

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cardiogen-82 3.3–5.6 GBq radionuclide generator

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Cardiogen-82 is a radionuclide generator of rubidium-82 (Rb-82) containing strontium-82 (Sr-82) 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 (Rb-82) chloride.

The activity of the generator is between 3.3 and 5.6 GBq Sr-82 at calibration time. The activity of the rubidium (Rb-82) 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:

- $\text{Sr-82} \leq 1 \times 10^{-5} \text{ MBq/MBq Rb-82}$
- $\text{Rb-83} \leq 5 \times 10^{-5} \text{ MBq/MBq Rb-82}$
- $\text{Sr-85} \leq 1 \times 10^{-4} \text{ MBq/MBq Rb-82}$
- for all other radio-contaminants: $\leq 5 \times 10^{-6} \text{ MBq/MBq Rb-82}$
- 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 $1 \times 10^{-5} \text{ MBq}$ of strontium-82 (Sr-82) and no more than $1 \times 10^{-4} \text{ MBq}$ of strontium-85 (Sr-85) per megabecquerel (MBq) of injectable solution of rubidium-82 (Rb-82) chloride.

Physical properties

Rubidium-82 (Rb-82) decays to stable krypton (Kr-82) 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 776.5 keV.

Strontium-82 (Sr-82) decays to rubidium-82 (Rb-82) with a half-life of 25.35 days. Decay is via capture of an electron, with no gamma ray or particulate emission.

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 (Rb-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 (Rb-82) 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 (CAD).

4.2 Posology and method of administration

Posology

In 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.

Do not exceed a single dose of 2220 MBq.

Renal and hepatic impairment

A reduction in hepatic or renal function is not anticipated to alter clearance of rubidium-82 (Rb-82) chloride solution, because Rb-82 decays to stable krypton-82 (Kr-82) gas with a half-life of 75 seconds, and Kr-82 gas is naturally expelled through the lungs. Therefore, no adjustments are required for renal and hepatic impairment.

Paediatric population

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

It is not expected that children would be a significant population for Rb-82 PET myocardial perfusion imaging (MPI). If Rb-82 PET MPI of a child is being considered under special circumstances, careful consideration of the administration is required, since the effective absorbed dose per MBq is higher than in adults. Alternative techniques which do not involve ionizing radiation should be considered.

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 preparation of the product before administration, see section 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-82).

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 (Rb-82) chloride solution.
- Start imaging 60 to 90 seconds after completion of the infusion of the rest dose, and acquire images for 5 minutes.

For myocardial perfusion *pharmacological stress* imaging:

- In order to avoid the presence of residual activity from the previous infusion, and to allow time for the generator to accumulate a sufficient quantity of Rb-82, wait at least 10 minutes after completion of the previous rubidium (Rb-82) chloride dose infusion before starting the pharmacological stress test.
- Administer the pharmacological stressor in accordance with its prescribing information (using a vasodilator approved for this purpose).
- After the interval recommended in the prescribing information of the pharmacological stressor, administer the second single dose of rubidium (Rb-82) chloride.
- Start imaging 60 to 90 seconds after completion of the infusion of the stress dose, and acquire images for 5 minutes.

Patients with severe heart failure

In patients with a clinically significant reduction in cardiac function (output, LVEF), a longer circulation time may be anticipated. In such case, it may be necessary to increase the interval between infusion and image acquisition, e.g., to 120 seconds. Such patients should be clinically monitored following the infusion (see section 4.4).

4.3 Contraindications

Pregnancy

The eluate must not be used if the specified generator eluate limits for strontium-82 (Sr-82) and/or strontium-85 (Sr-85) have been exceeded (see section 4.4).

Cardiogen-82 is contraindicated for use with solutions other than additive-free Sodium Chloride Infusion 9 mg/mL (0.9% w/v) (see section 4.4).

4.4 Special warnings and precautions for use

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.

The application of vasodilator pharmacologic stress may cause serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, broncho-

constriction, and cerebrovascular events. Perform testing only in setting where cardiac resuscitation equipment and trained staff are readily available.

For pharmacological stress imaging, the procedure should be performed at a medical facility where cardiac monitoring and resuscitation equipment are available. Please refer to the Summary of Product Characteristics of the pharmacological stress agent being administered.

