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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 (2.5)**
- **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 (2.10)**

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 (2.5)**
- **Strictly adhere to the generator eluate testing protocol (2.6, 2.7)**
- **Stop using the generator if it reaches any of its Expiration Limits (2.8)**

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

Dosage and Administration, 10/2020
Directions for Eluting Rubidium Rb 82 Chloride Injection (2.5)
CardioGen-82 Infusion System Model 1700 Eluate Testing Protocol (2.7)
CardioGen-82 Dose Delivery Limit (2.9)

----------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** (2.5).
- Use CardioGen-82 only with the CardioGen-82 Infusion System Model 510 or Model 1700. (2.4)
- The recommended adult (70 kg) single dose of rubidium Rb 82 chloride injection is 1,480 MBq (40 mCi), with a range of 1,110 MBq to 2,220 MBq (30 mCi to 60 mCi). Do not exceed a single dose of 2,220 MBq (60 mCi) per rest or stress component of a procedure. (2 2)
- Administer via intravenous infusion at a rate of 50 mL/minute (Model 510 and Model 1700), or **at a rate of 20 mL/minute (Model 1700 only**). (2.2)
- Use the lowest dose necessary to obtain adequate cardiac visualization. Individualize the dose depending on multiple factors, including patient weight, imaging equipment and acquisition type used to perform the procedure (2.2).
- Start imaging acquisition 60 to 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. (2.3)
- To obtain both 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. Then, at a time interval after the administration of the pharmacologic stress agent that is in accordance with its prescribing information, infuse the second dose of rubidium Rb 82 chloride and complete the stress image acquisition. (2.3)

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

CardioGen-82 consists of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3,330 MBq to 5,550 MBq (90 millicuries to 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. (5.3)

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

To report SUSPECTED ADVERSE REACTIONS, contact Bracco Diagnostics Inc. at 1-800-257-8151 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (6)

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

- Lactation: Do not resume breastfeeding until at least one hour after completion of Cardiogen-82 infusion. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 (2.5)]***
- **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 (2.10)]***

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 (2.5)]***
- **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 (2.6, 2.7)]***
- **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 (2.8)]***

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 Radiation Safety - Drug Handling

Rubidium Rb 82 is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration *[See Warnings and Precautions (5.5)]*.

- **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.

2.2 Rubidium Rb 82 Chloride Injection Dosage

The recommended adult single dose of rubidium Rb 82 chloride injection per rest or stress component of a PET myocardial perfusion imaging (MPI) procedure is 1,480 MBq (40 mCi) with a range of 1,110 MBq to 2,220 MBq (30 mCi to 60 mCi).

- Do not exceed a single dose of 2,220 MBq (60 mCi).
- Use the lowest dose necessary, consistent with the goal of as low as reasonably achievable (ALARA), to obtain adequate cardiac visualization. The choice of dosage and infusion rate should be made at the discretion of the physician performing the Rb 82 PET myocardial perfusion imaging scan, based on his/her consideration of multiple factors, including patient body mass, and the imaging equipment and acquisition methodology used to perform the procedure. For example, 3D image acquisition may require doses at the lower end of the recommended range, compared to 2D imaging.

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- Administer the single dose at 50 mL/minute, or **at 20 mL/minute (CardioGen-82 Infusion System Model 1700 only)**, through a catheter inserted into a large peripheral vein; do not to exceed a total infusion volume of 100 mL.
- Instruct patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.
- The maximum available activity (delivery limit) will decrease as the generator ages *[see Dosage and Administration (2.9)]*.

2.3 Image Acquisition Guidelines

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 to 90 seconds after completion of the infusion of the rest dose, and acquire images for 5 minutes.

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 the administration of the pharmacologic stress agent, administer the second dose of Rb 82 at the time interval according to the prescribing information of the pharmacologic stress agent;
- Start imaging 60 to 90 seconds after completion of the stress Rb 82 chloride dose infusion, and acquire images for 5 minutes.

For Both Rest and Stress Imaging:
- 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.
- Acquisition may be started immediately post-injection if dynamic imaging is needed.

2.4 Infusion System

Use CardioGen-82 only with the CardioGen-82 Infusion System Model 510 or the CardioGen-82 Infusion System Model 1700, which are specifically designed for use with the generator and capable of accurate measurement and delivery of doses of rubidium Rb 82 chloride injection.
  - If using the CardioGen-82 Infusion System Model 510, refer to the Eluate Testing Protocol in Section 2.6 *[see Dosage and Administration (2.6)]*.
  - If using the CardioGen-82 Infusion System Model 1700, refer to the Eluate Testing Protocol in Section 2.7 *[see Dosage and Administration (2.7)]*.
- Follow instructions in the CardioGen-82 Infusion System Model 510 or Model 1700 Operator's Manual for the set up and intravenous infusion of rubidium Rb 82 chloride injection dose(s).[1,2]
- The generator, when used with either infusion system, provides ± 10% accuracy for rubidium Rb 82 chloride injection between doses of 1,110 MBq to 2,220 MBq (30 mCi to 60 mCi).

