PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

RUBY-FILL®

Rubidium Rb 82 Generator

Radionuclide Generator, 3.7 GBq of ^{82}Sr per Generator

For elution of Rubidium Chloride Rb 82 Injection, USP for intravenous use

Diagnostic Radiopharmaceutical (Myocardial Imaging)
ATC V09GX04

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Sections or subsections that are not applicable at the time of authorization are not listed

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RUBY-FILL® (Rubidium Rb 82 Generator) produces a parenteral solution of ^{82}RbCl (Rubidium Chloride Rb 82 Injection) for intravenous infusion.

Rubidium Chloride Rb 82 Injection is indicated:

- as an accessory to positron emission tomography (PET) for imaging of the myocardium, to evaluate regional myocardial perfusion in adult patients, as an aid in the diagnosis or assessment of suspected or known coronary artery disease.

Rubidium Chloride Rb 82 Injection is used under rest and hyperemic (pharmacological) stress conditions.

RUBY-FILL® must be used with an infusion system specifically labelled for use with the generator and capable of accurate measurement and delivery of adequate doses of Rubidium Chloride Rb 82 Injection.

1.1 Pediatrics

Pediatrics (< 18 years of age): *No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use*.

1.2 Geriatrics

Geriatrics: Geriatric patients were included in the studies demonstrating the efficacy and safety of Rubidium Chloride Rb 82 Injection in the approved indication.

2 CONTRAINDICATIONS

RUBY-FILL® is contraindicated for use if a solution other than Additive-Free 0.9% Sodium Chloride Injection USP has been used to elute the generator.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Risk of High Level of Radiation Exposure with the Use of Incorrect Eluent

- Only Additive-Free 0.9% Sodium Chloride Injection USP should be used to elute the generator. ***See 4.7 Instructions for Preparation and Use***
- Additives present in other solutions (particularly calcium ions) have the potential to expose patients to high levels of radiation by causing the release of large amounts of ^{82}Sr and ^{85}Sr into the eluate regardless of the generator's age or prior use. ***See 7 Warnings and Precautions***
- Immediately stop the patient infusion and *discontinue* use of the affected generator if the *incorrect eluent* is used to elute the generator. ***See 7 Warnings and Precautions***
- Evaluate the patient's radiation absorbed dose and, **if excessive absorbed dose suspected or confirmed,** 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 may be present in the eluate, even with the subsequent use of Additive-Free 0.9% Sodium Chloride Injection USP. ***See 4.8 Dosimetry***
- *Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.*

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The optimal dose of Rubidium Chloride Rb 82 Injection has not been systematically investigated. As with all radiopharmaceuticals, only the lowest dose of ^{82}RbCl necessary to obtain adequate visualization should be used. A lower dose provides less radiation to patients, consistent with ALARA principles. Most procedures do not require use of the maximum dose of ^{82}RbCl. The dose to be used should be carefully individualized and factors should be considered such as: age, body size, anticipated pathology, degree and extent of visualization required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed.

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

Rubidium Chloride Rb 82 Injection should not be administered to pregnant women unless it is considered that the benefits to be gained by the patient outweigh the potential hazards to the fetus.

4.2 Recommended Dose and Dosage Adjustment

The administered activity of Rubidium Rb 82 Injection should be individualized by considering body size and PET imaging systems.

The typical adult single dose used for imaging on 3D scanners is 10 to 15 MBq/kg, whereas double this activity may be required on 2D scanners. **The maximum single dose of 3700 MBq should only be administered to patients in the range of 250 to 370 kg.** Most patients do not require the maximum dose of ^{82}RbCl.

A standard clinical ^{82}RbCl session will comprise two intravenous infusions – one at rest and the other at pharmacological stress conditions (for a mean total dose of 20 to 30 MBq/kg). Rest imaging should be performed before stress imaging.

Health Canada has not authorized an indication for pediatric use.

No dosage adjustment required in hepatic or renal impairment.

4.4 Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

RUBY-FILL® must be used with an elution system specifically labelled for use with the generator and capable of accurate measurement and delivery of doses of Rubidium Chloride Rb 82 Injection at a rate between 10 to 30 mL/min with a maximum volume per infusion of 60 mL. Two single doses (infusions) are used to complete a rest/stress imaging session. Typically, the rest infusion is administered first and then the second dose is administered (after an appropriate period) under pharmacologic stress conditions. The stress imaging is typically started about 10 minutes after the completion of the resting dose infusion and imaging to allow for sufficient isotope decay. These parameters for a single rest and stress session reflect the conditions of use under which drug development trials were conducted.

The PET imaging commences during, or shortly after patient's infusion, and is completed within a maximum of 10 minutes of elution.

Some medications may interfere with responses to a stress test (anti-anginal drugs, theophyllines) and should be withdrawn on the day of the examination. *See 9 DRUG INTERACTIONS*

Heavy meals should be avoided 4 hours before a stress test. Patient should abstain from caffeine-containing drugs and beverages for 12 hours prior to the test as prescribed by ASNC guidelines. *See 9 DRUG INTERACTIONS*

^{82}Rb assay, ^{82}Sr and ^{85}Sr breakthrough should be determined each day the generator is used in order to verify the quality of the ^{82}RbCl eluate before the administration to the patient. *See 4 DOSAGE AND ADMINISTRATION*

4.6 Image Acquisition and Interpretation

Cardiac PET myocardial perfusion imaging should be carried out only by physicians and institutions with adequate training and experience.