Paediatric population

For information on use in the paediatric population, see section 4.2.

Patient preparation

Patients must be fasting for at least 6 hours, and refrain from caffeinated beverages, food and drugs containing caffeine for at least 12 hours prior to the test.

Failure to respond to pharmacological stress may be due to prolonged caffeine effects or longer serum caffeine clearance, which is seen in some individuals.

Medications that may interfere with responses to a pharmacological stress test (e.g., anti-anginal medicines) should be evaluated for modifications prior to the test by the patient's physicians. Dipyridamole should be stopped for 24 hours, and xanthine-containing drugs for 48 hours, prior to the test.

After the PET scan

Due to the very short half-life of rubidium-82 (Rb-82), no special precautions need to be taken with regard to radioactivity.

Specific warnings

Rubidium-82 (Rb-82) 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-82) chloride, with a single dose not exceeding 2220 MBq and a cumulative dose not exceeding 4440 MBq, at a maximum rate of 50 mL/min, with a maximum volume per infusion of 100 mL, and a total volume not exceeding 200 mL.

Unintended patient exposure to ionising radiation due to contamination with strontium can occur in patients receiving rubidium-82 (Rb-82) 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).

High level radiation exposure to the bone marrow has occurred in some patients due to strontium-82 (Sr-82) and/or strontium-85 (Sr-85) breakthrough in the eluate when an incorrect solution was used to elute the Cardiogen-82 generator (see section 12.2).

Strontium-82 (Sr-82) and strontium-85 (Sr-85) impurities are subject to bone sequestration and subsequent accumulation in bone tissue due to their long half-lives (25.35 days for Sr-82 and 64.84 days for Sr-85). Long-term safety implications of exposure to Sr-82 and Sr-85 are unknown; therefore, the eluate must not be used if the specified generator eluate limits have been exceeded (see section 4.3).

Rubidium-82 (Rb-82) 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.

For precautions with respect to environmental hazard, see section 6.6

Rubidium-82 (Rb-82) chloride solution contributes to a cumulative ionising radiation exposure.

Use the lowest dose of rubidium-82 (Rb-82) chloride injection necessary for imaging and ensure safe handling to protect the patient and health care worker.

Encourage patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However, 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Drugs known to inhibit the activity of myocardial Na⁺/K⁺/ATPase pumps, such as cardiac glycosides (e.g., digoxin), may generally reduce Rb-82 myocardial uptake.

Proton pump inhibitor (PPI) use is associated with an increased gastric uptake of Rb-82. Spill over from gastric uptake could impact on the interpretation of adjacent myocardium on Rb-82 PET MPI studies. Withholding PPI > 36 hours prior to Rb-82 PET MPI may reduce the 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 (Rb-82) with regard to reproduction. The risks to the foetus when Rb-82 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 (Rb-82) is excreted in human milk. Due to the short half-life of Rb-82 (75 seconds) significant excretion is unlikely, and what is excreted will rapidly decay. However, because many active substances are excreted in human milk, including strontium-82 (Sr-82) and strontium-85 (Sr-85), which are present in the Cardiogen-82 generator, caution should be exercised when rubidium-82 (Rb-82) chloride solution is administered to nursing women. In general, it is sufficient for women to resume breastfeeding no sooner than one hour after the last rubidium-

82 (Rb-82) chloride infusion, after having expressed and discarded milk that has accumulated in the interim.

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.

High level radiation exposure to the bone marrow has occurred in some patients due to strontium-82 (Sr-82) and strontium-85 (Sr-85) breakthrough in the eluate when an incorrect solution was used to elute the rubidium-82 (Rb-82) generator (see Section 12.2).

Unintended patient exposure to ionising radiation due to contamination with strontium can occur in patients receiving rubidium-82 (Rb-82) 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Due to the nature of the product and its use, a clinically significant overdose of rubidium-82 (Rb-82) is unlikely. In order to avoid administration of a large quantity of strontium-82 (Sr-82) and/or strontium-85 (Sr-85) (breakthrough), 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

Rubidium-82 (Rb-82) is analogous to potassium ion (K⁺) in its biochemical behaviour and is rapidly extracted by the myocardium proportional to the blood flow. Rb-82 participates in the sodium-potassium (Na⁺/K⁺) ion exchange pumps that are present in cell membranes. The intracellular uptake of Rb-82 requires maintenance of an ionic gradient across cell membranes. Rb-82 radioactivity is increased in viable myocardium reflecting intracellular retention, while the tracer is cleared rapidly from necrotic or infarcted tissue.

