LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

1 October 2024

SUMMARY OF PRODUCT CHARACTERISTICS

for

Cardiogen-82, radionuclide generator

1. NAME OF THE MEDICINAL PRODUCT

Cardiogen-82

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The radionuclide generator contains strontium-82 (^{82}Sr) as the parent nuclide, which decays to rubidium-82 (^{82}Rb), the daughter nuclide.

Cardiogen-82 is a radionuclide generator of rubidium-82 (^{82}Rb) containing strontium-82 (^{82}Sr) adsorbed on stannic oxide in a chromatography column. It provides a means of obtaining, via elution, a sterile, non-pyrogenic injectable solution of rubidium-82 (^{82}Rb) chloride.

The activity of the generator is between 3.3 and 5.6 GBq ^{82}Sr at calibration time. The activity of the rubidium (^{82}Rb) chloride solution obtained from each elution depends on the elution capacity of the generator.

Specifications

At calibration date, when eluted at a rate of 50 mL/minute, the eluate has the following specifications:

- ^{82}Sr ≤ 2x10^{-5} MBq/MBq ^{82}Rb
- Rb-83 [*sic*] ≤ 5x10^{-5} MBq/MBq ^{82}Rb
- ^{85}Sr ≤ 2x10^{-4} MBq/MBq ^{82}Rb
- for all other radiocontaminants: ≤ 5x10^{-6} MBq/MBq ^{82}Rb
- the tin content should be less than 1 µg/mL

On each use, when eluted at a rate of 50 mL/minute, each generator eluate should contain no more than 1x10^{-5} MBq of strontium ^{82}Sr and no more than 1x10^{-4} MBq of strontium ^{85}Sr per megabecquerel of injectable solution of rubidium ^{82}Rb chloride.

Physical properties

Rubidium ^{82}Rb decays to stable krypton (^{82}Kr) with a half-life of 75 seconds

– either by positron emission resulting in the production of 2 annihilation photons of 511-keV

– or by capture of an electron which generates a gamma ray of 776.5keV

Excipient with known effect

1 mL of solution contains 9 mg of sodium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radionuclide generator.

For obtaining, via elution, solutions of rubidium-82 chloride for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

The generator eluate (solution of rubidium-82 (^{82}Rb) chloride for injection) is used for Positron Emission Tomography (PET) imaging of the myocardium at rest or under pharmacologic stress conditions to evaluate regional myocardial perfusion in adults with suspected or known coronary artery disease.

4.2 Posology and method of administration

Posology

Adults and the elderly

The recommended activity in adults is 1100 to 2220 MBq (this activity must be adjusted according to the patient's body size, PET equipment used and imaging technique employed). This activity must be administered via intravenous infusion.

Renal and hepatic impairment

A reduction in hepatic or renal function that alters clearance of rubidium ^{82}Rb chloride solution is not anticipated because ^{82}Rb decays to stable ^{82}Kr gas with a half-life of 75 seconds and ^{82}Kr gas is naturally expelled through the lungs.

Paediatric population

The safety and efficacy of Cardiogen-82 have not been established for children.

Method of administration

Intravenous administration via infusion. Cardiogen-82 should be used with an appropriate infusion system designed specifically for use with the Cardiogen-82 generator e.g. Cardiogen-82 Infusion System Model 510 or Model 1701.

For instructions on extemporary preparation of the medicinal product before administration, see sections 6.6 and 12.

For patient preparation, see section 4.4.

This radiopharmaceutical should be administered at a rate of 50 mL/minute (Model 510 or Model 1701) or 20 mL/minute (Model 1701 only) through a catheter inserted into a large peripheral vein, with the total volume not exceeding 100 mL. The elution rate should never exceed 50 mL/minute, as this could lead to breakthrough of strontium ^{82}Sr.

Image acquisition

In general, two single doses should be administered in order to carry out both a rest imaging and a pharmacological stress imaging session:

For myocardial perfusion *rest* imaging:

- administer a single dose of rubidium (^{82}Rb) chloride solution
- start imaging after the infusion ends. In general, image acquisition lasts 5 minutes.

For myocardial perfusion *pharmacological stress* imaging :

- in order to avoid the presence of residual activity from the previous infusion of rubidium (^{82}Rb) chloride, start the pharmacological test at least 10 minutes after completion of the previous rubidium (^{82}Rb) chloride dose infusion.
- perform the pharmacological test in accordance with the current procedure (using a vasodilator approved for this purpose)
- three minutes after the start of the pharmacological test, administer a single dose of rubidium (^{82}Rb) chloride

Patients with severe heart failure

In patients with a clinically significant reduction in cardiac function (output, LVEF), it may be necessary to increase the interval between infusion and image acquisition. Such patients should be clinically monitored following the infusion (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products, personnel and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification

For each patient, the ionising radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Heart failure patients

Patients with congestive heart failure should be monitored particularly carefully during infusion because of the transitory increase in blood volume.