Rest imaging should be performed prior to stress imaging. Following the infusion, image acquisition generally starts:

- 70 to 90 seconds after injection in patients with normal ventricular function (LVEF greater than 50%);
- 90 to 100 seconds after injection in patients with reduced ventricular function (LVEF 30% to 50%);
- 110 to 130 seconds after injection in patients with poor ventricular function (LVEF less 30%).

However, some protocols may call for the start of the image acquisition during the infusion.

Image acquisition is generally completed within 10 minutes. Dipyridamole infusion can begin immediately following the end of the rest image acquisition. A second dose of ^{82}Rb can be administered 7 to 8 minutes after the start of the dipyridamole infusion.

4.7 Instructions for Preparation and Use

An appropriate elution system labeled for use with RUBY-FILL® is required. The applicable operator's manual delivered with the elution system should be consulted for detailed directions on generator hook-up, daily quality control procedure, elution process, and patient administration. Prior to use with patients, a thorough understanding of the use and performance of the system should be established.

The RUBY-FILL® product monograph and the elution system operator's manual should be read before beginning elution. Additional information for eluting the RUBY-FILL® generator follows:

- *Waterproof gloves are to be worn during the preparation and elution processes;*
- *Aseptic techniques should be employed throughout the preparation and elution processes*;
- Allow at least 6 minutes between elutions for regeneration of ^{82}Rb;
- **Use <u>only</u> Additive-Free 0.9% Sodium Chloride Injection USP to elute the generator**:
  - Complete and sign the Saline Confirmation Label provided with RUBY-FILL®;
  - Apply the Saline Confirmation Label on the clear side of the Additive-Free 0.9% Sodium Chloride Injection USP bag and install on the RUBY Rubidium Elution System;
  - Replace the Additive-Free 0.9% Sodium Chloride Injection USP bag as part of the mandatory daily quality control procedure described below;
- Discard the first 75 mL eluate each day the generator is eluted; and
- Employ proper safety precautions considering that the eluate contains radioactivity.

Directions for Quality Control

The assay of ^{82}Rb and the ^{82}Sr and ^{85}Sr breakthrough are determined using an ionization chamber-type dose calibrator and are **<u>performed by the user through a daily quality control procedure</u>**. This procedure is mandatory so the Elution System will not start patient injections unless it is performed. As indicated in the applicable operator's manual delivered with the Elution System, the user must conduct a flush and a calibration at least once in 24 hours. These runs are intended to remove air bubbles from the lines, prime lines, and remove any unbound Strontium from the generator. Once a flush has been conducted, a calibration run is mandatory to validate the activity counter and to ensure that breakthrough activity is within acceptable limits. The calibration run serves as a thorough system test, and alerts the user when levels of ^{82}Sr and ^{85}Sr corresponding to 1/5 of the USP limits are reached. This will mandate at least one additional calibration run during the day, to ensure the proper functioning of the column and detect any premature breakthrough. In this unlikely event and for any additional information, the user should refer to the Elution System's User Manual.

<u>DO NOT infuse/use eluates obtained from the flush or calibration runs for patient administration.</u>

4.8 Radiation Dosimetry

The effective dose coefficient (ICRP 103) of Rubidium Chloride Rb 82 Injection is 7.3E-04 mSv/MBq. The effective dose following a single injected activity of 1050 MBq is 0.77 mSv. The estimated effective dose for the combined rest/stress procedure is 1.5 mSv (as administered and assessed under rest conditions).

The critical organ is the kidney (4.7E-03 mSv/MBq), followed by the heart (2.5E-03 mSv/MBq), and the lungs (1.9E-03 mSv/MBq).

Table 1. Absorbed Radiation Dose Estimates (mSv/MBq)

Organ	Mean	s.d.	LL 95% CI	UL 95% CI
Adrenals	3.9E-04	1.3E-05	3.8E-04	3.9E-04
Brain	1.1E-04	1.2E-05	1.1E-04	1.2E-04
Breasts	1.7E-04	3.5E-05	1.6E-04	1.9E-04
Colon	5.8E-04	2.3E-05	5.7E-04	5.9E-04
Gallbladder	5.1E-04	1.7E-05	5.0E-04	5.2E-04
Gonads	2.4E-04	1.2E-05	2.3E-04	2.4E-04
Heart	2.5E-03	6.6E-04	2.2E-03	2.7E-03
Kidneys	4.7E-03	3.2E-04	4.5E-03	4.8E-03
Liver	5.6E-04	9.9E-05	5.2E-04	5.9E-04
Lungs	1.9E-03	5.9E-04	1.7E-03	2.1E-03
Muscle	1.7E-04	2.5E-05	1.6E-04	1.8E-04
Pancreas	1.6E-03	2.5E-04	1.5E-03	1.7E-03
Red Marrow	2.8E-04	1.3E-05	2.8E-04	2.9E-04
Osteogenic Cells	4.3E-04	2.6E-05	4.2E-04	4.4E-04
Skin	2.8E-04	1.8E-05	2.8E-04	2.9E-04
Small Intestine	8.6E-04	1.0E-04	8.2E-04	9.0E-04
Spleen	1.0E-03	2.6E-04	9.2E-04	1.1E-03
Stomach	9.1E-04	1.9E-04	8.4E-04	9.8E-04
Thymus	3.5E-04	1.2E-05	3.5E-04	3.6E-04
Thyroid	7.7E-04	1.8E-04	7.0E-04	8.3E-04
Urinary Bladder	3.9E-04	3.2E-05	3.8E-04	4.1E-04
Uterus	4.2E-04	3.7E-05	4.0E-04	4.3E-04
Remainder	4.2E-04	2.2E-06	4.2E-04	4.2E-04
Effective dose coefficient	7.3E-04	9.2E-05	7.0E-04	7.7E-04

Based on OLINDA/EXM V1.1 analysis of biokinetic data from 275 organs in 30 subjects, (as administered under rest conditions).