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

Pharmacodynamic effects

At the chemical concentrations and activities recommended for diagnostic examinations, rubidium-82 (Rb-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 Rb-82. 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 (Rb-82) to reach and be taken up by the myocardium, and uptake may also be diminished (see section 4.4).

As the blood flow carries Rb-82 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

Hyafil et al. (*J Nucl Cardiol* 2020) conducted a prospective intra-individual comparison in a population of 169 men with BMI ≥ 25 kg/m² and 144 women referred for clinically indicated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), and with an intermediate prevalence of coronary artery disease (CAD) pre-test (> 30% with Diamond and Forrester clinical score or > 3 cardiovascular risk factors). Patients were not eligible if they had known CAD or cardiomyopathy, or had undergone coronary angiography (CA) in the previous 2 years. All individuals underwent Rb-82 positron emission tomography (PET) MPI with 3D PET/CT, and 99mTc-sestamibi SPECT MPI with a cadmium-zinc-telluride (CZT) gamma camera, performed within 90 days of each other. Experienced nuclear cardiologists analysed the MPI studies separately, and were blinded to the results of each other's analyses; automated methods were used to obtain summed stress, rest and difference scores. Myocardial blood flow (MBF) and flow reserve (MFR) were quantified on PET using data from dynamic acquisitions. Subjects who were negative for significant CAD on both scans were followed up for 1 year for the development of coronary events. Subjects who were positive for significant CAD on either or both MPI scans underwent invasive coronary angiography (ICA) with fractional flow reserve (FFR) measurements. Positivity on CA was defined as significant stenosis as follows: coronary stenosis $\geq 50\%$ and FFR ≤ 0.8 ; coronary stenosis $\geq 50\%$ for the left main artery; coronary stenosis $\geq 70\%$ or occlusion for other vessels. In the absence of CA, positivity was defined as an occurrence of an acute coronary event during the following year. Five patients were excluded (uninterpretable scans / inflammatory arteritis) and 14 declined CA or

follow-up, leaving 294 patients. Thirty-seven (37) patients had myocardial ischaemia. Overall, Rb-82 PET MPI was found to have a sensitivity of 83.8% and a specificity of 93.8%, while 99mTc-sestamibi SPECT MPI with a modern CZT camera had a sensitivity of 56.8% and a specificity of 96.1%. Receiver operating characteristic (ROC) curve analysis showed Rb-82 PET MPI to possess the highest area under the curve (AUC, 0.94, vs. 0.86 for 99mTc-sestamibi SPECT MPI). It was suggested that the greater sensitivity of Rb-82 PET MPI was due to more accurate detection of balanced myocardial ischemia, potentiated by the ability with PET to obtain myocardial flow and flow reserve data.

