Bracco Diagnostics

CardioGen-82®

Rubidium Rb 82 Generator

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CARDIOGEN-82 safely and effectively. See full prescribing information for CARDIOGEN-82.

CARDIOGEN-82® (rubidium Rb 82 generator)

To produce rubidium Rb 82 chloride injection, for intravenous use

Initial U.S. Approval: 1989

WARNING: HIGH LEVEL RADIATION EXPOSURE WITH USE OF INCORRECT ELUENT AND FAILURE TO FOLLOW THE ELUATE TESTING PROTOCOL

Please see full prescribing information for complete boxed warning

High Level Radiation Exposure with Use of Incorrect Eluent

Using the incorrect eluent can cause high Strontium (Sr) 82 and Sr 85 breakthrough levels (5.1)

• Use only additive-free 0.9% Sodium Chloride Injection USP to elute the generator (2.4)

• Immediately stop the patient infusion and permanently discontinue the use of the affected CardioGen-82 generator if the incorrect solution is used to elute the generator (4)

• Evaluate the patient's radiation absorbed dose and monitor for the effects of radiation to critical organs such as bone marrow (2.7)

Excess Radiation Exposure with Failure to Follow the Eluate Testing Protocol

Excess radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed limits. (5.2)

• Record eluate volume, including waste and test volumes. (2.4)

• Strictly adhere to the generator eluate testing protocol (2.5)

• Stop using the generator if it reaches any of its Expiration Limits (2.6)

----------RECENT MAJOR CHANGES----------

Boxed Warning, HIGH LEVEL RADIATION EXPOSURE WITH USE OF INCORRECT ELUENT AND FAILURE TO FOLLOW THE ELUATE TESTING PROTOCOL	04/2019
Dosage and Administration, Directions for Eluting Rubidium Rb 82 Chloride Injection (2.4)	04/2019
Contraindications (4)	04/2019
Warnings and Precautions, High Level Radiation Exposure with Use of Incorrect Eluent (5.1)	04/2019

----------INDICATIONS AND USAGE----------

CardioGen-82 is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease. (1)

----------DOSAGE AND ADMINISTRATION----------

- Use only additive free 0.9% Sodium Chloride Injection USP to elute the generator (2.4)
- Use CardioGen-82 with a specific infusion system. (2.1)
- The recommended adult (70 kg) dose of rubidium Rb 82 chloride injection is 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30-60 mCi) infused intravenously at a rate of 50 mL/minute, not to exceed a total volume of 100 mL. Do not exceed a single dose of 2220 MBq (60 mCi). (2.2)
- Start imaging acquisition 60-90 seconds after completion of the infusion; if a longer circulation time is anticipated, wait for 120 seconds. Image acquisition is typically 5 minutes long. (2.2)
- To obtain rest and stress images, wait 10 minutes after completion of the rest image acquisition then administer the pharmacologic stress agent in accordance with its prescribing information. Three minutes after administration of the pharmacologic stress agent, infuse the second dose of rubidium Rb 82 chloride and complete the stress image acquisition. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

CardioGen-82 consists of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr 82 at calibration time. (3)

----------CONTRAINDICATIONS----------

CardioGen-82 is contraindicated if a solution other than additive free 0.9% Sodium Chloride Injection USP has been used to elute the generator at any time. (4)

----------WARNINGS AND PRECAUTIONS----------

- Pharmacologic induction of cardiovascular 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. (5.2)
- Volume overload: Observe patients with congestive heart failure during infusion and for several hours following injection. (5.3)

----------ADVERSE REACTIONS----------

To report SUSPECTED ADVERSE REACTIONS, contact Bracco Diagnostics Inc at 1-800-257-5181 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (6)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Only administer Rb 82 if clearly needed. (8.1)
- Nursing Mothers: Do not resume breastfeeding until one hour after the last infusion. (8.3)
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HIGH LEVEL RADIATION EXPOSURE WITH USE OF INCORRECT ELUENT AND FAILURE TO FOLLOW THE ELUATE TESTING PROTOCOL

High Level Radiation Exposure with Use of Incorrect Eluent

Patients are exposed to high radiation levels when the CardioGen-82 generator is eluted with the incorrect eluent due to high Sr 82 and Sr 85 breakthrough levels *[see Warnings and Precautions (5.1)]*

