HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RUBY-FILL (rubidium Rb 82 generator)
To produce rubidium Rb 82 chloride injection, for intravenous use
Initial U.S. Approval: 1989

WARNING: UNINTENDED STRONTIUM 82 (Sr 82) AND STRONTIUM 85 (Sr 85) RADIATION EXPOSURE

Please see full prescribing information for complete boxed warning

- **Unintended radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed specific limits. (5.1)**
- **Perform generator eluate tests:**
  1) Determine Rb 82, Sr 82, Sr 85 levels in the eluate:
  - **Once daily, prior to any drug administration, and**
  - **With additional daily tests after detection of an Alert Limit. (2.6)**
  2) Stop use of the generator at its Expiration Limit. (2.7)

INDICATIONS AND USAGE

RUBY-FILL 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 RUBY-FILL with a specific Elution System. (2.4)

- The recommended weight-based dose of rubidium Rb 82 is between 10-30 Megabecquerels (MBq)/kg [0.27–0.81 millicuries (mCi)/kg]. (2.2)
- Do not exceed a single dose of 2220 MBq (60 mCi) per rest or stress component of a procedure. (2.2)
- Administer the single dose at a rate of 15-30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 mL. (2.2)
- Use the lowest dose necessary to obtain adequate cardiac visualization and 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 60-90 seconds after completion of the infusion; if a longer circulation time is anticipated, wait for 120 seconds. Acquisition may be started immediately post-injection if dynamic imaging is needed. Image acquisition is typically 3-7 minutes long. (2.3)
- 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. After administration of the pharmacologic stress agent, infuse the second dose of Rb 82, at the time interval according to the prescribing information of the pharmacological stress agent and complete the stress image acquisition. (2.3)

DOSAGE FORMS AND STRENGTHS

RUBY-FILL consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145 – 4255 MBq (85 – 115 mCi) Sr 82 at calibration time. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Unintended radiation exposure occurs when Sr 82 and Sr 85 levels in rubidium Rb 82 chloride injection exceed specified generator eluate limits. (5.1)
- Pharmacologic induction of cardiovascular stress: May be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform testing only in setting where cardiac resuscitation equipment and trained staff are readily available. (5.2)

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Jubilant DRAXIMAGE Inc. at 1-888-633-5343 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: UNINTENDED STRONTIUM 82 (Sr 82) AND STRONTIUM 85 (Sr 85) RADIATION EXPOSURE

Unintended 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 (5.1)]*.
Perform generator eluate tests:
1) The system automatically generates a record and saves the data for each generator eluate volume, including flushing and test volumes. Total cumulative eluate volumes are also recorded and saved for the life of the generator *[see Dosage and Administration (2.5)]*.
2) Determine Rb 82, Sr 82, Sr 85 in the generator eluate:
- **Once a day, prior to any drug administration, and**
- **At additional daily tests after detection of an Alert Limit. Alert Limits are:**
  - **20 L for the generator's cumulative eluate volume, or**
  - **An eluate Sr 82 level of 0.004 µCi/ mCi (kBq/MBq) Rb 82, or**
  - **An eluate Sr 85 level of 0.04 µCi/ mCi (kBq/MBq) Rb 82.**
- **Perform additional daily tests every 4 patients after detection of an alert limit *[see Dosage and Administration (2.6)]*.**

3) Stop use of a generator at any of the following Expiration Limits. Expiry Limits are:
- **30 L for the generator's cumulative eluate volume, or**
- **Expiration date of the generator (60 days post-manufacturing)**
- **An eluate Sr 82 level of 0.01 µCi /mCi (kBq/MBq) Rb 82, or**
- **An eluate Sr 85 level of 0.1 µCi /mCi (kBq/MBq) Rb 82 *[see Dosage and Administration (2.7)]*.**

1 INDICATIONS AND USAGE

RUBY-FILL 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 (5.3)]*.