In a systematic review and meta-analysis of 15 published Rb-82 PET MPI clinical studies including 1,344 patients, and 8 published 99mTc SPECT MPI studies including 1,755 patients (McArdle et al. *J Am Coll Cardiol* 2012), pooled accuracy using weighted averages according to the size of the patient populations was determined for PET and SPECT. Inclusion criteria were publication in peer-reviewed journals, patient populations with ischemic heart disease, MPI performed with either Rb-82 PET or 99mTc SPECT with both ECG gating and attenuation correction (AC) with either CT or transmission sources, the use of ICA as a reference standard for the diagnosis of obstructive CAD, and diagnostic performance being reported on a per-patient basis. For the PET compared to the SPECT studies, a higher proportion of patients were male (63.5% vs. 55%), with a higher baseline CAD prevalence (63% vs 50%), fewer patients with a low likelihood of CAD (13% vs 30%) and more patients with previous MI (30% vs 3.4%) and prior coronary intervention (32% vs. 3.2%). The overall pooled sensitivity and specificity of Rb-82 PET MPI for the detection of obstructive CAD were 90% (95% CI: 0.88 to 0.92) and 88% (95% CI: 0.85 to 0.91), respectively. Comparison of studies where >50% stenosis on ICA was used as a reference with >70% showed no significant difference in diagnostic accuracy (AUC: 0.948 vs. 0.954, respectively). The overall pooled sensitivity and specificity for 99mTc SPECT MPI with ECG-gating and AC were 85% (95% CI: 0.82 to 0.87) and 85% (95% CI: 0.82 to 0.87), respectively. Subgroup analysis showed that accuracy for a >50% stenosis on ICA was superior to >70% (AUC: 0.91 and 0.87, respectively). Analysis of SPECT studies where patients with known CAD or previous myocardial infarction were excluded did not alter diagnostic accuracy significantly. However, when patients with a low likelihood of CAD were excluded, there was a marked decrease in the specificity of SPECT, to 70% (95% CI: 0.66 to 0.75) with an AUC of 0.86. For PET, when patients with a low likelihood of CAD were excluded, diagnostic accuracy was unchanged (AUC 0.94), with a small decrease in specificity to 86% (95% CI: 0.82 to 0.90).

5.2 Pharmacokinetic properties

Distribution

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

Organ uptake

Rb-82 is taken up by the myocardial cells via Na^+/K^+ -ATPase pumps. The increase in Rb-82 uptake decreases as myocardial blood flow increases.

Myocardial uptake of Rb-82 is seen in the first minute following injection of Rb-82 chloride. Uptake may be delayed in patients with a clinically significant reduction in cardiac function.

Rb-82 uptake is also observed in the kidneys, liver, spleen and lungs.

Elimination

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

5.3 Preclinical safety data

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

There was no toxicity with repeated administration of 10 mL/kg/day or 3.0 mL/kg/day rubidium-82 (Rb-82) chloride for 14 days in mice and dogs, respectively.

Rubidium-82 (Rb-82) 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 Infusion 9 mg/mL (0.9% w/v)

6.2 Incompatibilities

This medicinal product must not be used with other medicinal products except those mentioned in section 12.2.

6.3 Shelf life

Generator: 42 days after the calibration date

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

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

- 42 days have passed since the calibration date,
- A total elution volume of 17 L has passed through the column since first use of the generator,
- Eluate Sr-82 level exceeds 1×10^{-5} MBq/MBq of Rb-82 after elution,
- Eluate Sr-85 level exceeds 1×10^{-4} MBq/MBq of Rb-82 after elution.

Rubidium-82 (Rb-82) chloride eluate: use immediately upon elution.

6.4 Special precautions for storage

Generator: Store below 25°C.

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

Eluate: Do not store. Use immediately upon elution; see section 6.3.

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

6.5 Nature and contents of container

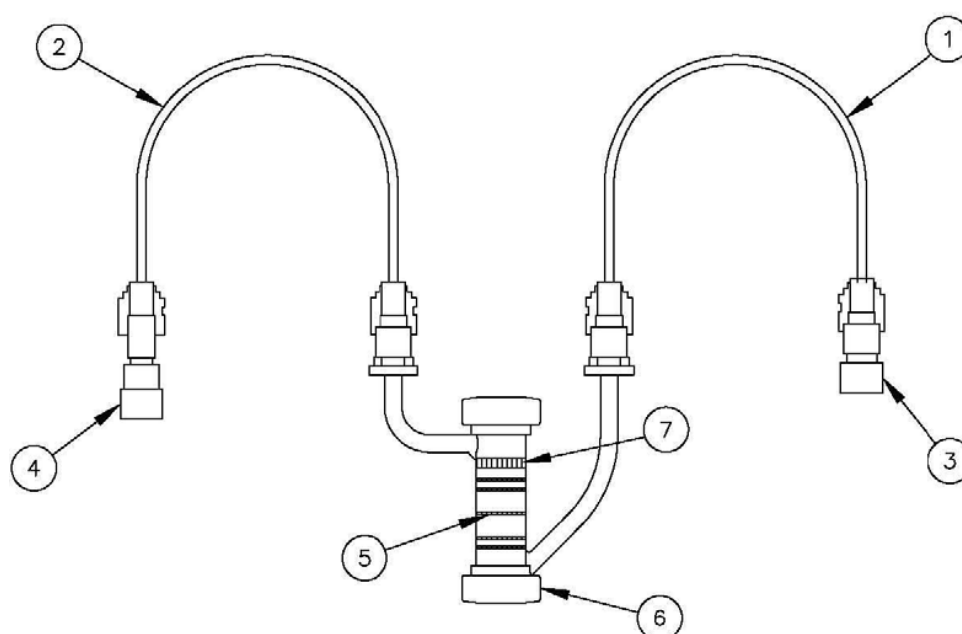
The generator is supplied in a type A transport container. It is housed in lead shielding surrounded by a labelled plastic container.