5 OVERDOSAGE

The administration of a radiation overdose related to ^{82}Rb is highly unlikely, as patients can safely be given the maximum available ^{82}Rb activity in the generator. The effective dose from 3700 MBq injected activity is 2.7 mSv.

In case of any reportable radiation overdose, please contact the Canadian Nuclear Safety Commission.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Intravenous (^{82}RbCl eluate)	Radionuclide Generator, 3.7 GBq of ^{82}Sr per Generator	None

RUBY-FILL® is supplied in the form of ^{82}Sr adsorbed on a hydrous stannic oxide column with an activity of 3.7 GBq of ^{82}Sr at calibration time.

The generator is encased in a lead shield container. Complete assay data for each generator are provided on the container label.

RUBY-FILL® provides an elution of Rubidium (^{82}RbCl) Chloride Injection which is a sterile, non-pyrogenic aqueous solution of ^{82}RbCl in 0.9% sodium chloride with pH of 4 to 8. The ^{82}RbCl activity delivered in a given elution depends on the volume, the elution rate, and the ^{82}Sr activity adsorbed on the generator column. At the end of the elution process, each generator eluate should not contain more than 0.02 kBq of ^{82}Sr and not more than 0.2 kBq of ^{85}Sr per MBq of rubidium-82 contained in the eluate, and not more than 1 mcg of tin per mL of Rubidium Chloride Rb 82 Injection. Rubidium Chloride Rb 82 Injection contains no carrier or stabilizing agent.

The generator is supplied with one additional sterile and non-pyrogenic set of RUBY CONNECTORS/ Luer adapters (*i.e.* one RUBY CONNECTOR body, one RUBY CONNECTOR stem and 2 Luer lock adapters fixed on each RUBY CONNECTOR). The RUBY CONNECTORS' end connecting to the generator (body and stem) is identical to the quick-connects connected to the generator. At the user's site and once the generator is installed, the sets of the quick-connects affixed to the generator is removed using aseptic techniques and replaced with RUBY CONNECTORS that serve to connect the generator to the RUBY RUBIDIUM ELUTION SYSTEM.

Saline Confirmation Labels are supplied to be used with RUBY-FILL® generator. The blank spaces on the labels are to be filled by users to confirm that only Additive-Free 0.9% Sodium Chloride Injection USP bag is to be used. The Saline Confirmation Label shall be applied on the clear side of the bag every time the bag is changed.

6.1 Physical Characteristics

^{82}Rb decays by positron emission (95.5%) and by orbital electron capture (4.5%), yielding principal radiation of two 511 keV annihilation photons (191%) useful for detection and imaging studies and a 776.5 keV photon (14.9%). ^{82}Rb decays with a physical half-life of 75.5 seconds (1.2575 min) to stable ^{82}Kr.

$$^{82}Rb_{37} \rightarrow {}^{82}Kr_{36} + e^{+} + \nu$$

The physical decay of ^{82}Rb is described by the following equation:

% remaining = $100\% \times e^{-0.009\,t}$ where *t* is time from calibration in **seconds**; or

% remaining = $100\% \times e^{-0.544\,t}$ where *t* is time from calibration in **minutes**.

6.2 External Radiation

The specific gamma-ray constant for ^{82}Rb is 0.3 Gy/hr/kBq (6.1 R/hr/mCi) at 1 cm. The narrow-beam attenuation half value layer is 4.1 mm for lead (and 3.4 cm for concrete). The broad-beam transmission factors at 511 keV for various thicknesses of lead (Pb) are given in Table 2.

For example, the use of a 7 mm thickness of Pb will attenuate the radiation emitted by a transmission factor of about 0.39.

Table 2. Broad-beam transmission factors at 511 keV in lead

mm Pb	Transmission	mm Pb	Transmission
1	0.89	9	0.29
2	0.79	10	0.25
3	0.69	12	0.18
4	0.60	14	0.13
5	0.52	16	0.10
6	0.45	18	0.07
7	0.39	20	0.05
8	0.34	30	0.01

From AAPM Task Group 108: PET and PET/CT shielding requirements.

^{82}Sr decays to ^{82}Rb with a physical half-life of 25.55 days (600 hours).

$^{82}Sr_{38} \rightarrow {}^{82}Rb_{37} + e^{+} + \nu$

The ^{82}Sr is produced in an accelerator by the reaction ^{85}Rb (p, 4n) ^{82}Sr and ^{87}Rb (p, 6n) ^{82}Sr, and by Mo (p, spallation). The ^{82}Sr produced has no carrier added. To correct for physical decay of ^{82}Sr, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

Table 3. Physical Decay Chart for ^{82}Sr

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

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
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 ^{82}Rb, the fractions that remain in all 15 second intervals up to 600 seconds after calibration time are shown in Table 4.