- **Use only additive-free 0.9% Sodium Chloride Injection USP to elute the generator *[see Dosage and Administration (2.4)]***
- **Immediately stop the patient infusion and permanently discontinue the use of the affected CardioGen-82 generator if the incorrect solution is used to elute the generator *[see Contraindications (4)]*.**
- **Evaluate the patient's radiation absorbed dose and monitor for the effects of radiation to critical organs such as bone marrow *[see Dosage and Administration (2.7)]***

Excess Radiation Exposure with Failure to Follow the Eluate Testing Protocol

Excess radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed specified limits *[see Warnings and Precautions (5.2)]*

- **Record each generator eluate volume, including waste and test volumes, and keep a record of the cumulative eluate volume *[see Dosage and Administration (2.4)]***
- **Strictly adhere to the generator eluate testing protocol, to minimize the risk of excess radiation exposure, including daily testing and additional testing at Alert Limits *[see Dosage and Administration (2.5)]***
- **Stop using the generator if it reaches any of its Expiration Limits:**
  - **17 L for the generator's cumulative eluate volume, or**
  - **42 days post generator calibration date, or**
  - **An eluate Sr 82 level of 0.01 µCi /mCi Rb 82, or**
  - **An eluate Sr 85 level of 0.1 µCi /mCi Rb 82 *[see Dosage and Administration (2.6)]***

1 INDICATIONS AND USAGE

CardioGen-82 is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

2 DOSAGE AND ADMINISTRATION

2.1 Infusion System

Use CardioGen-82 only with an infusion system specifically designed for use with the generator and capable of accurate measurement and delivery of doses of rubidium Rb 82 chloride injection. Follow instructions in the Infusion System User's Guide for the set up and intravenous infusion of rubidium Rb 82 chloride injection dose(s).

2.2 Rubidium Rb 82 Chloride Injection Dosage

The recommended adult single dose of rubidium Rb 82 chloride injection is 1480 MBq (40 mCi) with a range of 1110-2220 MBq (30-60 mCi).

- Do not exceed a single dose of 2220 MBq (60 mCi).
- Use the lowest dose necessary to obtain adequate cardiac visualization consistent with the dosing goal of as low as reasonably achievable (ALARA).
- Individualize the dose by considering factors such as body size, and the imaging equipment and technique.
- Administer the single dose at 50 mL/minute through a catheter inserted into a large peripheral vein; do not to exceed a total infusion volume of 100 mL.

Administer two separate single doses to complete rest and stress myocardial perfusion imaging as follows:

For rest imaging:

- Administer a single ("rest") rubidium Rb 82 chloride dose;
- Start imaging 60-90 seconds after completion of the infusion of the rest dose and acquire images for 5 minutes; if a longer circulation time is anticipated (e.g., in a patient with severe left ventricular dysfunction), start imaging 120 seconds after the rest dose.

For stress imaging:

- Begin the study 10 minutes after completion of the resting dose infusion, to allow for sufficient Rb 82 decay;
- Administer a pharmacologic stress agent in accordance with its prescribing information;
- After an interval of 3 minutes, infuse a single ("stress") rubidium Rb 82 chloride dose;
- Start imaging 60-90 seconds after completion of the stress Rb 82 chloride dose infusion and acquire images for 5 minutes; if a longer circulation time is anticipated start imaging 120 sec after the stress dose.

2.3 Radiation Safety-Drug Handling

- **Use only additive-free 0.9 % Sodium Chloride Injection USP to elute the generator** [*see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)*].
- Limit the use of radiopharmaceuticals to physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Wear waterproof gloves and effective shielding when handling rubidium Rb 82 chloride injection and the infusion system.
- Observe aseptic techniques in all drug handling.
- Visually inspect the drug for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer eluate from the generator if there is any evidence of foreign matter.