- Use waterproof gloves and effective shielding when handling rubidium Rb 82 chloride injection and the RUBY Rubidium Elution System.
- Use 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 Recommended Dose and Administration Instructions

- The recommended weight-based dose of rubidium Rb 82 chloride to be administered per rest or stress component of a PET myocardial perfusion imaging (MPI) procedure is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg].
- Do not exceed a single dose of 2220 MBq (60 mCi).
- Use the lowest dose necessary to obtain adequate cardiac visualization and individualize the weight-based dose depending on multiple factors, including, patient weight, imaging equipment and acquisition type used to perform the procedure. For example, 3D imaging acquisition may require doses at the lower end of the recommended range compared to 2D imaging.
- Administer the single dose at a rate of 15 – 30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 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 (2.8)]*.

2.3 Image Acquisition Guidelines

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 3-7 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 administration of the pharmacologic stress agent, administer the second dose of Rb 82 at the time interval according to the prescribing information of the pharmacological stress agent;
- Start imaging 60-90 seconds after completion of the stress rubidium Rb 82 chloride dose infusion and acquire images for 3-7 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 Elution System

- Use RUBY-FILL Rubidium Rb 82 Generator only with an elution system specifically designed for use with the generator (RUBY Rubidium Elution System) and capable of accurate measurement and delivery of doses of rubidium Rb 82 chloride injection.
- The generator used with the elution system provides ± 10% accuracy for rubidium Rb 82 chloride doses between 370-2220 MBq (10-60 mCi)
- Follow instructions in the RUBY Rubidium Elution System User Manual for the set up and intravenous infusion of rubidium Rb 82 chloride injection dose.

2.5 Directions for Eluting Rubidium Rb 82 Chloride Injection

- Allow at least 10 minutes between elutions for regeneration of Rb 82.
- Elute with additive-free 0.9% Sodium Chloride Injection USP only. Additives (particularly calcium ions, to which strontium ions are chemically analogous), may cause the release of substantial amounts of Sr 82 and/or Sr 85 into the eluate regardless of the age or prior use of the generator.
- The system will automatically discard the first 75 mL eluate each day the generator is first eluted.
- The RUBY Rubidium Elution System automatically generates records and saves data of all eluate volumes (from flushing, QC testing, patient infusions), representing the cumulative volume of eluate from the generator.

2.6 Eluate Testing Protocol

- **Elute with additive-free 0.9% Sodium Chloride Injection USP only.**
- Use the ionization chamber-type dose calibrator that is integrated into the elution system (used specifically with the RUBY-FILL Rubidium Rb 82 Generator) for eluate testing.
- Perform **Mandatory Eluate Testing** (i.e. Quality Control test) 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 every 4 patients after an **Alert Limit** has been detected.

     Alert Limits:
     - 20 L total elution volume has passed through the generator column, or
     - Sr 82 level reaches 0.004 µCi per mCi (kBq per MBq) Rb 82, or
     - Sr 85 level reaches 0.04 µCi per mCi (kBq per MBq) Rb 82.
  3. Immediately after detection of the volume alert limit (20 L).
- The elution system will automatically indicate when alert limits have been reached and require that additional tests be performed.

When the Quality Control test is performed as described in the User Manual, the system automatically performs the following eluate testing:

Rubidium Eluate Testing:

1. The dose calibrator is automatically set for Rb 82 within the Elution System.
2. The Quality Control test begins by automatically initiating a generator flush using 75 mL of 0.9% Sodium Chloride Injection USP. This eluate is by default diverted towards the waste container and is ultimately discarded.
3. After the generator flush, the system waits approximately 15.2 minutes to accomplish a complete generator recharge of 12 Rb 82 half-lives
4. The system then elutes a calibration sample (35 mL of 0.9% Sodium Chloride Injection USP at 20 mL/min). Using the dose calibrator, the system automatically quantifies the activity of Rb 82 in the calibration sample (Rb 82 decay does not need to be corrected for because of a real-time automated measurement).

