PRODUCT MONOGRAPH

Galli Eo™

Radionuclide generator, 0.74 to 1.85 GBq

For labeling diagnostic radiopharmaceuticals with
Gallium (^{68}Ga) chloride solution for labelling, Ph. Eur.

IRE ELiT
Avenue de l'Espérance
B-6220 Fleurus
Belgium

Date of Initial Approval:
November 13, 2019

Date of Revision:
November 13, 2019

Submission Control No: 221824

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

The gallium (^{68}Ga) chloride eluate from the Galli EO™ generator is not intended for direct administration to patients.

The gallium (^{68}Ga) chloride eluate is indicated for *in vitro* radiolabelling of radiopharmaceutical ligands for diagnostic procedures using positron emission tomography (PET).

2 CONTRAINDICATIONS

None known.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

The quantity of the gallium (^{68}Ga) chloride eluate required for radiolabelling and the quantity of ^{68}Ga-labelled radiopharmaceutical product that is subsequently administered will depend on the specific radiopharmaceutical that is radiolabelled and its intended use. Refer to the Product Monograph of the product to be radiolabelled.

4.1 Instructions for Preparation and Elution

Aseptic working technique must be applied when using the generator, especially when handling the elution port. This is critical for the maintenance of sterility.

The attachment of tubing, elution needles, in the elution of the generator and other activities potentially exposing the internal surfaces of generator to the environment should be undertaken using aseptic technique in an appropriately clean environment.

Appropriate shielding should be used throughout.

Elution vials should be sterile. Avoid uncoated chlorobutyl stoppers as they may contain considerable amounts of zinc that is extracted by the acidic eluate. Radiolabelling of carrier molecules with gallium (^{68}Ga) chloride solution is very sensitive to the presence of trace metal impurities.

It is recommended to use the vials provided with the non-radioactive tracer to be labelled or a material identical or equivalent to that provided as a starter kit with the generator (see 7. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

<u>Preparation</u>

1. Unscrew the cap from the Luer lock connector (fig. 1).
2. Connect a sterile tubing (extension line) to the Luer lock connector (fig. 2).

3. A For use with an automated synthesis unit (ASU), connect the other end of the tubing to the synthesis device. Avoid hard bending or pinching of the line. We recommend placing a single-use sterile check-valve between the male-to-male Luer lock adapter and the ASU (*e.g.,* MX745-01 from Smiths Medical).

   B. For manual elution, connect a sterile needle to the other end of the tubing using a male-to-male Luer lock adapter (fig. 3). Avoid hard bending or pinching of the line.

4. The Galli Eo generator is now ready for use.


Fig.1


Fig.2


Fig.3

Elution

1. Turn the green button by 90° to the loading position and wait for at least 10 seconds (fig.4).
2. Then, turn back the button by 90° to its initial position (fig. 5).

Fig.4

Fig.5

Fig.6

IMPORTANT: If the button was not returned to the elution position after having been put in the loading position for more than 6 hours, the eluate must be discarded.

3. The generator is now ready for elution either manually or by an ASU. In the latter case please go directly to step 7 after the labelling has been performed by the ASU.
4. Remove the cap from the needle and quickly pierce vertically right in the center of the septum of a shielded sterile evacuated elution vial (fig.6). Wait for at least 3 minutes for the elution process to take place (a fixed volume of 1.1 mL is eluted) and for the line to be drained by air.
5. Measure eluted activity with a calibrated dose calibrator to determine the yield (see 4.3 *Elution Yield*).
6. Remove the needle from the vial and replace the cap (fig. 7 and 8).

Fig. 7

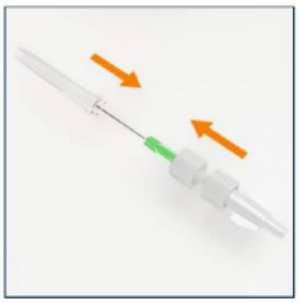

Fig. 8

Fig. 9

Fig. 10

7. Disconnect the tubing from the Luer lock connector and replace the cap in order to obturate the generator outlet (fig. 9 and 10).

