PRODUCT MONOGRAPH

RUBY-FILL®

Rubidium Rb 82 Generator

Radionuclide Generator, 3.7 GBq of Sr-82 per Generator

For elution of Rubidium Rb 82 chloride injection for intravenous use

Diagnostic Radiopharmaceutical (Myocardial Imaging)

Jubilant DraxImage Inc.
16751 TransCanada Highway,
Kirkland, Quebec H9H 4J4

Date of Initial Approval:
July 25, 2012

Date of Approval:
June 16, 2020

Submission Control No: 237823

TABLE OF CONTENTS

RUBY-FILL™

Rubidium Rb 82 Generator

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous (^{82}RbCl eluate)	Radionuclide Generator, 3.7 GBq of Sr-82 per Generator	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

RUBY-FILL™ (Rubidium Rb 82 Generator) contains accelerator-produced strontium-82 adsorbed on an α-hydrous tin oxide column in a shielded container and provides an elution of Rubidium Chloride Rb 82 Injection which is a sterile, non-pyrogenic aqueous solution of ^{82}RbCl in 0.9% sodium chloride with pH of 4.0 to 8.0. 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 μg of tin per ml of Rubidium Chloride Rb 82 Injection. Rubidium Chloride Rb 82 Injection contains no carrier or stabilizing agent.

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

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

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 1**. For example, the use of a 7.0 mm thickness of Pb will attenuate the radiation emitted by a transmission factor of about 0.39.

Table 1. Broad-beam transmission factors at 511 keV in lead

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

From AAPM Task Group 108: PET and PET/CT shielding requirements. Med Phys 2006[1]

^{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 2**.

Table 2. 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
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 3**.

Table 3. 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

INDICATIONS AND CLINICAL USE

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.

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

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

The oversight for use of this product, and the cardiac PET image interpretation, should be carried out only by physicians and institutions with adequate training and experience in conducting and interpreting these procedures.

CONTRAINDICATIONS

None known.

WARNINGS AND PRECAUTIONS

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 humans.

Rubidium Rb-82 chloride 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.

General

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.

Rubidium Chloride Rb 82 Injection generated from RUBY-FILL™ must be administered only with an appropriate infusion system capable of meeting the performance characteristics previously described (See **INDICATIONS AND CLINICAL USE**). The drug should be administered only by those health professionals with a thorough understanding of the use and performance of the generator and the infusion 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. Only 0.9% Sodium Chloride Injection USP should be used to elute the generator.

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 Sr-82 and of the impurity strontium Sr-85. Sensitive radiation monitoring equipment may detect residual radioactivity from these longer-lived isotopes ($t_{½}$ of 25 and 65 days respectively) for several months

following a ^{82}Rb-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.

Carcinogenesis and Mutagenesis

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

See **Special Populations, *Pregnant women***.

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.

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.

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.

Reproduction

Animal studies have not been performed to evaluate whether Rubidium Chloride Rb 82 Injection has an effect on fertility in males or females (See also ***Pregnant Women*** in **Special Populations** below).

Special Populations

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.

Ideally examinations using radiopharmaceuticals, especially elective procedures in women of childbearing capability, should be performed during the first ten days following the onset of menses.

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).

Nursing Women: 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.

Pediatrics (< 18 years of age): The efficacy and safety of Rubidium Chloride Rb 82 Injection in the approved indication have not been established in pediatric patients.

Geriatrics (≥ 65 years of age): 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.

ADVERSE REACTIONS

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.[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 is useful for identifying drug-related adverse events and for approximating rates.

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

DRUG INTERACTIONS

Interactions with drugs, food, herbs, laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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.

Dosage

The administered activity of Rubidium Chloride 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 – 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.

Administration

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

RUBY-FILL™ (Rubidium Rb 82 Generator) must be used with an infusion system specifically labeled for use with the generator and capable of accurate measurement and delivery of doses of Rubidium Chloride Rb 82 Injection at a rate of 10 to 30 mL/min with a maximum volume per infusion of 60 mL.

The standard clinical use of rubidium Rb 82 chloride is intended only for intravenous administration using an appropriate infusion system. 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.

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.

^{82}Rb assay and ^{82}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 **Directions for Quality Control**).

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 > 50%);
- 90 to 100 seconds after injection in patients with reduced ventricular function (LVEF 30%-50%);
- 110 to 130 seconds after injection in patients with poor ventricular function (LVEF < 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.

Patient preparation

Heavy meals should be avoided 4 hours before a stress test. For a diagnostic test, medications that may interfere with responses to a stress test (anti-anginal drugs, theophyllines) should be withdrawn on the day of the examination, and the patient should abstain from caffeine-containing drugs and beverages for 12 hours prior to the test as prescribed by ASNC guidelines.