2.4 Directions for Eluting Rubidium Rb 82 Chloride Injection

- **Use only additive-free 0.9 % Sodium Chloride Injection USP to elute the generator** [*see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1*)].
- Prepare the 0.9 % Sodium Chloride Injection USP for use with the Saline Tag
  - Prepare the intravenous port in accordance with the DOSAGE AND ADMINISTRATION section of the approved prescribing information of the 0.9 % Sodium Chloride Injection USP.
  - The intravenous administration port of the sodium chloride container must be penetrated only one time.
  - Strap the saline tag provided with the CardioGen-82 Infusion System on the additive-free 0.9% Sodium Chloride Injection USP container and install on the CardioGen-82 Infusion System.
  - Once the container port closure is penetrated, it should remain installed on the CardioGen-82 Infusion System for its entire period of use. A maximum of 12 hours from the initial port closure penetration is permitted, after which the bag must be replaced for the next patient.
- Allow at least 10 minutes between elutions for regeneration of Rb 82.
- Discard the first 50 mL eluate each day the generator is first eluted. Employ proper safety precautions since the eluate contains radioactivity.
- Maintain an on-going record of all eluate volumes (washing, testing, dosing volumes), including a summary of the cumulative volume of eluate from the generator.

2.5 Eluate Testing Protocol

Use only additive-free 0.9% Sodium Chloride Injection USP for all elutions *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)].*

Apply aseptic technique throughout.

Before administering rubidium Rb 82 chloride injection to the first patient each day, perform the following test:

Strontium Alert Limits and Mandatory Eluate Testing:

- Use an ionization chamber-type dose calibrator for eluate testing.
- Daily, before administering rubidium Rb 82 chloride injection to any patient, perform an eluate testing to determine Rb 82, Sr 82, and Sr 85 levels
- Perform additional daily eluate tests after detecting any of the following Alert Limits:
  - 14 L total elution volume has passed through the generator column, or
  - Sr 82 level reaches 0.002 µCi per mCi Rb 82, or
  - Sr 85 level reaches 0.02 µCi per mCi Rb 82.

Perform the additional daily eluate tests at time points determined by the day's elution volume; tests are performed every 750 mL.

- For example, if an Alert Limit were reached and the clinical site eluted less than 750 mL from the generator during the day, then no additional eluate tests would have been performed that day.
- If the same clinical site the next day eluted 1,500 mL from the generator, then the site would have performed three tests that day: 1) the required daily test that precedes any patient dosing, 2) a test at the 750 mL elution point, and 3) a test at the 1,500 mL elution point.
- If a generator's Alert Limit is reached, the clinical site performs the additional daily tests (at intervals of 750 mL) each subsequent day the generator is used. The additional tests are necessary to promptly detect excessive Sr 82 and/or Sr 85 in eluates.

Rubidium Eluate Level Testing:

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. Obtain the reading from the instrument in millicuries.
2. Elute the generator with 50 mL of Sodium Chloride Injection USP and discard the eluate (first elution).
3. Allow at least 10 minutes for the regeneration of Rb 82, then elute the generator with 50 mL of Sodium Chloride Injection USP at a rate of 50 mL/min and collect the eluate in a stoppered glass vial (plastic containers are not suitable). Note the exact time of end of elution (E.O.E.).
4. Using the dose calibrator, determine the activity of Rb 82 and note the time of the reading. Correct the reading for decay to the E.O.E. using the appropriate decay factor for Rb 82 (see Table 1).
   Note: If the reading is taken 2 ½ minutes after end of elution, multiply the dose calibrator reading by 4 to correct for decay.

Strontium Eluate Level Testing:

5. Using the sample obtained for the Rb 82 activity determination, allow the sample to stand for at least one hour to allow for the complete decay of Rb 82.
6. Measure the activity of the sample in a dose calibrator at the setting recommended by the manufacturer for Rb 82 and/or Sr 82. As an alternative, use the Co-60 setting and the reading obtained divided by 0.548. **Set the instrument to read in microcuries and record the reading in the display.**
7. Calculate the ratio (R) of Sr 85/Sr 82 on the day (postcalibration) of the measurement using the ratio of Sr 85/Sr 82 on the day of calibration provided on the generator label and the Sr 85/Sr 82 Ratio Factor from Table 2. Determine R using the following equation:

$$R = \frac{[Sr\ 85]}{[Sr\ 82]} \text{ on calibration date } X \quad \text{Ratio Factor on the day (post-calibration) of measurement}$$