First use of the generator

IMPORTANT: Prior to using the generator for the first time, a conditioning procedure must be performed. Conditioning consists of six consecutive discarded elutions, within 24 hours. There is no minimum time between elutions.

The first eluate following conditioning should be suitable for radiolabeling purposes provided it is performed within 24 hours of the last conditioning elution. Testing for ^{68}Ge breakthrough is recommended for this first post-conditioning eluate (see *4.2 Quality Control, ^{68}Ge breakthrough*). If the generator has not been eluted within the last 24 hours, the first elution should be discarded.

This 24-hour time frame applies only to eluates during the first four days of use.

Regular elutions

During the shelf life of the generator, all eluates are suitable for use provided that a previous elution has been performed within the last 72 hours. If the generator has not been eluted within the last 72 hours, the first elution should be discarded (see *4.2 Quality Control, ^{68}Ge breakthrough*).

Infrequent elutions

If the generator has not been eluted for more than a month, it must be reconditioned with three consecutive discarded elutions within 24 hours.

The first eluate following reconditioning should be suitable for radiolabeling purposes provided it is performed within 24 hours of the last reconditioning elution.

If the generator column has not been drained completely (due to e.g. unsatisfactory vacuum in the vial), a new vacuum vial can be connected for one minute to the needle placed at the end of the extension line (elution line) which is connected to the generator outlet. The green button on the generator should be kept to the elution/standby position. This operation will finalize the draining. The content of the new vial can be used if it is used immediately. If not used immediately, it must be discarded.

4.2 Quality Control

4.2.1 Visual inspection and pH

The solution should be checked for clarity and pH (≤ 2) before radiolabelling and discarded if it does not meet specifications.

4.2.2 ^{68}Ge breakthrough

The generator eluate should be tested for ^{68}Ge breakthrough after completion of conditioning (see *First use of the generator*) and 6 months thereafter. ^{68}Ge breakthrough should not be more than 0.001 % of the eluted ^{68}Ga activity.

The solution may be released for use before completion of the test.

To determine the amount ^{68}Ge and other γ -ray radionuclidic impurities with comparatively long half-lives, perform γ -ray spectrometry after allowing ^{68}Ga to decay for at least 48 h.

Warning: Breakthrough of ^{68}Ge can increase above 0.001 % if the generator is not eluted for more than 72 hours. If the generator has not been used for 72 or more, it should be pre-eluted (1 discarded elution). If the generator has not been eluted for more than a month 3 discarded elutions are to be performed and the first eluate intended for radiolabeling should be extracted within the next 24 hours.

4.2.3 Elution yield

Yield can be determined for each elution by dividing the decay-corrected measured eluted ^{68}Ga activity by the ^{68}Ga activity present on the column at date and time of elution which is calculated from the column ^{68}Ge activity at date and time of elution and from the elapsed time since the previous elution.

Given

- t_0 = date and time of generator nominal activity calibration
- t_1 = date and time of the last previous elution performed
- t_2 = date and time of the start of the considered present elution
- t_3 = date and time of measurement of the ^{68}Ga activity of the considered eluate
- $^{68Ga}T_{1/2}$ = ^{68}Ga radioactive decay half-life
- $^{68Ge}T_{1/2}$ = ^{68}Ge radioactive decay half-life
- $^{68Ga}\lambda$ = (ln 2)/($^{68Ga}T_{1/2}$)
- $^{68Ge}\lambda$ = (ln 2)/($^{68Ge}T_{1/2}$)

and

- $^{68Ge}A_{t0}$ = Nominal ^{68}Ge activity of the generator at generator calibration date and time (t_0)
- $^{68Ga\ column}A_{t2}$ = activity of ^{68}Ga on the generator column at date and time of start of elution (t_2)
- $^{68Ga}A_{t2}$ = Activity of ^{68}Ga eluate at date and time of elution (t_2)
- $^{68Ga}A_{t3}$ = Activity of ^{68}Ga eluate at date and time of its measurement in the dose calibrator (t_3)
- F_{RG} = ^{68}Ga regrowth factor between t_1 and t_2

$$Elution\ yield\ (\%) = \frac{^{68Ga}A_{t_2}}{^{68Ga\ column}A_{t_2}} \times 100$$