Paediatric population

The safety and efficacy of rubidium ^{82}Rb chloride have not been established for children. Careful consideration of the administration is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation

The patient should have fasted for at least 6 hours and should be well hydrated before the start of the examination. In addition, the patient should not consume food products which contain caffeine and/or other xanthine derivatives (e.g., coffee, tea, chocolate, cola and other soft drinks, maté, guarana) for at least 12 hours before the examination. The intake of medicinal products which could affect the results of the pharmacologic stress imaging should be avoided/stopped at least one day before the start of the examination based on the opinion of the attending nuclear physician/expert and the indication of the examination (see section 4.5).

After the PET scan

Due to the very short half-life, no special precautions need to be taken with regard to radioactivity.

Specific warnings

Rubidium (^{82}Rb) chloride solution for injection is intended only for intravenous administration using an appropriate infusion system (see section 12) capable of accurate measurement and administration of doses of rubidium (^{82}Rb) chloride, with a single dose not exceeding 2220 MBq and a cumulative dose 4440 MBq at a rate of 50 mL/min, with a maximum volume per infusion of 100 mL and a total volume not exceeding 200 mL.

Rubidium (^{82}Rb) chloride solution contains sodium. According to the time of injection, the content of sodium administered may in some cases be greater than 1 mmol. This should be taken into account in patients on strict low sodium diets.

Precautions with respect to environmental hazard, see section 6.6

Rubidium (^{82}Rb) chloride solution contributes to a cumulative ionising radiation exposure.

4.5 Interaction with other medicinal products and other forms of interaction

No studies have been performed on possible interactions between rubidium-82 and other medicinal products. The amount of ^{82}Rb per administration is minimal and it is not expected that ^{82}Rb exerts an effect on other medicinal products.

Drugs known to inhibit the activity of myocardial Na^+/K^+/ATPase pumps, such as cardiac glycosides (e.g., digoxin), and amiodarone and dronedarone, may generally reduce ^{82}Rb myocardial uptake. Cardiac glycosides should be stopped at least 48 hours before imaging. Due to the long mean apparent plasma terminal elimination half-lives of amiodarone, dronedarone and active metabolites (e.g., DEA), stoppage before imaging would likely be of limited value; further, amiodarone and dronedarone should only be stopped under close medical supervision for the possible occurrence of life-threatening ventricular arrhythmias.

Regarding the potential effects of other medicinal products on the imaging process:

- β-blockers, calcium antagonists and nitrates should be stopped at least 48 hours before imaging.
- Dipyridamole should be stopped at least 24 hours before imaging.
- Xanthine derivative medications (e.g., aminophylline, theophylline) should be stopped at least 48 hours before imaging.
- Intake of food and drink that contain caffeine and/or other xanthine derivatives should be stopped 12 hours before imaging (see section 4.4).
- Withholding proton pump inhibitors 36 hours before imaging may reduce potential spill over from gastric uptake.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy must be ruled out before the procedure is performed.

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise.

Pregnancy

The use of this medicinal product is contraindicated in pregnant women (see section 4.3).

No animal studies have been carried out with rubidium-82 with regard to reproduction. The risks to the foetus when ^{82}Rb is used in pregnant women are not known. However, radioactivity has the potential to cause genetic abnormalities, although these have not been observed at this activity level.

Breast-feeding

It is unknown whether rubidium-82 is excreted in human milk. Due to the short half-life of rubidium ^{82}Rb (75 seconds), it is unlikely that the drug would be excreted in human milk. However, because many active substances are excreted in human milk, caution should be exercised when rubidium ^{82}Rb chloride is administered to nursing women. In general, it is

sufficient for women to resume breastfeeding no sooner than one hour after the last infusion of ^{82}RbCl and to discard expressed milk.

Fertility

No studies have been carried out on fertility.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machines have not been studied.

The patient's cardiovascular status and any undesirable effects should be taken into account when judging this ability.

4.8 Undesirable effects

No undesirable effects associated with Cardiogen-82 have been observed during the clinical study.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 6 mSv when the maximal recommended cumulative radioactivity of 4440 MBq is administered, these adverse reactions are expected to occur with a low probability.