Table 4 Physical Decay Chart for ^{82}Rb

Seconds after Calibration	Fraction remaining	Seconds after Calibration	Fraction remaining	Seconds after Calibration	Fraction remaining
0*	1.000	210	0.145	420	0.021
15	0.871	225	0.127	435	0.018
30	0.759	240	0.110	450	0.016
45	0.662	255	0.096	465	0.014
60	0.576	270	0.084	480	0.012
75	0.502	285	0.073	495	0.011
90	0.438	300	0.064	510	0.009
105	0.381	315	0.055	525	0.008
120	0.332	330	0.048	540	0.007
135	0.290	345	0.042	555	0.006
150	0.252	360	0.037	570	0.005
165	0.220	375	0.032	585	0.005
180	0.192	390	0.028	600	0.004
195	0.167	405	0.024		

*Elution time

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

General

Rubidium Chloride Rb 82 Injection generated from RUBY-FILL® be administered only with an appropriate elution system capable of meeting the performance characteristics previously described. *See 1 INDICATIONS*

The drug should be administered only by those health professionals with a thorough understanding of the use and performance of the generator and of the elution system.

Since eluate obtained from the generator is intended for direct intravenous administration, aseptic techniques must be strictly observed in all handling. Do not administer eluate from the generator if there is any evidence of foreign matter.

Use only additive-free 0.9% Sodium Chloride Injection USP to elute the generator. Apply the provided Saline Confirmation Label to the additive-free 0.9% Sodium Chloride Injection USP bag before use. Additives present in other solutions (particularly calcium ions) may expose patients to high levels of radiation by potentially causing the release of large amounts of Sr 82 and Sr 85 into the eluate regardless of the generator's age or prior use.

Immediately stop the patient infusion and discontinue use of the affected RUBY-FILL 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 can be present in the eluate, even with the subsequent use of additive-free 0.9% Sodium Chloride Injection USP.

Because the introduction of air in the column can influence the generator performance, care should be taken to not introduce air inadvertently into the generator column during the elution system assembly, or during the patient infusion. However, any misuse that might affect the performance of the generator will be detected during the quality control test to be performed daily on the generator prior to use.

Rubidium Chloride Rb 82 Injection may contain traces of the parent radionuclide strontium 82Sr and of the impurity strontium 85Sr. Sensitive radiation monitoring equipment may detect residual radioactivity from these longer-lived isotopes (t½ of 25 and 65 days respectively) for several months following a 82Rb-PET myocardial perfusion imaging procedure. Although

detection of these trace amounts of radiation should not be a clinical concern, patients should be advised to contact their doctor if this were to occur.

Exposure to ionizing radiation may be linked with cancer induction. The effective patient dose from an average Rb-82 study is 1.8 mSv, when the typical activity of 2100 MBq per imaging procedure is administered. Rb-82 contribution to overall patient exposure to radiation is low. This level of absorbed dose is comparable to worldwide background radiation levels. Current scientific guidance in the BEIR VII report states that radiation dose under 100 mSv of low-LET radiation should not cause any increased induction of solid cancers from medical exposures such as those from Rb-82 procedures.

Carcinogenesis and Mutagenesis
Animal studies have not been performed to evaluate carcinogenic potential and mutagenic potential of ^{82}RbCl.

Cardiovascular

Caution should be used during infusion as patients with congestive heart failure may experience a transitory increase in circulatory volume load. These patients should be observed for several hours following the ^{82}Rb infusion procedure to detect delayed hemodynamic disturbances.

Contamination
Rubidium Chloride Rb 82 Injection has an ultra-short half-life of 1.27 minutes and decays rapidly *in-vivo* upon infusion, in the immediate minutes following receipt of the radiopharmaceutical. There are no special recommendations for voiding.

Driving and Operating Machinery

It is considered unlikely that rubidium (^{82}Rb) will affect your ability to drive or to use machines.

Endocrine and Metabolism

The effect of marked alterations of blood glucose, insulin or pH (such as is found in diabetic patients) on the quality of the ^{82}Rb-PET scan has not been studied in humans. During pre-scan evaluation of patients with multiple pathologies in addition to coronary artery disease, one should consider the fact that rubidium is physiologically similar to potassium. In as much as the transport of potassium is affected by these pathologies, the possibility exists that rubidium uptake may likewise be affected.

Renal

Careful consideration of the benefit risk ratio in ill patients with co-morbid conditions should always occur. Because of the very short half-life of ^{82}Rb and significant safety margin for Rubidium Chloride Rb 82 evaluations should not affect a patient with renal impairment.

Reproductive Health: Female and Male Potential

Animal studies have not been performed to evaluate whether Rubidium Chloride Rb 82 (^{82}RbCl) has an has an effect on fertility in males or females. *See 7 WARNINGS AND PRECAUTIONS*

Pharmacological Stress considerations

Induction and use of pharmacologic cardiovascular stress may be associated with such serious conditions such as myocardial infarction, dysrhythmia, hypotension, bronchoconstriction or cerebrovascular issues. Labelled directions for the stress agent should be followed and such

testing should be undertaken only in a setting where adequately trained and experienced staff and equipment are available.