Strontium Eluate Testing (Strontium Breakthrough):

1. Using the calibration sample obtained from the Rb 82 eluate testing, the system allows the sample to stand for 30 minutes to allow for the complete decay of Rb 82.
2. The system measures the activity of the sample to automatically determine the total Sr 82 and Sr 85 activity.
3. The system automatically determines the ratio (R) 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 the Sr 85/Sr 82 ratio factor from the Sr 85/Sr 82 ratio based on generator age using the following equation:

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

4. The system uses a correction factor (F) of 0.48 to compensate for the contribution of Sr 85 to the reading.
5. The system calculates the amount of Sr 82 in the sample using the following equation:

In Empirical Units (µCi):

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

Example: dose calibrator reading (µCi) = 0.8
Sr 85/Sr 82 ratio (R) = (1.48)
correction factor (F) = 0.48

$$\text{Sr 82 (µCi)} = \frac{0.8\ \text{µCi}}{[1 + (1.48)(0.48)]} = 0.47\ \text{µCi}$$

In International Units (kBq):

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

Example: dose calibrator reading (kBq) = 29.6 kBq
Sr 85/Sr 82 ratio (R) = (1.48)
correction factor (F) = 0.48

$$\text{Sr 82 (kBq)} = \frac{29.6\ \text{kBq}}{[1 + (1.48)(0.48)]} = 17.3\ \text{kBq}$$

6. The system determines if Sr 82 in the eluate exceeds an Alert or Expiration Limit by dividing the µCi (or kBq) of Sr 82 by the mCi (or MBq) of Rb 82 at End of Elution (see below for further instructions based on the Sr 82 level)

In Empirical Units (µCi):

Example: 0.47 µCi of Sr 82; 50 mCi of Rb 82

$$\frac{0.47\ \text{µCi Sr 82}}{50\ \text{mCi Rb 82}} = 0.0094\ \text{µCi Sr 82/mCi Rb 82}$$

(Sr 82 is above Alert Limit of 0.004 µCi/mCi; additional daily eluate testing must be performed)

In International Units (kBq):

Example: 17.3 kBq of Sr 82; 1850 MBq of Rb 82

$$\frac{17.3\ \text{kBq Sr 82}}{1850\ \text{MBq Rb 82}} = 0.0094\ \text{kBq Sr 82/MBq Rb 82}$$

(Sr 82 is above Alert Limit of 0.004 kBq/MBq; additional daily eluate testing must be performed)

7. The system determines if Sr 85 in the eluate exceeds an Alert or Expiration Limit by multiplying the result obtained in step 6 by (R) as calculated in step 3 (above).

In Empirical Units (µCi):

Example: 0.0094 x 1.48 = 0.014 µCi Sr 85/mCi Rb 82
(Sr 85 test result is below Alert and Expiration Limits)

In International Units (kBq):

Example: 0.0094 x 1.48 = 0.014 kBq Sr 85/MBq Rb 82
(Sr 85 test result is below Alert and Expiration Limits)

The system uses Table 1 to calculate the decay factor for Rb 82

TABLE 1

Physical Decay Chart: Rb 82 half-life 75 seconds

Seconds	Fraction Remaining	Seconds	Fraction Remaining
0*	1.00	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

The system uses Table 2 to calculate the ratio (R) of Sr 85/Sr 82.

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	21	1.43	42	2.05
1	1.02	22	1.46	43	2.08
2	1.03	23	1.48	44	2.12
3	1.05	24	1.51	45	2.15
4	1.07	25	1.53	46	2.19
5	1.09	26	1.56	47	2.23
6	1.11	27	1.58	48	2.27
7	1.13	28	1.61	49	2.30
8	1.15	29	1.64	50	2.34
9	1.17	30	1.67	51	2.38
10	1.19	31	1.70	52	2.43
11	1.21	32	1.73	53	2.47
12	1.23	33	1.76	54	2.51
13	1.25	34	1.79	55	2.55
14	1.27	35	1.82	56	2.60
15	1.29	36	1.85	57	2.64
16	1.31	37	1.88	58	2.69
17	1.34	38	1.91	59	2.73
18	1.36	39	1.95	60	2.78
19	1.38	40	1.98		
20	1.41	41	2.01		

* Day of calibration.