The primary packaging is composed of the “immediate” packaging in contact with the drug product which includes the column components.

[Figure 1](#) shows the complete column assembly. The polypropylene column comprises PVC connector tubing with non-sterile protective caps. The polypropylene column includes a glass fibre Millipore filter with an aluminium seal and a polypropylene spacer ring which locks into the polypropylene column.

For more information refer to the Bracco Cardiogen-82 Infusion System, Operator Manual.

Figure 1: Stannic oxide column assembly



ITEM	DESCRIPTION
1	PRESSURE TUBING – MALE/MALE CONNECTOR
2	PRESSURE TUBING – MALE/FEMALE CONNECTOR
3	FEMALE PROTECTIVE CAP
4	MALE PROTECTIVE CAP
5	MILLIPORE FILTER DISC (5)
6	SEPTA/SEAL (2)
7	POLYPROPYLENE RING SPACER

6.6 Special precautions for disposal

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 when installing the Bracco Cardiogen-82 Generator, infusion system tubing components and eluant sources. Aseptic techniques, including the use of a mask, sterile gloves and protective clothing, should be employed. If at any time in the preparation of this product the integrity of the radionuclide generator, infusion system tubing and/or eluant container is compromised, the product should not be used.

Administration procedures should be carried out in a way to minimise risk of 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.

The Bracco Cardiogen-82 Generator should only be used with the Cardiogen-82 Infusion System. Follow instructions in the Cardiogen-82 Infusion System Operator's Manual for the set up and intravenous infusion of rubidium (Rb 82) chloride injection dose(s).

The Cardiogen-82 Infusion System features safety features to reduce the potential for excessive radiation dose to patients while maintaining the expected functionality of the infusion system and improve the ease of use. These include improved technology to identify radionuclides in the generator eluate using an integrated onboard dual detector system, including the addition of an integrated Strontium (Sr) gamma detector (CZT crystal) and associated Multi-Channel Analyzer (MCA).

An on-board Panel PC with a graphical user interface (GUI), and software, provides integrated safety controls including Infusion System Calibration, and automated Daily Quality Control procedures. The system software prevents patient infusions if specified QC parameters or limits are not met, and system enforced limits for dose and volume are reached.

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-82) 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-82) and strontium-85 (Sr-85) after Rb-82 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

Any unused eluted medicinal product or used accessory waste material (e.g. infusion tubing) should be disposed of in accordance with local requirements. The generator must not be disposed of as normal waste; Bracco UK Ltd will provide the user with instructions and materials for the lawful and safe disposal of an expired generator.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/03/2023