Where

$$^{68Ga}A_{t_2} = {}^{68Ga}A_{t_3} exp\left[{}^{68Ga}\lambda(t_3 - t_2)\right]$$

$$^{68Ga\ column}A_{t_2} = {}^{68Ge}A_{t_0} exp\left[-{}^{68Ge}\lambda(t_2 - t_0)\right] F_{RG}$$

A Galli Eo generator in full equilibrium typically has a yield of approximately 70%.

The ^{68}Ga activity eluted at calibration and expiry is shown below in Table 1.

Table 1: Generator and Eluent Activity

Generator ^{68}Ge activity (GBq)		Eluent ^{68}Ga activity (MBq)*	
Calibration	Expiration	Calibration	Expiration
0.74	0.29	407	160
1.11	0.44	611	240
1.48	0.58	814	321
1.85	0.73	1018	401

* At 55% minimum yield when eluted at equilibrium

4.3 ^{68}Ga activity

The ^{68}Ga activity will depend upon the ^{68}Ge activity at the time of elution and the elapsed time since the previous elution. At full equilibrium, the ^{68}Ga activity will be equal to the ^{68}Ge activity.

^{68}Ga has a half-life of 68 minutes. ^{68}Ga activity at the start of elution is calculated by dividing the measured ^{68}Ga activity by the decay factor ($e^{-0.0102\,t}$), where -0.0102 is calculated from -ln(2)/68 min, and *t* is the time in minutes from the start of elution (Table 2).

For example, if the measured ^{68}Ga activity at 60 minutes is 150 MBq, the ^{68}Ga activity at the start of elution would be:

150 MBq / $e^{-0.0102*60}$ = 150 MBq / 0.54 = 278 MBq.

Table 2: ^{68}Ga Decay

Minutes	Fraction remaining	Minutes	Fraction remaining	Minutes	Fraction remaining	Minutes	Fraction remaining	Minutes	Fraction remaining
0	1.00	27	0.76	54	0.58	81	0.44	108	0.33
3	0.97	30	0.74	57	0.56	84	0.42	111	0.32
6	0.94	33	0.71	60	0.54	87	0.41	114	0.31
9	0.91	36	0.69	63	0.53	90	0.40	117	0.30
12	0.88	39	0.67	66	0.51	93	0.39	120	0.29
15	0.86	42	0.65	69	0.49	96	0.38	123	0.29
18	0.83	45	0.63	72	0.48	99	0.36	126	0.28
21	0.81	48	0.61	75	0.47	102	0.35	129	0.27
24	0.78	51	0.59	78	0.45	105	0.34	132	0.26

4.4 ^{68}Ge activity

^{68}Ge has a half-life of 270.95 days (≅ 39 weeks). ^{68}Ge activity is calculated by multiplying the labelled activity at calibration by the decay factor ($e^{-0.0179\,t}$), where -0.0179 is calculated from -ln(2)/38.7 weeks and *t* is the time in weeks from calibration (Table 3).