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

$$\text{Sr 82 (µCi)} = \frac{\text{dose calibration reading (µCi)}}{[1 + (R)\ (F)]}$$

Example: dose calibrator reading (µCi) = 0.8; Sr 85/Sr 82 ratio (R) =1.48; correction factor (F) = 0.478.

$$\text{Sr 82 (µCi)} = \frac{0.8}{[1 + (1.48)(0.478)]} = 0.47$$

10. Determine if Sr 82 in the eluate exceeds an Alert or Expiration Limit by dividing the µCi of Sr 82 by the mCi of Rb 82 at End of Elution (see below for further instructions based on the Sr 82 level)
    Example: 0.47 µCi of Sr 82; 50 mCi of Rb 82 E.O.E.

$$\frac{0.47\ \text{µCi Sr 82}}{50\ \text{mCi Rb 82}} = 0.0094\ \text{µCi/mCi Rb 82}$$ (is above Alert Limit of 0.002; additional daily eluate testing must be performed)

11. Determine if Sr 85 in the eluate exceeds an Alert or Expiration Limit by multiplying the result obtained in step 10 by (R) as calculated in step 7 (above).
    Example: 0.0094 x 1.48 = 0.014 µCi Sr 85/mCi Rb 82 (test result is below Alert and Expiration Limits)

Use Table 1 to calculate the decay factor for Rb 82; step 4 (above).

TABLE 1
Physical Decay Chart: Rb 82 half-life 75 seconds

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		

*Elution time

Use Table 2 to calculate the ratio (R) of Sr 85/Sr 82; step 7 (above).

TABLE 2
Sr 85/Sr 82 Ratio Chart (Sr 85 T ½ = 65 days, Sr 82 ½ = 25 days)

Days	Ratio Factor	Days	Ratio Factor	Days	Radio Facor
0*	1.00	15	1.29	30	1.67
1	1.02	16	1.31	31	1.70
2	1.03	17	1.34	32	1.73
3	1.05	18	1.36	33	1.76
4	1.07	19	1.38	34	1.79
5	1.09	20	1.41	35	1.82
6	1.11	21	1.43	36	1.85
7	1.13	22	1.46	37	1.88
8	1.15	23	1.48	38	1.91
9	1.17	24	1.51	39	1.95
10	1.19	25	1.53	40	1.98
11	1.21	26	1.56	41	2.01
12	1.23	27	1.58	42	2.05
13	1.25	28	1.61		
14	1.27	29	1.64		

*Day of calibration

2.6 CardioGen-82 Expiration

Stop use of the CardioGen-82 generator once any one of the following Expiration Limits is reached.

- A total elution volume of 17 L has passed through the generator column, or
- 42 days post calibration date, or
- An eluate Sr 82 level of 0.01 µCi/mCi Rb 82, or
- An eluate Sr 85 level of 0.1 µCi/mCi Rb 82.

2.7 Radiation Dosimetry

The estimated absorbed radiation doses for Rb 82, Sr 82, and Sr 85 from an intravenous injection rubidium Rb 82 chloride are shown in Table 3.

TABLE 3 Adult Absorbed Radiation Dose Coefficient

Organ[a,b]	Rb 82 (Average for Rest and Stress) mrem/mCi (µSv/3.7 MBq)[c]	Sr 82 mrem/µCi (µSv/3.7kBq)[c]	Sr 85 mrem/µCi (µSv/3.7kBq)[c]
Adrenals	7.56	10.6	5.03
Bone – Osteogenic cells	1.86	---	---
Bone Surface	---	107	9.81
Brain	0.60	8.29	2.96
Breast	0.82	7.03	1.72
Gall Bladder Wall	3.17	8.47	2.82
Heart Wall	16.5	8.18	2.67
Kidneys	20.04	9.18	2.50
Liver	4.20	8.10	2.50
Lower Large Intestine Wall	2.84	51.8	5.14
Lungs[d]	10.7	8.25	2.84
Muscles	1.29	8.14	2.66
Ovaries	1.41	10.2	4.29
Pancreas	8.85	9.10	3.46
Red Marrow	1.19	91.0	9.84
Skin	1.14	7.03	1.75
Small Intestine	4.76	9.62	4.03
Spleen	6.61	8.10	2.54
Stomach	8.14	7.84	2.26
Testes	0.82	7.25	1.70
Thymus	1.49	7.84	2.33
Thyroid	6.11	8.07	2.57
Upper Large Intestine	5.94	23.7	3.62
Urinary Bladder Wall	1.61	21.9	2.90
Uterus	3.72	9.14	3.32
Total Body	1.77	Not Calculated	Not Calculated
Effective Dose[e]	4.74 [f]	23.4	4.03