10 DATE OF REVISION OF THE TEXT

09/01/2024

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 (Rb-82) chloride

Organ	Dose absorbed per unit activity administered (mGy/MBq)				
	Adults	15 years old	10 years old	5 years old	1 year old
Adrenals	2.4×10^{-3}	3.6×10^{-3}	5.1×10^{-3}	7.0×10^{-3}	1.0×10^{-2}
Bone surfaces	4.2×10^{-4}	5.6×10^{-4}	8.5×10^{-4}	1.4×10^{-3}	3.1×10^{-3}
Brain	1.4×10^{-4}	1.4×10^{-4}	1.6×10^{-4}	1.9×10^{-4}	2.8×10^{-4}
Breast	1.9×10^{-4}	2.0×10^{-4}	1.3×10^{-2}	2.2×10^{-2}	4.3×10^{-2}
Gallbladder	7.2×10^{-4}	8.5×10^{-4}	1.2×10^{-3}	2.0×10^{-3}	5.7×10^{-3}
Stomach	8.3×10^{-4}	1.1×10^{-3}	1.6×10^{-3}	2.7×10^{-3}	5.4×10^{-3}
Small intestine	2.0×10^{-3}	2.6×10^{-3}	4.6×10^{-3}	7.7×10^{-3}	1.5×10^{-2}
Colon	1.1×10^{-3}	1.4×10^{-3}	2.5×10^{-3}	4.1×10^{-3}	7.8×10^{-3}
Ascending colon	1.1×10^{-3}	1.4×10^{-3}	2.5×10^{-3}	4.1×10^{-3}	7.9×10^{-3}
Descending colon	1.1×10^{-3}	1.4×10^{-3}	2.4×10^{-3}	3.9×10^{-3}	7.6×10^{-3}
Heart	4.0×10^{-3}	5.2×10^{-3}	8.2×10^{-3}	1.3×10^{-2}	2.4×10^{-2}
Kidneys	9.3×10^{-3}	1.1×10^{-2}	1.6×10^{-2}	2.4×10^{-2}	4.3×10^{-2}
Liver	9.8×10^{-4}	1.3×10^{-3}	2.0×10^{-3}	3.0×10^{-3}	5.8×10^{-3}
Lungs	2.6×10^{-3}	3.8×10^{-3}	5.5×10^{-3}	8.5×10^{-3}	1.7×10^{-2}
Muscles	2.3×10^{-4}	3.6×10^{-4}	7.2×10^{-4}	2.2×10^{-3}	4.3×10^{-3}
Oesophagus	1.5×10^{-3}	2.4×10^{-3}	3.7×10^{-3}	8.1×10^{-3}	1.5×10^{-2}
Ovaries	5.0×10^{-4}	4.9×10^{-4}	1.2×10^{-3}	2.0×10^{-3}	4.4×10^{-3}
Pancreas	2.6×10^{-3}	3.7×10^{-3}	7.6×10^{-3}	9.7×10^{-3}	2.1×10^{-2}
Red bone marrow	3.8×10^{-4}	4.6×10^{-4}	7.8×10^{-4}	1.5×10^{-3}	3.8×10^{-3}
Skin	1.8×10^{-4}	2.3×10^{-4}	3.7×10^{-4}	6.1×10^{-4}	1.2×10^{-3}
Spleen	1.8×10^{-4}	3.9×10^{-4}	2.4×10^{-3}	2.8×10^{-3}	3.8×10^{-3}
Testicles	2.6×10^{-4}	3.3×10^{-4}	5.0×10^{-4}	7.9×10^{-4}	1.5×10^{-3}
Thymus	1.5×10^{-3}	2.4×10^{-3}	3.7×10^{-3}	8.1×10^{-3}	1.5×10^{-2}
Thyroid	3.1×10^{-4}	3.8×10^{-4}	6.2×10^{-4}	1.0×10^{-3}	1.9×10^{-3}
Urinary bladder wall	1.8×10^{-4}	3.9×10^{-4}	2.4×10^{-3}	2.8×10^{-3}	3.8×10^{-3}

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Uterus	1.0×10^{-3}	1.1×10^{-3}	1.5×10^{-2}	2.3×10^{-2}	4.1×10^{-2}
Other tissue	3.1×10^{-4}	5.0×10^{-4}	9.3×10^{-4}	2.1×10^{-3}	4.7×10^{-3}
Effective dose per activity administered (mSv/MBq)	1.1×10^{-3}	1.4×10^{-3}	3.0×10^{-3}	4.9×10^{-3}	8.5×10^{-3}

For rubidium-82 (Rb-82), 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 (Rb-82 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 Sr-82 with potential adverse 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 onset of infusion are pre-defined electronically.

