated clinical settings shall receive, use, and administer radiopharmaceuticals.

In summary, SmPC-compliant handling and use of the radionuclide generator should make it very unlikely that the sterility of the eluate is compromised. Furthermore, the product will be used by trained, qualified staff, only, who is experienced in the handling of sterile products. 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 an discussed as a potential safety concern in PSURs for GalenVita 0.74 –3.70 GBq, radionuclide generator.

3) Presence of elemental impurities in the eluate

Adverse toxicological effects due to elemental impurities is a common safety concern for medicinal products. However, in case of GalenVita 0.74 –3.70 GBq, radionuclide generator, 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 SmPC, which is zinc, is controlled for release of each radionuclide generator assuring adherence to the SmPC limits for these metals. In conclusion, the risk of elemental impurities is not considered important for GalenVita 0.74 –3.70 GBq, radionuclide generator and does not require any surveillance or risk minimisation measures.

4) Use of the incorrect solution to produce the eluate

GalenVita 0.74 –3.70 GBq, radionuclide generator is eluted with sterile 0.1 mol/l hydrochloric acid supplied with the generator. Section 12 of the SmPC clearly instructs on the elution process. At least one container is delivered with each radionuclide generator and more containers can be purchased from the applicant 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 GalenVita 0.74 –3.70 GBq, radionuclide generator is used only by well-trained

and authorised 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 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 utilised, abundantly available in hospitals liquids like, for instance, sodium chloride for infusions, such liquids are not capable to elute ^{68}Ga from the radionuclide generator. 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 GalenVita 0.74 –3.70 GBq, radionuclide generator, the inadvertent radiation from the radionuclide generator itself is prevented by its built-in appropriately designed and reliable shielding. Moreover, specialised 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 GalenVita 0.74 –3.70 GBq, radionuclide generator (provided with each generator) addresses the need of appropriate shielding in several sections and 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, authorised nuclear medicine specialists operate the radionuclide generator, 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 GalenVita 0.74 –3.70 GBq, radionuclide 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 mentioned, 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 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 GalenVita 0.74 –3.70 GBq, radionuclide generator 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 GalenVita 0.74 –3.70 GBq, radionuclide generator 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 GalenVita 0.74 –3.70 GBq, radionuclide generator 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. 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 EU/EEA-approved 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 EU/EEA-approved product “LOCAMETZ”) form especially stable complexes with ^{68}Ga and other radioligands. 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 an important risk and therefore is not included as an important safety concern for GalenVita 0.74 –3.70 GBq, radionuclide generator 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. 1.48 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) and therefore substantially outweigh possible zinc amounts arising from ^{68}Ga. Thus, zinc toxicity is not considered as important risk and does not require any specific pharmacovigilance or risk minimization activities.

9) Hypersensitivity to any excipient of the Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride radionuclide generator

Hypersensitivity to the active substance or to any of the excipients is a contraindication and as such adequately addressed in section 4.3 of the SmPC of the product. The product will be handled in a medical setting only. Thus, healthcare professionals will be present during administration of the product as well as some time after the administration (e.g. during PET scan). Hypersensitivity symptoms are well-manageable in a medical environment and the healthcare professionals are qualified to intervene in case (serious) hypersensitivity syndroms are occurring in the patient. This risk is therefore not considered an important safety concern in the scope of this RMP section.

10)Accidental exposure during pregnancy and breastfeeding

Special precautions and additional measures during pregnancy and breastfeeding are clearly addressed in SmPC section 4.6 and are therefore not considered an important safety concern in the scope of this RMP section.

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 also been defined as important potential risk in the RMP of other authorised products with the same active ingredients. 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 (taking routine risk minimisation measures into account), it is included in this RMP due to a potential impact on the benefit-risk profile of the product. However, also for the above mentioned authorised products with the same ingredients the risk has never been promoted to identified, confirming the status as potential risk.

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 mechanism:

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 GalenVita 0.74 –3.70 GBq, radionuclide generator 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:

So far, the applicant is not aware of any quality issues regarding elevated ^{68}Ge breakthrough levels in eluates of the Germanium (^{68}Ge) chloride / Gallium (^{68}Ga) chloride radionuclide generator. The applicant has also not received to date any adverse events reports pointing to elevated ^{68}Ge breakthrough as 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, published data from a dosimetry study in rats with direct injection of the eluate indicated no safety concerns with specified breakthrough limit of 0.001 % (Aghanejad et al. 2015[1]). 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. 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 (Aghanejad et al. 2015[1]). 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

[1] Aghanejad A, Jalilian AR, Ardaneh K, Bolourinovin F, Yousefnia H, Samani AB. Preparation and Quality Control of (68)Ga-Citrate for PET Applications. Asia Ocean J Nucl Med Biol. 2015 Summer;3(2):99-106. PMID: 27408889; PMCID: PMC4937647.

for 72 hours or more, it should be pre-eluted with 10 ml of sterile 0.1 mol/l hydrochloric acid (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) are known, the applicant does not possess sufficient information to completely refute this potential risk / safety concern, hence, it is considered a safety concern 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 (with one discarded elution) if not used for 72 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 1 year.

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

The applicant is not aware of any adverse reaction attributable to this risk. 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

Not applicable. There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed.