[a] Rb 82 doses are averages of rest and stress dosimetry data (see Senthamizhchelvan et al.[1,2]). To calculate organ doses (mrem) from Rb 82, multiply the dose coefficient for each organ by the administered activity in mCi.

[b] Sr 82 and Sr 85 doses are calculated using software package DCAL and ICRP dose coefficients. To calculate organ doses (mrem) attributable to Sr 82, and Sr 85, multiply the dose coefficients by the calculated amounts of strontium in µCi.[3]

[c] To convert to SI units, insert the dose coefficient into the formula in parentheses, e.g. for adrenals 7.56 mrem/mCi = 7.56 µSv/37 MBq = 2.04 x 10^{-13} Sv/Bq.

[d] Calculated from ICRP 66

[e] Calculated from ICRP 60

[f] Stress phase only

3 DOSAGE FORMS AND STRENGTHS

CardioGen-82 is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. CardioGen-82 consists of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr 82 at calibration time.

4 CONTRAINDICATIONS

CardioGen-82 is contraindicated if a solution other than additive free 0.9% Sodium Chloride Injection USP has been used to elute the generator at any time. Immediately stop the patient infusion and permanently discontinue the use of the affected CardioGen-82 generator whenever the incorrect eluent is used *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 High Level Radiation Exposure with Use of Incorrect Eluent

Use only additive free 0.9% Sodium Chloride Injection USP to elute the generator. Apply the provided saline tag to the additive free 0.9% Sodium Chloride Injection USP container before use. Additives present in other solutions (particularly calcium ions) expose patients to high levels of radiation by causing the release of large amounts of Sr 82 and Sr 85 into the eluate regardless of the generator's age or prior use *[Dosage and Administration (2.3, 2.4, 2.5)]*.

Immediately stop the patient infusion and discontinue use of the affected CardioGen-82 generator if the incorrect eluent is used and evaluate the patient's radiation absorbed dose and monitor for the effects of radiation to critical organs such as bone marrow. When solutions containing calcium ions are used to elute the generator, high levels of radioactivity are present in any subsequent eluate, even with the use of additive free 0.9% Sodium Chloride Injection USP. *[see Boxed Warning, Dosage and Administration (2.7) and Contraindications (4)]*.

5.2 Excess Radiation Exposure with Failure to Follow Eluate Testing Protocol

Excess radiation exposure occurs when the Sr 82 and Sr 85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits.

Strictly adhere to the eluate testing protocol to minimize radiation exposure to the patient. Stop using the rubidium generator when the expiration limits are reached *[see Dosage and Administration (2.5) and (2.6)]*.

5.3 Risks Associated with Pharmacologic Stress

Pharmacologic induction of cardiovascular stress may be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform pharmacologic stress testing in accordance with the pharmacologic stress agent's prescribing information and only in the setting where cardiac resuscitation equipment and trained staff are readily available.

5.4 Volume Overload

Patients with congestive heart failure or the elderly may experience a transitory increase in circulatory volume load. Observe these patients during infusion and for several hours following rubidium chloride injection administration to detect delayed hemodynamic disturbances.

5.5 Cumulative Radiation Exposure: Long-Term Risk of Cancer

Rubidium Rb 82 chloride injection, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Use the lowest dose of rubidium Rb 82 chloride injection necessary for imaging and ensure safe handling to protect the patient and health care worker *[see Dosage and Administration (2.2) and (2.3)]*. Encourage patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

The following serious adverse reactions have been identified during postapproval use of CardioGen-82. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Radiation Exposure

High level radiation exposure to the bone marrow has occurred in some patients due to Sr 82 and Sr 85 breakthrough in the eluate when an incorrect solution was used to elute the rubidium Rb 82 generator *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Excess radiation exposure has occurred in some patients who received rubidium Rb 82 chloride injections at clinical sites where generator eluate testing appeared insufficient *[see Boxed Warning, Warnings and Precautions (5.2), and Dosage and Administration (2.5)]*.