Unintended patient exposure to ionising radiation due to contamination with strontium can occur in patients receiving rubidium ^{82}Rb chloride from the Cardiogen-82 generator at clinical sites where quality control is not carried out correctly. Strict adherence to the instructions regarding quality control at clinical sites is required (see section 12).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Website: www.meldenbivirkning.dk

4.9 Overdose

Due to the nature of the product and its use, a clinically significant overdose of rubidium ^{82}Rb is unlikely. In order to avoid administration of a large quantity of strontium ^{82}Sr and ^{85}Sr (breakout), the instructions for use should be strictly adhered to and the maximum elution rate should not exceed 50 mL/minute.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for the cardiovascular system, ATC code: V09GX04

Mechanism of action

No pharmacological activity has been observed in the dose levels administered for diagnostic purposes. The use of Cardiogen-82 in medical diagnostics is based on the biodistribution properties of ^{82}Rb.

Pharmacodynamic effects

At the chemical concentrations and activities recommended for diagnostic examinations, rubidium-82 chloride does not appear to have any pharmacodynamic activity.

In human studies, myocardial activity was noted within the first minute after peripheral intravenous infusion of ^{82}Rb. When areas of infarction or ischaemia are present in the myocardium, these appear as photon-deficient areas within 2-7 minutes after infusion.

In patients with reduced cardiac function (LVEF < 50%), it may take longer for the rubidium ^{82}Rb to reach and be taken up by the myocardium, and uptake may also be diminished (see section 4.4).

As the blood flow carries ^{82}Rb to all parts of the body during the first circulation, uptake of the tracer is also observed in other tissues such as the kidneys, liver, spleen and lungs.

Clinical efficacy and safety

In a descriptive, prospective, blinded image interpretation study of adult patients with known or suspected coronary artery disease, myocardial perfusion deficits in stress and rest PET images obtained with ammonia N-13 (n = 111) or rubidium ^{82}Rb chloride (n = 82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. PET perfusion defects for seven regions of the heart (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were measured, at rest and under stress, on a scale of 0 (normal) to 5 (severe). Values for stenosis flow reserve, defined as the relationship between flow at maximum coronary vasodilatation and flow at rest, ranged from 0 (total occlusion) to 5 (normal). The subjective severity of PET defects increased as impairment of coronary flow reserve increased. There was a positive correlation between flow reserve impairment (SFR < 3) and a PET defect score of 2 or more.

A systematic review of published literature was carried out using pre-defined inclusion/exclusion criteria which enabled identification of 10 studies evaluating the use of myocardial perfusion imaging (MPI) with ^{82}Rb PET for the identification of coronary artery disease as determined by catheter angiography. In these studies, the unit of analysis was the patient and the threshold for clinically significant coronary artery disease (CAD) was 50% stenosis. Of these 10 studies, 9 were included in a sensitivity meta-analysis (excluding one study with 100% sensitivity) and 7 were included in a specificity meta-analysis (excluding 3 studies with 100% specificity). Using a random effects model A [*sic*] overall estimates of sensitivity and specificity were obtained, which were of 92% (95% CI: 89% to 95%) and 81% (95% CI: 76% to 86%), respectively. The use of meta-analysis in establishing performance characteristics is limited, particularly by the possibility of publication bias (whereby positive results are more likely to be published than negative results), which is difficult to detect, especially where there are only a limited number of small studies.

5.2 Pharmacokinetic properties

Absorption and distribution

^{82}Rb is taken up by the myocardial cells via Na^+/K^+-ATPase pumps. The increase in ^{82}Rb uptake decreases as myocardial blood flow increases. Myocardial uptake of ^{82}Rb is seen in the first minute following injection of ^{82}Rb chloride. Myocardial areas with ischemia or infarct can be visualised as photo-deficient areas in the myocardial image. Uptake may be delayed in patients with a clinically significant reduction in cardiac function. ^{82}Rb uptake is also observed in the kidneys, liver, spleen and lungs.

After intravenous administration, blood clearance of ^{82}Rb takes place quickly due to the high rate of diffusion from the capillaries of the myocardium into the interstitial fluid; the extraction fraction of ^{82}Rb is 65%.

Elimination

With a physical half-life of 75 seconds, ^{82}Rb is converted very rapidly by radioactive decay into a trace amount of stable ^{82}Kr gas which is expelled naturally by the lungs. Renal and hepatic excretion is not expected to play an essential role in the elimination of ^{82}Rb, although some of the ^{82}Rb dose may be excreted in the urine before radioactive decay.