2.5 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.
- If the CardioGen-82 Infusion System Model 510 is used, discard the first 50 mL eluate each day the generator is eluted, and employ proper safety precautions since the eluate contains radioactivity. If the CardioGen-82 Infusion System Model 1700 is used, the system will automatically discard the first 50 mL of eluate each day the generator is eluted.
- If the CardioGen-82 Infusion System Model 510 is used, 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. If the CardioGen-82 Infusion System Model 1700 is used, the system software automatically records and saves all eluate volumes (all flushing, Quality Control (QC) testing, and patient infusions), representing the cumulative volume of eluate each day the generator is eluted.

2.6 CardioGen-82 Infusion System Model 510 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)]***.**

Observe aseptic technique throughout.

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Follow all instructions in the CardioGen-82 Infusion System Model 510 Operator's Manual for performing all eluate testing as described.

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

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 points.
- 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 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:

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

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; Sr85/Sr82 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 or Sr 82; 50 mCi of Rb 82 E.O.E.

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$$\frac{0.47\ \mu Ci\ Sr\ 82}{50\ mCi\ Rb\ 82} = 0.0094\ \mu Ci/mCi\ Rb\ 82$$ (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 $T_{½}$ = 25 days)

Days	Ratio Factor	Days	Ratio Factor	Days	Ratio Factor
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

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2.7 CardioGen-82 Infusion System Model 1700 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)]*.

Observe aseptic technique throughout.

Follow all instructions in the CardioGen-82 Infusion System Model 1700 Operator's Manual for performing all elute testing as described.

Perform Mandatory Eluate Testing to determine Rb 82, Sr 82, and Sr 85 levels:

1. Daily – Before administering rubidium Rb 82 chloride injection to the first patient each day.
2. Repeat as indicated after an Alert Limit has been detected.

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.

3. The CardioGen-82 Infusion System Model 1700 will automatically indicate when alert limits have been reached, and will require that additional tests be performed, to facilitate the prompt detection of excessive levels of Sr 82 and/or Sr 85 should they occur.
4. These additional daily eluate tests will be performed at intervals determined by the day's elution volume, and will be enforced by the System software. Specifically, the infusion system will require the user to perform additional eluate testing after each 750 mL of elution volume when any Alert Limit parameter has been reached.

Infusion System Calibration: Before administering rubidium Rb 82 chloride injection to the first patient:

After installation of a new generator and / or installation of a new CardioGen-82 Accessory Package, Item # 001710, perform the Rubidium Rb 82 Chloride Injection Dose Calibration (performed using an external dose calibrator).

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 1700, elute the generator with additive-free 0.9% Sodium Chloride Injection USP 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 1700 (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 1700, 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.

Daily Quality Control: Eluate (Strontium Level) Testing and Dose Constancy

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

Daily Quality Control (performed on-board the CardioGen-82 Infusion System Model 1700, using the gamma (Sr) detector):

1. Place the stoppered vial, which is specifically provided for use with the CardioGen-82 Infusion System, Model 1700 (alternative vials, glass or plastic are not suitable) in the Sr detector well on the CardioGen-82 Infusion System Model 1700 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 1700).
   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 µCi Sr 82/mCi Rb 82 and µCi Sr 85/mCi Rb 82. The GUI will automatically indicate if the results exceed Alert or Expiration Limits.

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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.

2.8 CardioGen-82 Expiration

If using the CardioGen-82 Infusion System Model 510, stop use of the CardioGen-82 generator once any one of the following Expiration Limits is reached. If using the CardioGen-82 Infusion System Model 1700, the software will automatically indicate, and will 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.

2.9 CardioGen-82 Dose Delivery Limit

The maximum available activity (delivery limit) will decrease as the generator ages. Certain doses, including the maximum recommended dose [60 mCi (2,220 MBq)] are not achievable for the entire shelf-life of the generator. Table 3 provides an estimate of the maximum available activity of Rubidium Rb 82 (Delivery Limit) as a function of generator age.

Table 3 Rubidium Rb 82 Dose Delivery Limit Based on Generator Age[1]

Generator Age (days)[2]	Maximum Rubidium Dose (Delivery Limit)
0-17	60 mCi (2,220 MBq)
24	50 mCi (1,850 MBq)
32	40 mCi (1,480 MBq)
42	30 mCi (1,110 MBq)

[1]Estimate is based on a 100 mCi (3,700 MBq) Sr 82 generator at calibration.

[2]Generator age at which delivery limit is reached varies with generator activity at release. For example, a 90 mCi (3,330 MBq) generator and a 150 mCi (5,550 MBq) generator will reach a delivery limit <60 mCi at ≥ 14 days and ≥ 33 days, respectively.

2.10 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 4.