For example, a 1.11 GBq generator after 26 weeks would have a remaining activity of:

$$1.11\ \text{GBq} * e^{-0.0179*26} = 1.11\ \text{GBq} * 0.63 = 0.70\ \text{GBq}$$

Table 3: ^{68}Ge Decay

Weeks	Fraction remaining	Weeks	Fraction remaining	Weeks	Fraction remaining	Weeks	Fraction remaining	Weeks	Fraction remaining
0	1.00	11	0.82	22	0.67	33	0.55	44	0.45
1	0.98	12	0.81	23	0.66	34	0.54	45	0.45
2	0.96	13	0.79	24	0.65	35	0.53	46	0.44
3	0.95	14	0.78	25	0.64	36	0.52	47	0.43
4	0.93	15	0.76	26	0.63	37	0.52	48	0.42
5	0.91	16	0.75	27	0.62	38	0.51	49	0.42
6	0.90	17	0.74	28	0.61	39	0.50	50	0.41
7	0.88	18	0.72	29	0.59	40	0.49	51	0.40
8	0.87	19	0.71	30	0.58	41	0.48	52	0.39
9	0.85	20	0.70	31	0.57	42	0.47		
10	0.84	21	0.69	32	0.56	43	0.46		

4.5 Re-charging (regrowth)

After an elution of the generator, ^{68}Ga will build up by the continuous decay of the parent ^{68}Ge. The generator requires four hours after being eluted to achieve 91% of the equilibrium.

Build-up can be calculated by the formula $1- e^{-0.0102\,t}$, where -0.0102 is calculated from -ln(2)/68 min, and *t* is the time in minutes from the last elution (Table 4).

For example, 180 minutes after the last elution, the generator will have built up 84% of its potential ^{68}Ga activity:

$$1- e^{-0.0102*180} = 0.84$$

Table 4: ^{68}Ga Build-up Factor

Minutes	Build-up factor	Minutes	Build-up factor	Minutes	Build-up factor	Minutes	Build-up factor	Minutes	Build-up factor
0	0.00	100	0.64	200	0.87	300	0.95	400	0.98
10	0.10	110	0.67	210	0.88	310	0.96	410	0.98
20	0.18	120	0.71	220	0.89	320	0.96	420	0.99
30	0.26	130	0.73	230	0.90	330	0.97	430	0.99
40	0.33	140	0.76	240	0.91	340	0.97	440	0.99
50	0.40	150	0.78	250	0.92	350	0.97	450	0.99
60	0.46	160	0.80	260	0.93	360	0.97	460	0.99
70	0.51	170	0.82	270	0.94	370	0.98	470	0.99
80	0.56	180	0.84	280	0.94	380	0.98	480	0.99
90	0.60	190	0.86	290	0.95	390	0.98	490	0.99

5 RADIATION DOSIMETRY

The radiation dose received by the various organs following intravenous administration of a ^{68}Ga-labelled radiopharmaceutical is dependent upon the specific radiopharmaceutical administered. Refer to the Product Monograph of the product to be radiolabelled.

The effective dose coefficient for ^{68}Ga is 2.8E-02 mSv/MBq. The effective dose following the inadvertent administration of 1.1 mL of eluent containing the potential maximum of 1850 MBq would be 52 mSv.

6 OVERDOSAGE

Not applicable. Gallium (^{68}Ga) Chloride solution is not intended for direct administration to patients.

7 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Galli Eo is a ^{68}Ge/^{68}Ga radionuclide generator, available in activities of 0.74, 1.11, 1.48, and 1.85 GBq.

The generator consists of a TiO_2 column and integrated HCl 0.1N eluent.

The column is enclosed in tungsten and in lead radiation shields. The shielded column and the eluent bag are contained within a plastic case.

The following supplies are also included:

- 5 sterile 10-ml evacuated vials (Huayi product n° SVV-10A)
- 5 sterile female Luer-lock to male Luer-lock tubings (Vygon product n° 1155.03 or 1155.05)
- 5 sterile needles 0.8 X 16 mm 21G 5/8'' (Terumo product n° AN*2116R1)
- 5 sterile male Luer-lock to male Luer-lock connectors (Vygon product n° 893.00)

8 DESCRIPTION

8.1 Physical Characteristics

Table 5: Decay Characteristics

	^{68}Ge	^{68}Ga
Half-life	270.95 days	67.71 minutes
Type of decay	Electron capture	Positron emission
Daughter	^{68}Ga	^{68}Zn

See Table 2 and Table 3**Error! Reference source not found. Error! Reference source not found.** for decay graphs of ^{68}Ga and ^{68}Ge, respectively.