5.3 Preclinical safety data

A single intravenous injection of rubidium (^{82}Rb) chloride samples at the maximum dose (20 mL/kg at a rate of 0.1 mL/5 seconds) did not result in toxicity in mice.

Toxicity with repeated administration of 10 mL/kg/day over 14 days in mice and repeated administration of 3.0 mL/kg/day over 14 days in dogs was not observed.

Rubidium (^{82}Rb) chloride is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solution for elution: sodium chloride 9 mg/mL
Column matrix: hydrous stannic oxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

Generator: 42 days after the calibration date

The calibration date and expiration date are stated on the generator labelling.

Rubidium-82 (^{82}Rb) chloride eluate: use immediately after elution due to the very short half-life.

6.4 Special precautions for storage

Generator: Store below 25°C.

Eluate: For storage conditions after elution of the medicinal product, see section 6.3.

The generator must not be used if any of its expiration limits are reached:

- use 42 days after the calibration date,
- a total elution volume of 17 L has passed through the column since first use of the generator,
- ^{82}Sr level exceeds $1x10^{-5}$ MBq/MBq of ^{82}Rb after elution,
- ^{85}Sr level exceeds $1x10^{-4}$ MBq/MBq of ^{82}Rb after elution.

Due to the short half-life of ^{82}Rb, almost all radioactivity in the eluate disappears within 15 minutes following the end of elution.

Storage of radiopharmaceuticals should be in accordance with current regulation on radioactive materials.

6.5 Nature and contents of container

Each pack contains one generator supplied in a type A transport container. It is housed in a plastic container with lead shielding.

6.6 Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If at any time in the preparation of this product the integrity of this container is compromised, the product should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must be taken.

Prior to administration, the product should be inspected visually for particulate and signs of discoloration, if the solution and container permit. Do not administer the generator eluate if the presence of foreign matter is suspected.

Rubidium ^{82}Rb activity in the eluate should be measured at the start of each day that the generator is used, along with the levels of strontium ^{82}Sr and ^{85}Sr after ^{82}Rb decay (the breakthrough test). Elution is carried out exactly the same way whether it is for the purposes of testing or for administering to patients (see section 12).

Disposal

Hospital staff should confirm the amount of radioactivity present in the generator before disposal. The generator must not be disposed of as normal waste. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRACCO IMAGING SPA
Via Egidio Folli, 50
20134 Milan
Italien

Representative
BRACCO IMAGING SCANDINAVIA AB
Fabrikstorget 1
412 50 Göteborg
Sverige

8. MARKETING AUTHORISATION NUMBER(S)

68262

9. DATE OF FIRST AUTHORISATION

10 January 2023

10. DATE OF REVISION OF THE TEXT

1 October 2024

11. DOSIMETRY

The data listed in Table 1 are from ICRP (International Commission on Radiological Protection) Publication 128.

Table 1: Absorbed radiation doses for rubidium-82 (^{82}Rb) chloride

Organ	Dose absorbed per unit activity administered (mGy/MBq)				
	Adults	15 years old	10 years old	5 years old	1 year old
Adrenals	2.4 x 10-3	3.6 x 10-3	5.1 x 10-3	7.0 x 10-3	1.0 x 10-2
Bone surfaces	4.2 x 10-4	5.6 x 10-4	8.5 x 10-4	1.4 x 10-3	3.1 x 10-3
Brain	1.4 x 10-4	1.4 x 10-4	1.6 x 10-4	1.9 x 10-4	2.8 x 10-4
Breast	1.9 x 10-4	2.0 x 10-4	1.3 x 10-2	2.2 x 10-2	4.3 x 10-2
Gallbladder	7.2 x 10-4	8.5 x 10-4	1.2 x 10-3	2.0 x 10-3	5.7 x 10-3
Digestive tract					
Stomach	8.3 x 10-4	1.1 x 10-3	1.6 x 10-3	2.7 x 10-3	5.4 x 10-3
Small intestine	2.0 x 10-3	2.6 x 10-3	4.6 x 10-3	7.7 x 10-3	1.5 x 10-2
Colon	1.1 x 10-3	1.4 x 10-3	2.5 x 10-3	4.1 x 10-3	7.8 x 10-3
Ascending colon	1.1 x 10-3	1.4 x 10-3	2.5 x 10-3	4.1 x 10-3	7.9 x 10-3
Descending colon	1.1 x 10-3	1.4 x 10-3	2.4 x 10-3	3.9 x 10-3	7.6 x 10-3
Heart	4.0 x 10-3	5.2 x 10-3	8.2 x 10-3	1.3 x 10-2	2.4 x 10-2
Kidneys	9.3 x 10-3	1.1 x 10-2	1.6 x 10-2	2.4 x 10-2	4.3 x 10-2
Liver	9.8 x 10-4	1.3 x 10-3	2.0 x 10-3	3.0 x 10-3	5.8 x 10-3
Lungs	2.6 x 10-3	3.8 x 10-3	5.5 x 10-3	8.5 x 10-3	1.7 x 10-2
Muscles	2.3 x 10-4	3.6 x 10-4	7.2 x 10-4	2.2 x 10-3	4.3 x 10-3
Oesophagus	1.5 x 10-3	2.4 x 10-3	3.7 x 10-3	8.1 x 10-3	1.5 x 10-2
Ovaries	5.0 x 10-4	4.9 x 10-4	1.2 x 10-3	2.0 x 10-3	4.4 x 10-3
Pancreas	2.6 x 10-3	3.7 x 10-3	7.6 x 10-3	9.7 x 10-3	2.1 x 10-2