Fertility

No studies have been conducted on fertility impact after a Rubidium Chloride Rb 82 evaluation. Because the absorbed dose is not meaningfully different from background radiation, no significant impact on fertility is expected nor reported.

7.1 Special Populations

7.1.1 Pregnant Women

Adequate reproduction studies have not been performed in animals to determine whether ^{82}RbCl has a teratogenic potential, or has other adverse reactions on the fetus. Therefore, Rubidium Chloride Rb 82 Injection should not be administered to pregnant women unless it is considered that the potential benefits outweigh the potential hazards to the fetus.

The absorbed radiation dose to the fetus has not been estimated. The estimated absorbed radiation dose to the uterus is 0.6 mSv for an administered dose of 1500 MBq (0.00042 mSv/MBq).

Data from literature reported no congenital malformations, growth retardation, neurodevelopmental abnormalities or other reproductive effects from radiation exposure less or equal to an effective dose of 50 mSv to the embryo, fetus or nursing child. In addition to no individual fetal radiation risk below 50 mSv, statistical, random stochastic population risk resulting from a 50 mSv radiation dose is significantly less than one percent.

Ideally examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability, should be performed during the first ten days following the onset of menses. or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

7.1.2 Breast-feeding

The excretion of ^{82}RbCl in human milk has not been studied. Since breast milk is known to contain trace amounts of dietary (non-radioactive) rubidium, it should be assumed that ^{82}Rb is secreted in breast milk. However, due to the short half-life of ^{82}Rb (76 sec), excretion of the agent during lactation is unlikely to result in significant radiation exposure to the breast-feeding infant.

Nevertheless, caution should be exercised when Rubidium Chloride Rb 82 Injection is administered to nursing mothers and formula feeding should be substituted for breast feeding.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use

7.1.4 Geriatrics

Geriatric patients were included in the studies demonstrating the efficacy and safety of Rubidium Chloride Rb 82 Injection in the approved indication. There are no known limitations on the clinical use of Rubidium Chloride Rb 82 Injection in geriatric patients.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

A systematic review of the published literature, of publicly available reference sources, and of adverse drug reaction reporting systems found no reports of adverse reactions to Rubidium Chloride Rb 82 Injection.

In a large published study in 22 PET centres, no adverse reactions to positron-emitting radiopharmaceuticals were reported retrospectively for 33 295 doses and prospectively for 47 876 doses.

8.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In Canada, no adverse reactions specifically attributed to Rubidium Chloride Rb 82 Injection were reported from clinical trial(s) use in over 7200 patients.

8.5 Post-Market Adverse Reactions

No adverse reactions specifically attributed to Rubidium Chloride Rb 82 Injection were reported to date.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Medications that may interfere with responses to a stress test (anti-anginal drugs, theophyllines) should be withdrawn on the day of the examination. *See 4 DOSAGE AND ADMINISTRATION*

9.5 Drug-Food Interactions

Heavy meals should be avoided 4 hours before a stress test. Patient should abstain from caffeine-containing drugs and beverages for 12 hours prior to the test as prescribed by ASNC guidelines. *See 4 DOSAGE AND ADMINISTRATION*

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Following intravenous administration, ^{82}Rb rapidly clears from the blood and is extracted by myocardial tissue in a manner analogous to potassium. The myocardial uptake of ^{82}Rb reflects

blood flow through the myocardium, and is useful for qualitative infarct imaging and for the detection of coronary artery stenosis and its severity.

10.2 Pharmacodynamics

With the mass dose administered in pictogram amounts, rubidium has no pharmacodynamic effects. ^{82}Rb is extracted by myocardial tissue in a manner analogous to potassium.

In human studies, myocardial activity is noted within the first minute after injection. When areas of myocardial infarction are detected with Rubidium Chloride Rb 82 Injection, they are visualized within three to eight minutes after injection as count-deficient or "cold" areas on the myocardial scan. Uptake is also observed in kidney, liver, spleen, and lung.

10.3 Pharmacokinetics

^{82}Rb in plasma crosses the capillary membrane relatively freely and is extracted by healthy myocardium in proportion to blood flow. The first-pass extraction of ^{82}Rb by the myocardium has been shown to be approximately 60% at rest. The pharmacokinetics of ^{82}Rb follows a two-compartment model. ^{82}Rb is primarily eliminated by radioactive decay to stable ^{82}Kr has which is in turn eliminated by the lungs.

Duration of Effect

Due to the short life of ^{82}Rb radionuclide, Rubidium Chloride Rb 82 Injection should be administered immediately and directly by infusion to the patient for PET imaging, which commences during, or shortly after infusion, and is completed within a maximum of 10 minutes of elution.

Special Populations and Conditions

Please see 7.1 SPECIAL POPULATIONS

11 STORAGE, STABILITY AND DISPOSAL

RUBY-FILL® should be kept in its lead shield container. RUBY-FILL® should be stored at room temperature (15 to 25˚C).

The shelf life of RUBY-FILL® is 60 days from the date of calibration. The expiry date is provided on the generator container label.

The generator should not be disposed of in regular refuse systems. Disposal of the generator should be in accordance with the conditions of *Nuclear Safety and Control Act* of the Canadian Nuclear Safety Commission (CNSC) for licensed radioactive materials.

12 SPECIAL HANDLING INSTRUCTIONS

RUBY-FILL® is intended for use only with an appropriate, properly calibrated infusion system labelled for use with the generator.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclide, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radionuclides.