Instructions for Preparation and Use

An appropriate infusion system labeled for use with RUBY-FILL™ (Rubidium Rb 82 Generator) is required. The applicable operator's manual delivered with the infusion system should be consulted for detailed directions on generator hook-up, daily quality 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™ (Rubidium Rb 82 Generator) product monograph and the infusion 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;
- Elute with additive free 0.9% Sodium Chloride Injection USP only;
- Discard the first 75 mL eluate each day the generator is eluted; and
- Since the eluate contains radioactivity, it must be handled employing proper safety precautions.

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 **performed by the user through a daily procedure**. This procedure is mandatory so the system will not start unless it is performed. As indicated in the applicable operator's manual delivered with the infusion 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 Sr-82 and Sr-85 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, the user should refer to the Infuser's User Manual for additional information.

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

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 4. 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).

OVERDOSAGE

Cases of overdose are not known to have occurred with ^{82}Rb chloride. Overdose 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.

ACTION AND CLINICAL PHARMACOLOGY

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. 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. ^{82}Rb is eliminated from the circulation by the kidney via the urine.

^{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.

Special Populations and Conditions

No data available.

STORAGE AND STABILITY

RUBY-FILL™ (Rubidium Rb 82 Generator) should be stored at room temperature (15 ^{o}C to 25 ^{o}C).

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.

The shelf life of RUBY-FILL™ (Rubidium Rb 82 Generator) is 60 days from the date of calibration. The expiry date is provided on the generator container label.

SPECIAL HANDLING INSTRUCTIONS

RUBY-FILL™ (Rubidium Rb 82 Generator) 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. 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RUBY-FILL™ (Rubidium Rb 82 Generator) 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.

The generator is supplied with one additional sterile and pyrogens free set of quick-connects/ Luer adapters (i.e one quick-connect body, one quick-connect stem and 2 Luer lock adapters fixed to the quick-connects). The quick connects of this set are identical to the ones connected to the generator. At the user's site and once the generator is installed, the upper sets of the quick-connects affixed to the generator is removed using aseptic techniques and replaced with the additional set that serves to connect the generator to the infusion system

PART II: SCIENTIFIC INFORMATION

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

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: rubidium chloride Rb 82

Chemical name: rubidium chloride Rb 82

Molecular formula: ^{82}RbCl

Molecular mass: 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 4.0 to 8.0. Rubidium Chloride Rb 82 Injection is eluted from

RUBY-FILL™ (Rubidium Rb 82 Generator) 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.

CLINICAL TRIALS

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
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

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 ($CI_{95\%}$ 86%-97%) and 88% specific ($CI_{95\%}$ 67% -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 81.0%, sensitivity as 93% (CI 95%, 83-97%) and specificity as 81% (CI 95%, 54-95%).

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.[3] 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 > 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 1986-2007 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[4-9] and three retrospective studies.[10,11,12] Due to flaws in the design or reporting of the study, data from two retrospective studies[10,11] 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 – 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 – 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%-100%)	82% (59%-94%)
Demer 1989	174	55.2%	94	2	66	12	98% (92%-100%)	85% (74%-91%)
Go 1990	202	75.2%	142	10	39	11	93% (88%-97%)	78% (64%-88%)
Stewart 1991	81	74.1%	50	10	18	3	83% (71%-91%)	86% (63%-96%)
Marwick 1992	74	94.6%	63	7	4	0	90% (80%-96%)	100% (40%-100%)
Grover-McKay 1992	31	51.6%	16	0	11	4	100% (76%-99%)	73% (45%-91%)
Bateman 2006	112	66.1%	64	10	38	0	86% (76%-93%)	100% (89%-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% (88.7-93.9)	85.4% (79.7-89.8)
Restricted to ^{82}Rb-PET	Fixed effects	500*	74.4%	90.1% (86.0-93.1)	85.9% (77.3-91.7)
Restricted to ^{82}Rb-PET	Random effects	500*	74.4%	90.2% (81.9-95.0)	89.3% (57.5-98.1)

* 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[13], 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 4 143 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 4 143 patients.

DETAILED PHARMACOLOGY

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. See "ACTION AND CLINICAL PHARMACOLOGY" in Part I.

TOXICOLOGY

No toxicology studies have been conducted with ^{82}RbCl. The typical daily dietary intake of rubidium is 1 to 5 mg.[14] 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.[15] Chronic administration of 'cold' rubidium chloride to three generations of Sprague-Dawley rats had no effect on fertility, gestation, or fetal development.[16] 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.