Red bone marrow	3.8 x 10-4	4.6 x 10-4	7.8 x 10-4	1.5 x 10-3	3.8 x 10-3
Skin	1.8 x 10-4	2.3 x 10-4	3.7 x 10-4	6.1 x 10-4	1.2 x 10-3
Spleen	1.8 x 10-4	3.9 x 10-4	2.4 x 10-3	2.8 x 10-3	3.8 x 10-3
Testicles	2.6 x 10-4	3.3 x 10-4	5.0 x 10-4	7.9 x 10-4	1.5 x 10-3
Thymus	1.5 x 10-3	2.4 x 10-3	3.7 x 10-3	8.1 x 10-3	1.5 x 10-2
Thyroid	3.1 x 10-4	3.8 x 10-4	6.2 x 10-4	1.0 x 10-3	1.9 x 10-3
Urinary bladder wall	1.8 x 10-4	3.9 x 10-4	2.4 x 10-3	2.8 x 10-3	3.8 x 10-3
Uterus	1.0 x 10-3	1.1 x 10-3	1.5 x 10-2	2.3 x 10-2	4.1 x 10-2
Other tissue	3.1 x 10-4	5.0 x 10-4	9.3 x 10-4	2.1 x 10-3	4.7 x 10-3
Effective dose per activity administered (mSv/MBq)	1.1 x 10-3	1.4 x 10-3	3.0 x 10-3	4.9 x 10-3	8.5 x 10-3

For rubidium-82 (^{82}Rb), the effective dose resulting from administration of a maximal activity of 2220 MBq is 2.44 mSv.

For this activity of 2200 MBq, the typical radiation doses delivered to the critical organs below are as follows: kidneys: 20.65 mGy, heart: 8.88 mGy, lungs: 5.77 mGy and pancreas: 5.77 mGy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

12.1 Operator training

The user must have undergone training by the generator distributor and must be given specific documentation. When the product is first introduced to a nuclear medicine site, all personnel must undergo training under the supervision of the Marketing Authorisation Holder.

Cardiogen-82 (82Rb generator) must only be used with an appropriate infusion system designed specifically for use with the Cardiogen-82 generator e.g. Cardiogen-82 Infusion System Model 510 or Model 1701.

12.2 Operating principle:

A syringe pump is used to pass sterile NaCl 9 mg/mL solution through the generator.

Only a NaCl 9 mg/mL solution that meets pharmacopeia quality standards and with no impurities or additives should be used for generator elution. The use of any other solutions (in particular those containing calcium, even in trace amounts, or additives) is strictly forbidden as this may result in significant breakthrough of the parent nuclide ^{82}Sr with potential consequences for the patient.

The eluate obtained from the generator contains rubidium-82. If the activity of the eluate as measured by a positron detector reaches a sufficient level, the valve directs the eluate toward the patient infusion line. The desired activity level and therefore the dose infused are pre-defined electronically.

12.3 Radionuclidic purity and quality control: measurement of ^{82}Rb, ^{82}Sr and ^{85}Sr concentrations

At the start of each day the generator is used, before administering the product to the first patient, it is essential that the radionuclidic purity of the eluate be tested as follows:

The first 50 mL of eluate should be discarded (the Model 1701 infusion system will do this automatically), with due consideration of proper safety precautions. After regeneration of the column (10 minutes), quality control testing (rubidium ^{82}Rb activity and levels of ^{82}Sr and ^{85}Sr in

the eluate) should be performed carefully and with strict adherence to the instructions below. Test results should be kept.