Hospital personnel should monitor the amount of radioactivity present at the generator prior to its disposal. The generator should not be disposed of in regular refuse systems.

PART II: SCIENTIFIC INFORMATION

This section only pertains to Rubidium Chloride Rb 82 Injection, the drug product solution eluted from RUBY-FILL® (Rubidium Rb 82 Generator).

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Rubidium Chloride Rb 82

Chemical name: Rubidium Chloride Rb 82

Molecular formula and molecular mass: ^{82}RbCl and 117 Da

Physicochemical properties: Clear, colorless solution.

Product Characteristics:

Rubidium Chloride Rb 82 Injection is a sterile, non-pyrogenic aqueous solution of ^{82}RbCl in 0.9% sodium chloride with pH of 4 to 8. Rubidium Chloride Rb 82 Injection is eluted from RUBY-FILL® which contains accelerator-produced strontium-82 adsorbed on an α-hydrous tin oxide column in a shielded container. The ^{82}Rb activity delivered in a given elution depends on the volume, the elution rate, and the ^{82}Sr activity adsorbed on the column. Rubidium Chloride Rb 82 Injection contains no carrier or stabilizing agent.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The trial design and demographics for the studies and data assessments undertaken to support the use of RUBY-FILL® are summarized below and in Table 5.

Table 5 Summary of Clinical Trials

Title	Objectives	Design	Subjects
A retrospective study of the efficacy and safety of [^{82}Rb]-Rubidium Chloride MPI in the diagnosis of CAD	To assess the sensitivity, specificity, and safety of ^{82}Rb-PET MPI in the diagnosis of CAD	• Retrospective • Rest and stress scans • Angiography as truth standard Blinded read	• 116 patients with known or suspected CAD 69% male
A comprehensive literature review of [^{82}Rb] Rubidium Chloride – PET in the assessment of myocardial perfusion in patients with suspected or existing CAD	To assess the sensitivity, specificity, and safety of ^{82}Rb-PET MPI in the diagnosis of CAD	• MEDLINE search for ^{82}Rb-PET MPI studies of 30 patients or more • Coronary angiography as the truth standard	• 674 patients with known or suspected CAD • 70% male

Title	Objectives	Design	Subjects
The biodistribution and dosimetry of Rubidium Chloride [^{82}Rb] Injection in man	To determine the biodistribution and dosimetry of ^{82}Rb	• Prospective • Thoracic and extra-thoracic scans • Dynamic acquisition of 15 time frames over 10 minutes	• 26 patients with known or suspected CAD; 4 healthy volunteers • 60% male
A retrospective study of the safety of [^{82}Rb]-Rubidium Chloride MPI in the diagnosis of CAD	To assess the safety of ^{82}RbCl PET MPI	• Retrospective review of data from a cardiac PET registry	• 4143 consecutive patients with known or suspected CAD • 56.4% male
Inter-reader reliability	Determine inter-reader agreement	• Blinded read • Two readers	• 448 consecutive patients with known or suspected CAD • 46% male

14.2 Study Results

Diagnostic Performance - sensitivity and specificity estimates

A retrospective study was performed in 116 patients with known or suspected coronary artery disease, using invasive coronary angiography as the truth standard. The patient population included: patients with single-, double- and triple-vessel disease; patients with a previous history of myocardial infarction, percutaneous coronary intervention, or coronary bypass grafting; patients with and without angina; patients with and without congestive heart failure.

The overall prevalence of coronary artery disease in this patient population was 80.2%. ^{82}Rb-PET myocardial perfusion imaging was 94% sensitive (CI95% 86% to 97%) and 88% specific (CI95% 67% to 97%) for the detection of coronary artery disease. The six false negatives all had single-vessel disease. The three false positives all had summed stress scores (SSS) at the cut-off value of 3. Using a higher SSS value of 3.5 resulted in a specificity of 100% and a slightly lower specificity of 88%.

The sensitivity and specificity results were also assessed excluding data for patients with repeat procedures, patients who exceeded a 90-day time frame (for angiography) and those for whom a precise date of angiography could not be determined. In this instance (n = 84), prevalence was noted as 81%, sensitivity as 93% (CI 95%, 83% to 97%) and specificity as 81% (CI 95%, 54% to 95%).

These results are within the range of those data reported in a comprehensive literature review (see below).

Diagnostic Performance - inter-reader agreement

Inter-reader agreement was assessed using data from a previously published 448-patient prospective outcome study in patients with known or suspected CAD who had undergone ^{82}Rb-PET MPI scans. Results of the two blinded reads were available for 415 patients.

Both readers agreed on 126 positive ^{82}Rb-PET scans (30%), and on 276 negative scans (67%) for an overall agreement rate of 97% (when CAD = SSS ≥ 3). The chance-corrected agreement rate was excellent, with a kappa coefficient of 0.93.

When the inter-reader reliability was also compared for CAD = SSS greater than 3.5, both readers agreed on 112 positive ^{82}Rb-PET scans (27%) and on 292 negative scans (70%), thus also representing an overall agreement of 97% and a kappa coefficient of 0.93.