12.3 Radionuclidic purity and quality control: measurement of Rb-82, Sr-82 and Sr-85 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 eluate of the day must be discarded to ensure that a false positive for strontium breakthrough does not occur. This 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), daily quality control testing (rubidium (Rb-82) activity and levels of Sr-82 and Sr-85 in the

eluate) should be performed carefully on the fixed 50 ml volume eluted for the second elution and with strict adherence to the instructions below. Records of 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 (Rb-82) 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 Rb-82.
- elute only with Sodium Chloride Infusion 9 mg/mL (0.9% w/v) 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:

- 42 days have passed since the calibration date,
- a total elution volume of 17 L has already passed through the column since first use of the generator,
- eluate Sr-82 level exceeds 1×10^{-5} MBq/MBq Rb-82 after elution,
- eluate Sr-85 level exceeds 1×10^{-4} MBq/MBq Rb-82 after elution.

12.5 Additional tests

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,
- eluate Sr-82 level exceeds 2×10^{-6} MBq/MBq Rb-82 after elution,
- eluate Sr-85 level exceeds 2×10^{-5} MBq/MBq Rb-82 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 (Rb 82) chloride injection dose(s).

12.6.1 Cardiogen-82 Infusion System Model 510 Eluate Testing Protocol

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

Procedures 1 to 11 below should be performed.

The **rubidium (Rb-82) chloride content** of the injectable solution is determined as follows:

1. Set a dose calibrator for Rb-82 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 additive-free Sodium Chloride Infusion 9 mg/mL (0.9% w/v) of pharmacopeia quality, and discard the eluate (first elution).
3. Allow at least 10 minutes for the regeneration of Rb-82 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 Rb-82 ($A_{Rb}(t)$) and note the time (t) of the reading. Correct the reading to the end of elution using the relevant fraction remaining for Rb-82 (see Table 5).

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

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 Sr-82** in the eluate, proceed as follows:

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

6. Measure the activity of the sample using a dose calibrator at the setting recommended by the manufacturer for Rb-82 and/or Sr-82. 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 Sr-85/Sr-82 on the calibration date from the generator label. Use Table 2 to read off the correction factor for the ratio of Sr-85/Sr-82 on the day of use after calibration.

Calculate the ratio R using the following formula:

$$R = \frac{{}^{85}\text{Sr}}{{}^{82}\text{Sr}} \text{ on calibration date} \times \text{correction factor for the ratio on the date of measurement}$$

8. Apply a correction factor (F) of 0.478 to compensate for the contribution of Sr-85 to the measured value.
9. Calculate the amount of Sr-82 in the sample using the following equation:

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

Example:

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

Sr-85/Sr-82 ratio on day of calibration: 1.0172

Day of use after day of calibration: 22

Correction factor for the ratio at 22 days according to Table 2 1.46

$$R = 1.0172 \times 1.46 = 1.48$$

Correction factor (F) = 0.478

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

$$\text{Sr-82(MBq)} = 1.734 \times 10^{-2}$$

10. Determine the Sr-82 content by dividing the MBq of Sr-82 by the MBq of Rb-82 at the end of elution.

Example:

1.734×10^{-2} MBq of Sr-82

1850 MBq of Rb-82 at the end of elution

$$(1.734 \times 10^{-2} \text{ MBq Sr-82}) / (1850 \text{ MBq Rb-82}) = 9.4 \times 10^{-6} \text{ MBq/MBq Rb-82}$$

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

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

Example:

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

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

Table 2: Sr-85/Sr-82 ratio

Days	Correction factor for the ratio	Days	Correction factor for the ratio
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 (Rb-82). To correct for physical decay of strontium Sr-82, 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 (Rb-82), Table 5 shows the fraction of the rubidium (Rb 82) 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 (Rb-82) chloride** content of the injectable solution is determined as follows:

1. Set a dose calibrator for Rb-82 as recommended by the manufacturer. Obtain the reading from the instrument in millicuries.
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 Rb-82 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 Sr-82** in the eluate, proceed as follows:

Each day, before administering rubidium Rb-82 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 Rb-82 and strontium in the 50 mL elution.
 - c. The infusion system software will automatically calculate the Sr-82 and Sr-85 levels on the day (post calibration) of the measurement using the ratio of Sr-85/Sr-82 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 Rb-82 and strontium measurements, the infusion system software will automatically calculate MBq Sr-82/MBq Rb-82 and MBq Sr-85/MBq Rb-82. 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.
 - b. The infusion system software will automatically calculate the constancy of the Sr detector versus the external constancy source when instructed.