Information on eluting the Cardiogen-82 generator follows below:

- Waterproof gloves and effective protection should be worn while handling the rubidium (^{82}Rb) chloride solution.
- Aseptic techniques should be employed throughout the preparation and elution processes.
- Leave at least 10 minutes between each elution so as to allow for regeneration of the ^{82}Rb.
- Elute only with an injectable solution of sodium chloride 9 mg/mL which meets pharmacopeia quality standards and contains no impurities or additives.
- Traceability in terms of infusion volume and activity should be ensured for the entire procedure.

12.4 Limits

The generator must not be used if any of its expiration limits are reached:

- use 42 days after the calibration date,
- a total elution volume of 17 L has already passed through the column since first use of the generator,
- ^{82}Sr level exceeds $1x10^{-5}$ MBq/MBq ^{82}Rb after elution,
- ^{85}Sr level exceeds $1x10^{-4}$ MBq/MBq ^{82}Rb after elution.

12.5 Additional tests

Each time the NaCl 9 mg/mL eluent is changed (connection of a new bottle), a new quality control test should be carried out on the eluate.

It is also necessary to carry out an additional quality control test if one of the following alert limits is reached:

- a total elution volume of 14 L has passed through the column since first use of the generator,
- ^{82}Sr level exceeds $2x10^{-6}$ MBq/MBq ^{82}Rb after elution,
- ^{85}Sr level exceeds $2x10^{-5}$ MBq/MBq ^{82}Rb after elution.

These additional quality controls should also be performed at times determined by the day's elution volume. Tests should be performed every 750 mL.

- For example, if the clinical site has eluted less than 750 mL from the generator during the day, no additional test is performed that day
- If the same clinical site elutes 1500 mL from the generator the next day, it will have to perform 3 tests that day:
    1) the routine test required prior to use on the first patient,
    2) a test after 750 mL has been eluted,
    3) a test after 1500 mL has been eluted.

As soon as an alert limit is reached and throughout the life of the generator, additional quality tests should be performed after 750 mL has been eluted, in accordance with the procedures described below.

12.6 Procedure and calculation methods

Use Cardiogen-82 with an appropriate infusion system designed specifically for use with the Cardiogen-82 generator e.g. Cardiogen-82 Infusion System Model 510 or Model 1701.

- If using the Cardiogen-82 Infusion System Model 510, refer to the Eluate Testing Protocol in Section 12.6.1
- If using the Cardiogen-82 Infusion System Model 1701, refer to the Eluate Testing Protocol in Section 12.6.2

Follow instructions in the Cardiogen-82 Infusion System Model 510 or Model 1701 Operator's Manual for the set up and intravenous infusion of rubidium ^{82}Rb chloride injection dose(s).

12.6.1 Cardiogen-82 Infusion System Model 510 Eluate Testing Protocol

Levels of rubidium ^{82}Rb, ^{82}Sr and ^{85}Sr are determined using an ionisation chamber-type dose calibrator.

Procedures 1 to 11 below should be performed.

The rubidium ^{82}Rb chloride content of the injectable solution is determined as follows:

1. Set a dose calibrator for ^{82}Rb as recommended by the manufacturer or use the Co-60 setting and divide the reading obtained by 0.548. Read off the value given by the instrument in MBq (megabecquerel).

2. Elute the generator aseptically using 50 mL of sodium chloride solution for injection (pharmacopeia quality, with no additives or impurities) and discard the eluate (first elution).

3. Allow at least 10 minutes for the regeneration of ^{82}Rb and then elute the generator aseptically with 50 mL of sodium chloride 9 mg/mL solution for injection (pharmacopeia quality, with no additives or impurities) at a rate of 50 mL/minute and collect the eluate in a stoppered glass vial (plastic containers should not be used). Note the exact time (hh:mm:ss) of the end of elution (EOE).

4. Using the dose calibrator, determine the activity of the ^{82}Rb (A_{Rb} (t)) and note the time (t) of the reading. Correct the reading to the end of elution using the relevant fraction remaining for ^{82}Rb (see Table 1).

A_{Rb} (EOE) = A_{Rb} (t) / Fraction Remaining

Example: if the reading is taken 2.5 minutes after the end of elution, correction for decay is carried out by dividing the dose calibrator reading by 0.25.

To measure the **concentration of** ^{82}Sr in the eluate, proceed as follows:

5. Using the sample obtained for determination of ^{82}Rb activity, let the sample stand for at least one hour to allow ^{82}Rb to decay completely.