Table 4 Adult Absorbed Radiation Dose Coefficient

Organ[a,b]	Rb 82 (Average for Rest and Stress) mrem/mCi (µSv/3.7MBq)[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 Bone	1.86	---	---
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

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Organ[a,b]	Rb 82 (Average for Rest and Stress) mrem/mCi (µSv/3.7MBq)[c]	Sr 82 mrem/µCi (µSv/3.7kBq)[c]	Sr 85 mrem/µCi (µSv/3.7kBq)[c]
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 3,330 MBq to 5,550 MBq (90 millicuries to 150 millicuries) Sr 82 at calibration time.

4 CONTRAINDICTIONS

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 (2.1. 2.5, and 2.6, 2.7)]*.

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 (2.10) 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 (2.6, 2.7) and (2.8)]*.

5.3 Risk 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.

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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 (2.1) and (2.2)]*. Encourage patients to void as soon as a study is completed and as often as possible thereafter for a 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 (2.6 or 2.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on the use of rubidium Rb 82 chloride in pregnant women. Animal reproductive studies have not been conducted with rubidium Rb 82 chloride injection. 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.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Rb 82 chloride in human milk, the effects on the breastfed infant or the effects on milk production. Due to the short half-life of rubidium Rb 82 (75 seconds), exposure of a breastfed infant through breast milk can be minimized by temporary discontinuation of breastfeeding [See Clinical Considerations]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rb 82 chloride injection, any potential adverse effects on the breastfed child from Rb 82 or from the underlying maternal condition.

Clinical Considerations

Minimizing Exposure
Exposure to Rb 82 chloride through breast milk can be minimized if breastfeeding is discontinued when Rb 82 chloride injection is administered. Do not resume breastfeeding until at least one hour after completion of rubidium Rb 82 chloride injection 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 (2.3)]*. Observe for the possibility of fluid overload *[see Warnings and Precautions (5.4)]*.

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.

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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 5 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 5
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 6 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 6
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}

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Sr 82 (half-life of 25 days (600 hrs.) decays to Rb 82. To correct for physical decay of Sr 82, Table 7 shows the fractions that remain at selected intervals after the time of calibration.

TABLE 7
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 (2.6, 2.7)]*.

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 (2.3)]*.

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.

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, posterolateral, 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

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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 system 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; 15:1592-99.
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3. Eckerman, K. F. et al. User's Guide to the DCAL System, ORNL/TM-2001-190; Oak Ridge National Laboratory, Oak Ridge, TN, August, 2006.
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), used to produce rubidium Rb 82 chloride injection, consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3,330 MBq to 5,550 MBq (90 millicuries to 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. Use CardioGen-82 (rubidium Rb 82 Generator) only with an appropriate, properly calibrated infusion system labeled for use with the generator.

16.2 Storage and Handling

- Store the generator at 20° to 25°C (68° to 77°F) [See USP].
- Receipt, transfer, possession, storage, disposal or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission (NRC), Agreement States or Licensing States as appropriate. Do not dispose of the generator in regular refuse systems.
- For questions about the disposal of the CardioGen-82 generator, contact Bracco Diagnostics Inc. at 1-800-447-6883, option 3.

17 PATIENT COUNSELING INFORMATION

Pregnancy
Advise a pregnant woman of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

Lactation
Advise lactating women that exposure to Rb-82 chloride through breast milk can be minimized if breastfeeding is discontinued when Rb 82 chloride injection is administered. Advise lactating women not to resume breastfeeding for at least one hour after completion of rubidium Rb 82 infusion *[see Use in Specific Populations (8.2)]*.

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 *[see Warnings and Precautions (5.5)]*.

Manufactured for
Bracco Diagnostics Inc.
Monroe Twp, NJ 08831

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

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CardioGen-82® Rubidium 82 Generators, Infusion Systems, and Accessories contain proprietary technology covered by one or more patents listed at www.braccoimaging.com/us-en/patents.

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Bracco Diagnostics

CAUTION

RADIOACTIVE MATERIAL

List 09101 **DIAGNOSTIC**

Must be handled only by qualified personnel in conformity with regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate

CARDIOGEN-82 ®

Rubidium Rb 82 Generator

Rx only

For Elution of sterile nonpyrogenic Rubidium Chloride Rb 82
Generator column contains Strontium Sr 82 adsorbed on hydrous stannic oxide
Recommended Dosage See Prescribing nformation
Refer to CardioGen 82 nfusion System Operator Manual for proper use of the Rubidium Rb 82 Generator

WARNING: Maintain proper radiation safety precautions at all times.
Generator column must not be removed from lead shield.
Store the generator at 20° to 25°C (68° to 77°F) [See USP].

Manufactured for Bracco Diagnostics nc
Monroe Twp NJ 08831

by GE Healthcare, Medi-Physics, nc ,
South Plain ield, NJ 07080

Made in USA

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