Table 6. Principle Emission Data for ^{68}Ge and ^{68}Ga

	^{68}Ge		^{68}Ga		
Radiation	Energy (keV)	Intensity (%)	Energy (keV)	Intensity (%)	End-point energy
X-ray	1.10	1.52 %	1.01	0.15 %	
	9.23	13.10 %	8.62	1.40 %	
	9.25	25.80 %	8.64	2.75 %	
	10.26	1.64 %	9.57	0.33 %	
	10.26	3.20 %	9.57	0.17 %	
	10.37	0.03 %			
Gamma (γ)			511.00	177.82 %	
			578.52	0.03 %	
			805.83	0.09 %	
			1077.34	3.22 %	
			1261.08	0.09 %	
			1883.16	0.14 %	
Positron (ß +)			352.59	1.19 %	821.7
			836.02	87.72 %	1899.1

8.2 External Radiation

The exposure rate constant for ^{68}Ga is 1.05E-12 C m^2/kg MBq s.

The lead shielding half value layer (HVL) for the 511 keV photons is 5.1 mm. The range of attenuation coefficients for this radionuclide is shown in Table 7. For example, an 9.8 mm thick lead shield has an attenuation coefficient of 25% and will decrease the external radiation by 75%.

Table 7: Radiation Attenuation of 511 keV Photons by Lead Shielding

Value layer	HVL	QVL	TVL	CVL	MVL
Lead thickness (mm)	5.12	9.84	16	33.8	61.7

9 WARNINGS AND PRECAUTIONS

The gallium (^{68}Ga) chloride eluate from the generator is not intended for direct administration to patients; it is indicated for *in vitro* radiolabelling.

The radiolabelled product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

For information concerning warnings and precautions for the use of ^{68}Ga-labelled radiopharmaceuticals, refer to the Product Monograph of the product to be radiolabelled.

10 ADVERSE REACTIONS

There are no known adverse reactions to the nanogram mass dose of gallium administered as gallium (^{68}Ga) chloride.

For information concerning adverse reactions to the use of ^{68}Ga-labelled radiopharmaceuticals, refer to the Product Monograph of the product to be radiolabelled.

11 DRUG INTERACTIONS

There are no known drug interactions.

For information concerning drug interactions with the use of ^{68}Ga-labelled radiopharmaceuticals, refer to the Product Monograph of the product to be radiolabelled.

12 ACTION AND CLINICAL PHARMACOLOGY

The gallium (^{68}Ga) chloride eluate from the generator is not intended for direct administration to patients; it is indicated for *in vitro* radiolabelling.

For information concerning the action and clinical pharmacology of ^{68}Ga-labelled radiopharmaceuticals, refer to the Product Monograph of the product to be radiolabelled.

13 STORAGE, STABILITY, AND DISPOSAL

The Galli Eo generator should be stored upright and at a temperature at or below 25 °C.

The eluate should be used immediately after elution.

The generator has a shelf-life of 12 months from the calibration date.

Expired generators must be returned to IRE ELiT. The residual activity of the generator must be estimated before return.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Proper name:	The eluate is Gallium (^{68}Ga) chloride solution for radiolabelling Ph. Eur.
Chemical name:	Gallium (^{68}Ga) chloride
Molecular formula:	$^{68}GaCl_3$
Molecular mass:	174.3 Daltons

Gallium (^{68}Ga) chloride solution for radiolabelling Ph. Eur. is a clear, sterile and colourless solution, with a pH not more than 2.0, and a radiochemical purity greater than 95 %.