The applicant did not identify outstanding needs for pharmacovigilance investigations at the time of their approval. There are no safety studies imposed as condition of the marketing authorisation (category 1), as specific obligations in the context of a marketing authorisation under exceptional circumstances or conditional marketing authorisation (category 2), or requested by the competent authority (category 3).

III.3 Summary table of additional pharmacovigilance activities

Not applicable. There are no on-going or planned categories 1-3 safety studies included in the Pharmacovigilance Plan.

Part IV: Plans for post-authorisation efficacy studies

Not applicable. There are no planned or on-going imposed post-authorisation efficacy studies.

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

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine risk minimisation measures

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

Safety concern	**Routine risk minimisation measures**
Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)	Routine risk communication: *Proposed text in SmPC* • Detailed instructions in section 12. • Information/warning in section 12: *Routine risk minimisation activities recommending specific clinical measures to address the risk:* "^{68}Ge breakthrough A small amount of ^{68}Ge is washed from the radionuclide generator column with each elution. ^{68}Ge breakthrough is expressed as a percentage of total ^{68}Ga activity eluted from the column, corrected for decay, and does not exceed 0.001 % of the eluted ^{68}Ga activity. ^{68}Ge breakthrough can, however, increase above 0.001 % if the radionuclide generator is not eluted for several days. Therefore, if the radionuclide generator has not been eluted for 72 hours or more, it should be pre-eluted with 10 ml of sterile 0.1 mol/l hydrochloric acid at least 7 hours prior to the intended use (the time between the pre-elution and the elution for radiolabelling can be reduced if the intended radiolabelling procedure does not require maximum achievable eluate activity). When this instruction is followed, the ^{68}Ge breakthrough should constantly stay below 0.001 % in eluates obtained for radiolabelling. To keep the breakthrough low, the generator should be eluted at least once per working day. When used according to these instructions, the breakthrough should stay below 0.001 % for 12 months. For testing the ^{68}Ge breakthrough the activity levels of the ^{68}Ga and ^{68}Ge in the eluate should be compared. For further details please refer to Ph. Eur. monograph 2464. *Other routine risk minimisation measures beyond the Product Information:* Receipt, use and administration restricted to authorized persons in designated clinical settings. As a radiopharmaceutical product receipt, use and administration restricted to authorized persons in designated clinical settings

V.2. Additional risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety profile of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization 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: • **Detailed instructions for use given in SmPC section 12.** Additional risk minimisation measures: • **None**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • **None** Additional pharmacovigilance activities: • **None**

PART VI: Summary of risk management plan for GalenVita 0.74 – 3.70 GBq, radionuclide generator (germanium (^{68}Ge) chloride / gallium (^{68}Ga) chloride solution).

This is a summary of the risk management plan (RMP) for GalenVita 0.74 – 3.70 GBq, radionuclide generator. The RMP details important risks of GalenVita 0.74 – 3.70 GBq, radionuclide generator, and how more information will be obtained about GalenVita 0.74 – 3.70 GBq, radionuclide generator's risks and uncertainties (missing information).

The summary of product characteristics (SmPC) of GalenVita 0.74 – 3.70 GBq, radionuclide generator and its package leaflet give essential information to healthcare professionals and patients on how GalenVita 0.74 – 3.70 GBq, radionuclide generator should be used.

This summary of the RMP for GalenVita 0.74 – 3.70 GBq, radionuclide generator 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 RMP for GalenVita 0.74 – 3.70 GBq, radionuclide generator.

I. The medicine and what it is used for

The sterile eluate from the radionuclide generator GalenVita is authorised 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 (see SmPC for full indication). The eluate contains gallium (^{68}Ga) chloride as the active substance and is not intended for direct use in patients.

Further information about the evaluation of GalenVita 0.74 – 3.70 GBq, radionuclide generator's benefits can be found in GalenVita 0.74 – 3.70 GBq, radionuclide generator's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *<URL to EPAR will be added after EoP>*.

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

Important risks of GalenVita 0.74 – 3.70 GBq, radionuclide generator with measures to minimise such risks and the proposed studies for learning more about GalenVita 0.74 – 3.70 GBq, radionuclide generator's risks, are outlined below.

Measures to minimise the risks identified for 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 regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of GalenVita 0.74 –3.70 GBq, radionuclide generator 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 GalenVita 0.74 – 3.70 GBq, radionuclide generator.

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).

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

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important potential risks: Long-term exposure to radiation (in case of undetected elevated ^{68}Ge-breakthrough)	
Evidence for linking the risk to the medicine	So far, no quality issues regarding elevated 68Ge breakthrough levels in eluates of the Germanium (68Ge) chloride / Gallium (68Ga) chloride radionuclide generator or adverse events reports pointing to elevated 68Ge breakthrough as root cause have been received. Nevertheless, there is a clear potential for radiation induced adverse events in case of excessive 68Ge amount in an eluate, given the relatively long half-life of this radionuclide (270.95 days).
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: SmPC section 12. Additional risk minimisation measures: No risk minimisation measures.

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 for GalenVita 0.74 –3.70 GBq, radionuclide generator.

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

There are no studies required for GalenVita 0.74 – 3.70 GBq, radionuclide generator.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.