6. Measure the activity of the sample using a dose calibrator at the setting recommended by the manufacturer for ^{82}Rb and/or ^{82}Sr. Alternative method: use the Co-60 setting and divide the reading obtained by 0.548. Read off the value given by the instrument in MBq (megabecquerel).

7. Read off the ratio of ^{85}Sr /^{82}Sr on the calibration date from the generator label. Use Table 2 to read off the correction factor for the ratio of ^{85}Sr /^{82}Sr on the day of use after calibration.

Calculate the ratio R using the following formula:

$R = \frac{^{85}Sr}{^{82}Sr}$ on calibration date x correction factor on the date of measurement

8. Apply a correction factor (F) of 0.478 to compensate for the contribution of ^{85}Sr to the measured value.

9. Calculate the amount of ^{82}Sr in the sample using the following equation:

^{82}Sr (MBq)= $\frac{\text{measured value (MBq)}}{[1 + (R \times F)]}$

Example:

Dose calibration reading (MBq) = 2.96×10^{-2}

^{85}Sr /^{82}Sr ratio on day of calibration: 1.0172

Day of use after day of calibration: 22

Correction factor at 22 days according to Table 2: 1.46

R = 1.0172 x 1.46 = 1.48

Correction factor (F) = 0.478

^{82}Sr (MBq) = $2.96 \times 10^{-2}/[1 + (1.48 \times 0.478)]$

^{82}Sr (MBq) = 1.734×10^{-2}

10. Determine the ^{82}Sr content by dividing the MBq of ^{82}Sr by the MBq of ^{82}Rb at the end of elution.

Example:

1.734×10^{-2} MBq of ^{82}Sr

1850 MBq of ^{82}Rb at the end of elution

(1.734×10^{-2} MBq ^{82}Sr)/(1850 MBq ^{82}Rb) = 9.4×10^{-6} MBq/MBq ^{82}Rb

In this example, the ^{82}Sr content is greater than the alert limit of 2×10^{-6} MBq/MBq of ^{82}Rb. Consequently, an additional breakthrough test should be performed.

11. Determine the ^{85}Sr content by multiplying the result obtained in step 10 by the ratio (R) ^{85}Sr /^{82}Sr.

Example:

$9.4 \times 10^{-6} \times 1.48 = 1.4 \times 10^{-5}$ MBq ^{85}Sr /MBq ^{82}Rb

In this example, the ^{85}Sr content is less than the alert limit of 2×10^{-5} MBq/MBq of ^{82}Rb.

Table 2: $^{85}Sr/^{82}Rb$ ratio

Days	Correction factor	Days	Correction factor
0*	1.00	22	1.46
1	1.02	23	1.48
2	1.03	24	1.51
3	1.05	25	1.53
4	1.07	26	1.56
5	1.09	27	1.59
6	1.11	28	1.61
7	1.13	29	1.64
8	1.15	30	1.67
9	1.17	31	1.70
10	1.19	32	1.73
11	1.21	33	1.76
12	1.23	34	1.79
13	1.25	35	1.82
14	1.27	36	1.85
15	1.29	37	1.88
16	1.31	38	1.91
17	1.34	39	1.95
18	1.36	40	1.98
19	1.38	41	2.01
20	1.41	42	2.05
21	1.43		

* day of calibration

Radiation emission

The half-value layer is 0.7 cm of lead (Pb). Table 3 shows a range of values for the relative attenuation of the radiation emitted by radionuclides, which results from the interposition of various thicknesses of lead. For example, the use of a 7.0-cm thickness of lead will attenuate the radiation emitted by a factor of about 1000.

Table 3: Radiation attenuation by lead shielding

Shield thickness (Pb, in cm)	Attenuation factor
0.7	0.5
2.3	10^{-1}
4.7	10^{-2}
7.0	10^{-3}
9.3	10^{-4}

Strontium-82, with its half-life of 25 days (600 hours), decays to rubidium-82 ^{82}Rb. To correct for physical decay of strontium ^{82}Sr, Table 4 shows the fractions that remain at selected intervals after the time of calibration.