Radiation Dosimetry Estimates

Twenty-six patients with known or suspected CAD and 4 healthy volunteers underwent two rest ^{82}RbCl scans. Following a first 10 MBq/kg infusion, dynamic images were acquired in 15 frames over 10 minutes. Organs in the thoracic area were imaged in all patients (heart wall, heart content, liver, lungs, spleen, and stomach). Following a second infusion, organs were imaged in one of five extra-thoracic areas: (head, neck, abdomen, pelvis, or thigh). The number of organs imaged per patient ranged from 7 to 13. The number of images per organ ranged from 4 to 30. A total of 275 time-activity curves were generated for 20 different organs. Mean values were used as input variables for OLINDA/EXM V1.1. Corrections were made for hollow organs. Effective dose coefficients were calculated using ICRP 103 tissue weightings and definitions. The results are presented in the "RADIATION DOSIMETRY" section.

Literature review

A MEDLINE search was conducted for the period 1986 to 2007 to identify studies that assessed myocardial perfusion using rest-stress ^{82}Rb-PET for the diagnosis of coronary artery disease. Only studies of 30 or more patients were retained. Studies must have had a truth standard consisting of coronary angiography and must have presented sufficient data to permit re-calculation of sensitivity and specificity.

A single reviewer assessed study eligibility and quality and abstracted data on the study objective, study design, patient population, prevalence of CAD, and the sensitivity and specificity of the imaging test.

Nine studies met the inclusion criteria, six prospective and three retrospective studies. Due to flaws in the design or reporting of the study, data from two retrospective studies were excluded from the pooled dataset.

In all studies the truth standard was coronary angiography. The number of readers of ^{82}Rb-PET scans varied from 1 to 4; all readers were blinded to clinical data. In the pooled studies, the mean sample size was 112 patients (range 31 to 202); 70% were male; and the mean age was 60.9 years. The mean disease prevalence in the pooled studies was 69.4% (range 50 to 95).

The results of the individual studies are presented in Table 6; those of the pooled analyses, in Table 7.

Table 6 Summary of Literature Review Data

Study	N	Prevalence	TP	FN	TN	FP	Sensitivity	Specificity
†Gould 1986	(44)	50.0%	(21)	(1)	(18)	(4)	95% (75% to 100%)	82% (59% to 94%)
Demer 1989	174	55.2%	94	2	66	12	98% (92% to 100%)	85% (74% to 91%)
Go 1990	202	75.2%	142	10	39	11	93% (88% to 97%)	78% (64% to 88%)
Stewart 1991	81	74.1%	50	10	18	3	83% (71% to 91%)	86% (63% to 96%)
Marwick 1992	74	94.6%	63	7	4	0	90% (80% to 96%)	100% (40% to 100%)
Grover-McKay 1992	31	51.6%	16	0	11	4	100% (76% to 99%)	73% (45% to 91%)
Bateman 2006	112	66.1%	64	10	38	0	86% (76% to 93%)	100% (89% to 100%)

† These patients are included in the Demer study and are not double-counted in the pooled population.

Analyses restricted to ^{82}Rb-PET were done on a dataset that excluded the 174 patients in the Gould/Demer study, as nearly half the patients had undergone $^{13}NH_3$-PET, not ^{82}Rb-PET. Both fixed- and random-effects models were used. The exclusion of the Gould/Demer study had no dramatic effect on the estimates of and confidence intervals for sensitivity and specificity from the fixed effect model. The wider confidence intervals found when using the random-effects model suggests that the true sensitivities and specificities may have varied by study. In this case, the results from the random effects model are usually more conservative and accurate.

Table 7 Pooled Analyses

Analysis	Model	N	Prevalence	Sensitivity	Specificity
Per protocol (Included $^{13}NH_3$-PET)	Fixed effects	674	69.4%	91.7% (88.7% to 93.9%)	85.4% (79.7% to 89.8%)
Restricted to ^{82}Rb-PET	Fixed effects	500*	74.4%	90.1% (86.0% to 93.1%)	85.9% (77.3% to 91.7%)
Restricted to ^{82}Rb-PET	Random effects	500*	74.4%	90.2% (81.9% to 95.0%)	89.3% (57.5% to 98.1%)

* The Gould/ Demer study was excluded since a number of patients had undergone $^{13}NH_3$-PET

An independent published review of PET myocardial perfusion imaging studies, including both ^{13}N-ammonia and ^{82}Rb studies, reported both sensitivity and specificity of 89%.

Retrospective Safety Study

Safety data were reviewed from consecutive patients who received ^{82}RbCl from 2002 to 2008. The population consisted of 4143 patients with known or suspected coronary artery disease, having undergone rest-stress ^{82}Rb-PET myocardial perfusion imaging studies at the University of Ottawa Heart Institute. The mean age was 62.1 ± 11.9 years; 54.6% of the population was male. The mean BMI was 30.2 ± 7.0.

Patients received a mean total dose (± s.d.) of 2203 ± 785 MBq (26.1 ± 8.2 MBq/kg). The mean initial rest dose was 1098 ± 393 MBq (13.0 ± 4.1 MBq/kg). The mean stress dose was dose of 1102 ± 398 MBq (13.0 ± 4.2 MBq/kg). Seventy percent (70%) of patients received a dose of less than 30 MBq/kg.

Blood pressure and ECG were monitored throughout the procedure.

No adverse events due to Rubidium Chloride Rb 82 Injection were reported in any of these 4143 patients.