7 DRUG INTERACTIONS

Specific drug-drug interactions have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Animal reproductive studies have not been conducted with rubidium Rb 82 chloride injection. It is also not known whether rubidium Rb 82 chloride injection can cause fetal harm when administered to a pregnant woman; however, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering rubidium Rb 82 chloride injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from rubidium Rb 82 and the gestational timing of exposure. Administer rubidium Rb 82 to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether rubidium Rb 82 chloride injection is excreted in human milk. Due to the short half-life of rubidium Rb 82 (75 seconds) it is unlikely that the drug would be excreted in human milk during lactation. However, because many drugs are excreted in human milk, caution should be exercised when rubidium Rb 82 chloride injection is administered to nursing women. Do not resume breastfeeding until one hour after the last infusion.

8.4 Pediatric Use

Rubidium Rb 82 chloride injection safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In elderly patients with a clinically important decrease in cardiac function, lengthen the delay between infusion and image acquisition *[see Dosage and Administration (2.2)]*. Observe for the possibility of fluid overload *[see Warnings and Precautions (5.3)]*.

8.6 Renal Impairment

Reductions in renal function are not anticipated to alter clearance of rubidium Rb 82 chloride injection because Rb 82 decays to stable Kr 82 with a half-life of 75 seconds and Kr 82 is exhaled through the lungs.

8.7 Hepatic Impairment

Reductions in hepatic function are not anticipated to alter clearance of rubidium Rb 82 chloride injection.

11 DESCRIPTION

11.1 Chemical Characteristics

CardioGen-82 contains accelerator-produced Sr 82 adsorbed on stannic oxide in a lead-shielded column and provides a means for obtaining sterile nonpyrogenic solutions of rubidium Rb 82 chloride injection. The chemical form of Rb 82 is ^{82}RbCl.

The amount (millicuries) of Rb 82 obtained in each elution will depend on the potency of the generator.

When eluted at a rate of 50 mL/minute, each generator eluate at the end of elution should not contain more than 0.02 microcurie of Sr 82 and not more than 0.2 microcurie of Sr 85 per millicurie of rubidium Rb 82 chloride injection, and not more than 1 microgram of tin per mL of eluate.

11.2 Physical Characteristics

Rb 82 decays by positron emission and associated gamma emission with a physical half-life of 75 seconds.[4] Table 4 shows the annihilation photons released following positron emission which are useful for detection and imaging studies.

The decay modes of Rb 82 are: 95.5% by positron emission, resulting in the production of annihilation radiation, i.e., two 511 keV gamma rays; and 4.5% by electron capture, resulting in the emission of "prompt" gamma rays of predominantly 776.5 keV. Both decay modes lead directly to the formation of stable Kr 82.[4]

TABLE 4
Principal Radiation Emission Data

Radiation	Mean Percent Per Disintegration	Mean Energy (keV)
Annihilation photons (2)	191.01	511 (each)
Gamma rays	13-15	776.5

The specific gamma ray constant for Rb 82 is 6.1 R/hour-millicurie at 1 centimeter. The first half-value layer is 0.7 centimeter of lead (Pb). Table 5 shows a range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of lead.[5] For example, the use of a 7.0 centimeter thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE 5
Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Attenuation Factor
0.7	0.5
2.3	10^{-1}
4.7	10^{-2}
7.0	10^{-3}
9.3	10^{-4}

Sr 82 (half-life of 25 days (600 hrs)) decays to Rb 82. To correct for physical decay of Sr 82, Table 6 shows the fractions that remain at selected intervals after the time of calibration.

TABLE 6
Physical Decay Chart: Sr 82 half-life 25 days

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 time

To correct for physical decay of Rb 82, Table 1 shows the fraction of Rb 82 remaining in all 15 second intervals up to 300 seconds after time of calibration *[see Dosage and Administration (2.5)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rb 82 is analogous to potassium ion (K^+) in its biochemical behavior and is rapidly extracted by the myocardium proportional to the blood flow. Rb^+ 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 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.