2.7 RUBY-FILL Expiration

Stop use of the RUBY-FILL Rubidium Rb 82 Generator once any one of the following **Expiration Limits** is reached:

- A total elution volume of 30 L has passed through the generator column, or
- Expiration date of the generator (60 days post-manufacturing), or
- An eluate Sr 82 level of 0.01 μCi/mCi (kBq/MBq) Rb 82, or
- An eluate Sr 85 level of 0.1 μCi/mCi (kBq/MBq) Rb 82.

2.8 RUBY-FILL Dose Delivery Limit

The maximum available activity (delivery limit) will decrease as the generator ages. Certain doses, including the maximum recommended dose [60 mCi (2220 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 (2220 MBq)
24	50 mCi (1850 MBq)
32	40 mCi (1480 MBq)
42	30 mCi (1110 MBq)
57	20 mCi (740 MBq)

[1] Estimate is based on a 100 mCi (3700 MBq) Sr 82 generator at calibration.
[2] Generator age at which delivery limit is reached varies with generator activity at release. For example, an 85 mCi (3145 MBq) generator and a 115 mCi (4255 MBq) generator will reach a delivery limit < 60 mCi at ≥ 12 days and ≥ 23 days, respectively.

2.9 Radiation Dosimetry

The estimated radiation absorbed dose coefficients for Rb 82, Sr 82, and Sr 85 from an intravenous injection of rubidium Rb 82 chloride are shown in Table 4.

Table 4
Adult absorbed dose per radioisotope activity associated with injection

Organ	^{82}Rb[1] (μGy/MBq)	^{82}Sr[2] (μGy/kBq)	^{85}Sr[2] (μGy/kBq)
Adrenals	2.4	2.9	1.4
Bone surfaces	0.42	29	2.7
Brain	0.14	2.2	0.8
Breast	0.19	1.9	0.5
Gallbladder wall	0.72	2.3	0.8
Gastrointestinal tract			
Esophagus[3]	1.5	2.1	0.6
Stomach wall	0.83	2.1	0.6
Small intestine wall	2.0	2.6	1.1
Colon wall	1.1	9.7	1.2
(ULI wall)	1.1	6.4	1.0
(LLI wall)	1.1	14	1.4
Heart wall	4.0	2.2	0.7
Kidneys	9.3	2.5	0.7
Liver	1.0	2.2	0.7
Lungs	2.6	2.2	0.8
Muscles	0.23	2.2	0.7
Ovaries	0.50	2.8	1.2
Pancreas	2.6	2.5	0.9
Red marrow	0.38	25	2.7
Skin	0.18	1.9	0.5
Spleen	0.18	2.2	0.7
Testes	0.26	2.0	0.5
Thymus	1.5	2.1	0.6
Thyroid	0.31	2.2	0.7
Urinary bladder wall	0.18	5.9	0.8
Uterus	1.0	2.5	0.9
Remaining organs	0.31	–	–
Effective dose per unit activity	1.1 μSv/MBq	6.3 μSv/kBq	1.1 μSv/kBq

[1] Rb- 82 doses are averages of rest and stress dosimetry data. To calculate organ doses (μGy) from Rb- 82, multiply the dose coefficient for each organ by the administered activity in MBq.
[2] To calculate organ doses attributable to Sr-82 and Sr-85, multiply those dose coefficients by the respective strontium activities associated with the injection.
[3] The absorbed dose to the thymus is used as a substitute.

3 DOSAGE FORMS AND STRENGTHS

RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. RUBY-FILL consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145-4255 MBq (85-115 mCi) Sr 82 at calibration time.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Unintended Sr 82 and Sr 85 Radiation Exposure

Unintended radiation exposure occurs when the Sr 82 and Sr 85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits. To minimize the risk of unintended radiation exposure, strict adherence to a daily eluate testing protocol is required. Stop using the rubidium generator when the expiration limits are reached *[see Dosage and Administration (2.6) and (2.7)]*.

5.2 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.