Table 4: Radioactive decay table:

Days	Fraction remaining	Days	Fraction remaining	Days	Fraction remaining
0*	1.000	15	0.660	30	0.435
1	0.973	16	0.642	31	0.423
2	0.946	17	0.624	32	0.412
3	0.920	18	0.607	33	0.401
4	0.895	19	0.591	34	0.390
5	0.871	20	0.574	35	0.379
6	0.847	21	0.559	36	0.369
7	0.824	22	0.543	37	0.359
8	0.801	23	0.529	38	0.349
9	0.779	24	0.514	39	0.339
10	0.758	25	0.500	40	0.330
11	0.737	26	0.486	41	0.321
12	0.717	27	0.473	42	0.312
13	0.697	28	0.460		
14	0.678	29	0.448		

* Calibration date

To correct for physical decay of rubidium ^{82}Rb, Table 5 shows the fraction of the rubidium ^{82}Rb chloride injectable solution remaining in 15-second intervals up to 300 seconds after time of calibration.

Table 5: Radioactive decay table:

Seconds	Fraction remaining	Seconds	Fraction remaining
0*	1.000	165	0.218
15	0.871	180	0.190
30	0.758	195	0.165
45	0.660	210	0.144
60	0.574	225	0.125
75	0.500	240	0.109
90	0.435	255	0.095
105	0.379	270	0.083
120	0.330	285	0.072
135	0.287	300	0.063
150	0.250		

*Time elapsed since elution.

12.6.2 Cardiogen-82 Infusion System Model 1701 Eluate Testing Protocol

The **rubidium ^{82}Rb chloride** content of the injectable solution is determined as follows:

1. Set a dose calibrator for ^{82}Rb as recommended by the manufacturer. Obtain the reading from the instrument in megabecquerels (MBq).
2. Following the prompts in the Graphical User Interface (GUI) for the Cardiogen-82 Infusion System Model 1701, elute the generator with additive-free Sodium Chloride Infusion 9 mg/mL (0.9% w/v) at a rate of 50 mL/min and collect the eluate in the stoppered vial specifically provided for use with the Cardiogen-82 Infusion System Model 1701 (alternative vials, glass or plastic are not suitable). Note the exact time of end of elution (EOE).
3. Using the external dose calibrator, assay the eluate at exactly 2:30, 3:45, or 5:00 minutes after EOE.
4. Following the prompts in the GUI for the Cardiogen-82 Infusion System Model 1701, enter the ^{82}Rb reading from the dose calibrator and the time since EOE.
5. The infusion system software will automatically calculate the Calibration Ratio.
   - If the ratio is within +/- 2% (0.98 to 1.02), the infusion system will allow acceptance of the calibration factor that was used for the elution.
   - If the ratio is not within +/- 2% (0.98 to 1.02), the system requires another calibration elution (steps 1 through 4).
6. Repeat steps 1 through 4 for a flow rate of 20 mL/min.

Perform additional system calibration every 14 days.

To measure the **concentration of ^{82}Sr** in the eluate, proceed as follows:

Each day, before administering rubidium ^{82}Rb chloride injection, perform the following test, including Mandatory Eluate Testing:

1. Place the stoppered vial, which is specifically provided for use with the Cardiogen-82 Infusion System, Model 1701 (alternative vials, glass or plastic are not suitable) in the Sr detector well on the Cardiogen-82 Infusion System Model 1701 and, following the prompts in the GUI for the infusion system, initiate the Daily Quality Control workflow.
2. The infusion system will automatically perform the Sr Detector Background Reading.
3. The infusion system will automatically perform the Generator Column Wash.
4. Strontium Level Test and Dose Constancy:
    a. The infusion system will elute the generator with 50 mL of additive-free 0.9% Sodium Chloride Injection USP at a rate of 50 mL/min into the stoppered vial (which is specifically provided for use with the Cardiogen-82 Infusion System Model 1701).
    b. The Sr detector measures the ^{82}Rb and strontium in the 50 mL elution.
    c. The infusion system software will automatically calculate the ^{82}Sr and ^{85}Sr levels on the day (post calibration) of the measurement using the ratio of ^{85}Sr /^{82}Sr on the day of calibration provided on the generator label, and using the full exponential decay calculation for each, accounting for the generator's age.
    d. Using the ^{82}Rb and strontium measurements, the infusion system software will automatically calculate MBq ^{82}Sr/MBq ^{82}Rb and MBq ^{85}Sr /MBq ^{82}Rb. The GUI will automatically indicate if the results exceed Alert or Expiration Limits.
    e. The infusion system software will automatically calculate Dose Constancy.
5. Constancy Check of the Sr detector: The infusion system GUI will prompt the user to perform the constancy check of the Sr detector.
    a. Place the external constancy source in the detector well of the infusion system.

The infusion system software will automatically calculate the constancy of the Sr detector versus the external constancy source when instructed.