12.2 Pharmacodynamics

In human studies, myocardial activity was noted within the first minute after peripheral intravenous injection of Rb 82. When areas of infarction or ischemia are present in the myocardium, they are visualized within 2-7 minutes after injection as photon-deficient, or "cold", areas on the myocardial scan. In patients with reduced cardiac function, transit of the injected dose from the peripheral infusion site to the myocardium may be delayed *[see Dosage and Administration (2.2)]*.

Blood flow brings Rb 82 to all areas of the body during the first pass of circulation. Accordingly, visible uptake is also observed in other highly vascularized organs, such as the kidneys, liver, spleen and lungs.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 chloride injection may affect fertility in males or females.

14 CLINICAL STUDIES

In a descriptive, prospective, blinded image interpretation study[6] 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 Rb 82 chloride (n = 82) were compared to changes in stenosis flow reserve (SFR) as determined by coronary angiography. PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a scale of 0 (normal) to 5 (severe). Values for stenosis flow reserve, defined as flow at maximum coronary vasodilatation relative to rest flow, ranged from 0 (total occlusion) to 5 (normal). With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

A systematic review of published literature was conducted using pre-defined inclusion/exclusion criteria which resulted in identification of 10 studies evaluating the use of Rb 82 PET myocardial perfusion imaging (MPI) for the identification of coronary artery disease as defined by catheter-based angiography. In these studies, the patient was the unit of analysis and 50% stenosis was the threshold for clinically significant coronary artery disease (CAD). Of these 10 studies, 9 studies were included in a meta-analysis for sensitivity (excluding one study with 100% sensitivity) and 7 studies were included in a meta-analysis of specificity (excluding 3 studies with 100% specificity). A random effects model yielded overall estimates of sensitivity and specificity 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 (positive results being more likely to be published than negative results) which is difficult to detect especially when based on a limited number of small studies.

15 REFERENCES

1. Senthamizhchelvan S. et al. Human biodistribution and radiation dosimetry of ^{82}Rb. J Nucl Med, 2010; 51:1592 – 99.
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4. Lederer, M and Shirley, V. Table of Isotopes, 7th Edition.
5. Judge, S et al. Applied radiation and isotopes (1987); vol 38, no. 3: pp 185-90.
6. Demer, L.L. et al. Assessment of coronary artery disease severity by PET: Comparison with quantitative arteriography in 193 patients. Circulation 1989; 79: 825-35.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CardioGen-82® (rubidium Rb 82 generator) consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr 82 at calibration time. A lead shield surrounded by a labeled plastic container encases the generator. The container label provides complete assay data for each generator. Directions for determining the activity of Rb 82 eluted from the generator are described above *[see Dosage and Administration (2.5)]*. Use CardioGen-82 (rubidium Rb 82 Generator) only with an appropriate, properly calibrated infusion system labeled for use with the generator.

Receipt, transfer, handling, possession or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

16.2 Disposal

Licensee personnel should monitor the amount of radioactivity present within the generator prior to its disposal. Do not dispose of the generator in regular refuse systems. Store and/or dispose of the generator in accordance with the conditions of NRC radioactive materials license pursuant to 10 CFR, Part 20, or equivalent conditions pursuant to Agreement State Regulation. For questions about the disposal of the CardioGen-82 generator, contact Bracco Diagnostics Inc. at 1-800-447-6883, option 3.

16.3 Storage

Store the generator at 20-25°C (68-77°F) [See USP].

17 PATIENT COUNSELING INFORMATION

17.1 Women of Childbearing Potential

Patients should be advised to inform their physician or healthcare provider if they are pregnant or breastfeeding.

17.2 Post-study Breastfeeding Avoidance

Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for one hour after administration of rubidium Rb 82 chloride injection.

17.3 Post-study Voiding

Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after completion of the PET scan.

Manufactured for Bracco Diagnostics Inc.
Monroe Twp., NJ 08831

By GE Healthcare
Medi-Physics, Inc.,
South Plainfield, NJ 07080

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