5.3 Radiation Risks

RUBY-FILL use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care providers. Encourage patients to void as soon as a study is completed and as often as possible thereafter for at least one hour *[see Dosage and Administration (2.1) and (2.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reaction associated with the use of rubidium Rb 82 chloride was identified in clinical trials or post marketing reports. 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.

Unintended Sr 82 and Sr 85 Radiation Exposure: Unintended radiation exposure has occurred in some patients who received rubidium Rb 82 chloride injection at clinical sites where generator eluate testing appeared insufficient *[see Boxed Warning, Warnings and Precautions (5.1), Dosage and Administration (2.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on the use of rubidium Rb 82 in pregnant women. Animal reproduction studies with rubidium Rb 82 chloride have not been conducted. 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 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 Rb 82 chloride (75 seconds), exposure of a breast fed 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, 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 RUBY-FILL infusion.

8.4 Pediatric Use

The safety and effectiveness of rubidium Rb 82 chloride injection 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 from the infusion.

11 DESCRIPTION

11.1 Chemical Characteristics

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

The amount (mCi) of Rb 82 obtained in each elution will depend on the potency of the generator. When used with the RUBY Rubidium Elution System, the generator provides ± 10% accuracy for rubidium Rb 82 chloride doses between 370-2220 MBq (10-60 mCi).

When eluted at a rate of 15-30 mL/minute, each generator eluate at the end of elution should not contain more than 0.02 μCi (0.74 kBq) of Sr 82 and not more than 0.2 μCi (7.4 kBq) of Sr 85 per mCi of rubidium Rb 82 chloride injection, and not more than 1 μg 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. 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.

TABLE 5
Principal Radiation Emission Data

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

The specific gamma ray constant for Rb-82 is 6.33 R cm^2 / mCi h (1.23×10^{-12} C m^2 / kg MBq s). The first half-value layer is 0.53 cm 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 Pb. For example, the use of a 6.15 cm 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
0.53	0.5
1.68	10^{-1}
3.55	10^{-2}
6.15	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 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	21	0.559	41	0.321
1	0.973	22	0.543	42	0.312
2	0.946	23	0.529	43	0.304
3	0.920	24	0.514	44	0.295
4	0.895	25	0.500	45	0.287
5	0.871	26	0.486	46	0.279
6	0.847	27	0.473	47	0.272
7	0.824	28	0.460	48	0.264
8	0.801	29	0.448	49	0.257
9	0.779	30	0.435	50	0.250
10	0.758	31	0.423	51	0.243
11	0.737	32	0.412	52	0.237
12	0.717	33	0.401	53	0.230
13	0.697	34	0.390	54	0.224
14	0.678	35	0.379	55	0.218
15	0.660	36	0.369	56	0.212
16	0.642	37	0.358	57	0.206
17	0.624	38	0.349	58	0.200
18	0.607	39	0.339	59	0.195
19	0.591	40	0.330	60	0.189
20	0.574				

* 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)]*.

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 in viable myocardium is higher than in infarcted tissue, reflecting intracellular retention.

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 perfusion scan. In patients with reduced cardiac function, transit of the injected dose from the peripheral infusion site to the myocardium may be delayed.

Blood flow brings Rb 82 to all areas of the body during the first pass of circulation. Accordingly, visible uptake is observed in 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 converted by radioactive decay into 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 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 Rb 82 (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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RUBY-FILL Rubidium Rb 82 Generator consists of Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 3145-4255 MBq (85-115 mCi) Sr 82 at calibration time. A lead shield encases the generator. The container label provides complete assay data for each generator. Use RUBY-FILL Rubidium Rb 82 Generator only with an appropriate, properly calibrated Elution System (RUBY Rubidium Elution System) labeled for use with the generator.

16.2 Storage and Handling

- Store the generator at 20-25 °C (68-77 °F).
- 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 RUBY-FILL Rubidium Rb 82 Generator, contact Jubilant DraxImage Inc. at 1-888-633-5343.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risk to a fetus.

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.

General Safety Precautions

Advise 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 by:

Jubilant DRAXIMAGE Inc.
16751 TransCanada Highway
Kirkland, Québec, Canada
H9H 4J4

Version: 1