15 MICROBIOLOGY

No microbiological information is required for this drug product

16 NON-CLINICAL TOXICOLOGY

No toxicology studies have been conducted with ^{82}RbCl. The typical daily dietary intake of rubidium is 1 to 5 mg. The dose of ^{82}Rb administered for PET myocardial perfusion imaging is in the picogram range. ^{82}Rb-PET results in lower radiation exposure than ^{99m}Tc-sestamibi SPECT, ^{201}Tl SPECT, or ^{18}FDG PET.

The LD_{50} of intraperitoneally administered 'cold' Rubidium Chloride in rats is 1.2 g/kg. Chronic administration of 'cold' Rubidium Chloride to three generations of Sprague-Dawley rats had no effect on fertility, gestation, or fetal development. Animal reproductive studies have not been conducted with ^{82}RbCl.

No long-term studies have been performed to evaluate carcinogenic potential, mutagenic potential, or to determine whether rubidium ^{82}Rb may affect fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

RUBY-FILL® (Rubidium Rb 82 Generator)

Rubidium Chloride Rb 82 Injection is the medication solution eluted from RUBY-FILL® to be administered to the patient.

Read this carefully before you start taking RUBY-FILL®. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about RUBY-FILL®.

Serious Warnings and Precautions

- *Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.*

What the RUBY-FILL® used for?

- RUBY-FILL® produces a parenteral solution of Rubidium Chloride Rb 82 Injection for intravenous infusion.
- Rubidium Chloride Rb 82 Injection is a radioactive tracer, which is used as part of a Nuclear medicine test called a Positron Emission Tomography (PET) scan, to see whether your arteries are providing enough blood to your heart muscle, or whether they are blocked.

How does the RUBY-FILL® work?

Rubidium Chloride Rb 82 is a radioisotope (a medical product that contains a small amount of radioactivity) that behaves just like the potassium that helps your heart muscle work. If the arteries are not providing enough blood to your heart muscle, Rubidium Chloride Rb 82 will not be captured by the heart muscle. The heart muscle will show a blank area when a picture is taken with a special camera (PET)

What are the ingredients in RUBY-FILL®?

The medicinal ingredient, rubidium Rb 82, is a radioactive form of an element that is already contained in our blood, but in a non-radioactive form. Rubidium is found in coffee, black tea, fruits, vegetables (especially asparagus), poultry and fish.

RUBY-FILL® comes in the following dosage forms:

RUBY-FILL® is supplied in the form of ^{82}Sr adsorbed on a hydrous stannic oxide column with an activity of 3.7 GBq of ^{82}Sr at calibration time.

Do not use RUBY-FILL® if:

- if you are pregnant or suspect that you may be.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RUBY-FILL®. Talk about any health conditions or problems you may have, including if you:

- if you think you might be pregnant;
- if you are a nursing mother who is breast feeding an infant;
- if you are taking medication for angina (a heart disorder) or asthma (a breathing disorder);
- if you have ingested (eaten or drank) large amounts of caffeine containing products (coffee, tea, cola or chocolate, etc.) in the 12 hours before this test procedure.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RUBY-FILL®:

Drug-drug interactions with Rubidium Chloride Rb 82 have not been evaluated. You should not be taking caffeine-containing beverages for 12 hours prior to the procedure. Your doctor will also tell if you should stop taking some of your medications, as some may interfere with the test.

You may be asked to avoid eating large or heavy meals for four hours prior to this test and PET scan. You may also be asked to avoid eating or drinking caffeine containing products (coffee, tea, cola or chocolate, etc.) in the 12 hours before the procedure.

The health professionals who administer the test may ask you about any medication you may be taking so the doctors can assess if any slight (one dose) adjustment might be necessary.

The usual test and PET scan with this product involves two infusions (doses) that are administered within minutes of each other and imaging (pictures with a special type of camera) are then taken right after; the whole process is completed on the same day and usually within a couple of hours.

How to take RUBY-FILL®:

Rubidium Chloride Rb 82 Injection will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

Usual dose:

The typical adult single dose used for imaging on 3D scanners is 10 to 15 MBq/kg, whereas double this activity may be required on 2D scanners. **The maximum single dose of 3700 MBq should only be administered to patients in the range of 250 to 370 kg.** Most patients do not require the maximum dose of ^{82}RbCl.

Overdose:

The administration of a radiation overdose related to ^{82}Rb is highly unlikely.

What are possible side effects from using RUBY-FILL®?

There have been no reported side effects for this product. Rubidium Chloride Rb 82 Injection is called a 'tracer' meaning that it is given in very small doses and at such low doses, has no anticipated effect or known adverse (side) effects of its own, on your body. A normal diet contains more than 1 million times more rubidium than the dose of rubidium you will receive. The radioactive dose you will receive is less than a barium enema or a CT scan of the chest.

However, if you do happen to experience any unusual effects in the few hours after receiving this tracer, contact your doctor or pharmacist.

In rare instances, very small amounts of leftover radiation (trace amounts) may remain and be present in your body after you have undergone this procedure. This may trigger radiation monitoring equipment (for example at border crossings and security check-points at airports) for several months following the procedure. This small amount of radiation is not considered cause for worry or health concern, but should this occur, contact your doctor.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RUBY-FILL® should be stored at room temperature (15 to 25°C).

If you want more information about RUBY-FILL®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website https://www.draximage.com or by calling 1-888-633-5343 / 514-630-7080

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