REFERENCES

1 Madsen MT, Anderson JA, Halama JR, Kleck J, Simpkin DJ, Votaw JR, Wendt RE 3rd, Williams LE, Yester MV. AAPM Task Group 108: PET and PET/CT shielding requirements. Med Phys. 2006 Jan;33(1):4-15. Erratum in: Med Phys. 2006 Sep;33(9):3579

2 Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med. 1998 Dec;39(12):2190-2

3 Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, Lok-Tin Szeto A, Aung M, Davies RA, Ruddy TD, Beanlands RS. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 2006;48:1029-39

4 Gould LK, Goldstein RA, Mullani NA, Kirkeeide RL, Wong WH, Tewson TJ, Berridge MS, Bolomey LA, Hartz RK, Smalling RW, Fuentes F, Nishikawa A. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. J Am Coll Cardiol 1986;7:775-89

5 Demer LL, Gould LK, Goldstein RA, Kirkeeide RL, Mullani NA, Smalling RW, Nishikawa A, Merhige ME. Assessment of coronary artery disease severity by PET: comparison with quantitative arteriography in 193 patients. Circulation 1989;79:825-35

6 Go RT, Marwick TH, MacIntyre WJ, Saha GB, Neumann DR, Underwood DA, Simpfendorfer CC. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. J Nucl Med 1990;31:1899-905

7 Stewart RE, Schwaiger M, Molina E, Popma J, Gacioch GM, Kalus M, Squicciarini S, al-Aouar ZR, Schork A, Kuhl DE. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. Am J Cardiol. 1991;67:1303-10

8 Marwick TH, Nemec JJ, Stewart WJ, Salcedo EE. Diagnosis of coronary artery disease using exercise echocardiography and positron emission tomography: comparison and analysis of discrepant results.. J Am Soc Echocardiogr. 1992 May-Jun;5(3):231-8.

9 Grover-McKay M, Ratib O, Schwaiger M, Wohlgelernter D, Araujo L, Nienaber C, Phelps M, Schelbert HR. Detection of coronary artery disease with positron emission tomography and rubidium 82. Am Heart J. 1992 Mar;123(3):646-52.

10 Simone GL, Mullani NA, Page DA, Anderson BA Sr. Utilization statistics and diagnostic accuracy of a nonhospital-based positron emission tomography center for the detection of coronary artery disease using rubidium-82. Am J Physiol Imaging 1992;7:203-9

11 Williams BR, Mullani NA, Jansen DE, Anderson BA. A retrospective study of the diagnostic accuracy of a community hospital-based PET center for the detection of coronary artery disease using rubidium-82. J Nucl Med 1994;35:1586-92.

12 Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, Hertenstein GK, Moutray KL, Reid K, Cullom SJ. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol 2006;13:24-33.

13 Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M, Leong-Poi H, Miller RM, Nichol G, Freeman M, Bogaty P, Honos G, Hudon G, Wisenberg G, Van Berkom J, Williams K, Yoshinaga K, Graham J; Canadian Cardiovascular Society; Canadian Association of Radiologists; Canadian Association of Nuclear Medicine; Canadian Nuclear Cardiology Society; Canadian Society of Cardiac Magnetic Resonance. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease--executive summary. Can J Cardiol. 2007 Feb;23(2):107-19

14 Nielsen, F. H. (1996) Other Trace Elements. In: Present Knowledge in Nutrition (Ziegler, E. E. and Filer, L. J. Jr., eds.), 7th ed., pp. 353-377. International Life Sciences Institute Press, Washington, DC. Available at http://jn.nutrition.org/nutinfo/

15 Stecher PG (Ed.). The Merck Index, Eighth edition. Rahway, N.J.: Merck and Company, Inc., 1968.

16 Meltzer HL;Lieberman KW. Chronic ingestion of rubidium without toxicity: implications for human therapy. Citation: Experientia 1971 Jun;27(6):672-4

PART III: CONSUMER INFORMATION

Rubidium Chloride Rb 82 Injection

Rubidium Chloride Rb 82 Injection is the medication solution eluted from RUBY-FILL™ (Rubidium Rb 82 generator) to be administered to the patient. This leaflet is part III of a three-part "Product Monograph" published when RUBY-FILL™ generator was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Rubidium Chloride Rb 82 Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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.

What it does:

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).

When it should not be used:

This product should not be used if you are pregnant or suspect that you may be.

What the medicinal ingredient is:

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.

What the important non-medicinal ingredients are:

There are no important non-medicinal ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Rubidium Rb 82 Chloride Injection should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

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

BEFORE you receive Rubidium Chloride Rb 82 Injection talk to your doctor or pharmacist:

- 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 caffeinecontaining products (coffee, tea, cola or chocolate, etc) in the 12 hours before this test procedure.

INTERACTIONS WITH THIS MEDICATION

Drug-drug interactions with Rubidium Chloride Rb 82 Injection 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.

PROPER USE OF THIS MEDICATION

This product will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

No serious side effects have been reported for Rubidium Chloride Rb 82 Injection.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online: www.healthcanada.gc.ca/medeffect

By Toll-free telephone: 1-866-234-2345

By Toll-free fax: 1-866-678-6789

By Postage Paid Mail:

Canada Vigilance Program
Health Canada
AL 0701C
Ottawa. Ontario K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Jubilant DraxImage Inc. at 1-888-633-5343 / 514-630-7080

This leaflet was prepared by Jubilant DraxImage Inc.

Last revised: June 16, 2020