



ENGLISH



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 a 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 caffeine-containing 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

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table with 3 columns: Route of Administration, Dosage Form / Strength, Clinically Relevant Non-medicinal Ingredients

DESCRIPTION

RUBY-FILL® (Rubidium Rb 82 Generator) contains accelerator-produced strontium-82 adsorbed on an alpha-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 82RbCl in 0.9% sodium chloride with pH of 4.0 to 8.0. The 82RbCl activity delivered in a given elution depends on the volume, the elution rate, and the 82Sr 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 82Sr and not more than 0.2 kBq of 82Sr 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

82Rb 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%). 82Rb decays with a physical half-life of 75.5 seconds (1.2575 min) to stable 82Kr.



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

% remaining = 100% x e^-0.0091t where t is time from calibration in seconds; or

% remaining = 100% x e^-0.544t where t is time from calibration in minutes.

External Radiation

The specific gamma-ray constant for 82Rb 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. Table with 11 columns (mm Pb) and 11 rows (Transmission).

From AAPM Task Group 108: PET and PET/CT shielding requirements. Med Phys 2006<sup>1</sup>

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



The 82Sr is produced in an accelerator by the reaction 85Rb (p, 4n) 82Sr and 87Rb (p, 6n) 82Sr, and by Mo (p, spallation). The 82Sr produced has no carrier added. To correct for physical decay of 82Sr, the fractions that remain at selected intervals after the time of calibration are shown in Table 2.

Table 2. Physical Decay Chart for 82Sr

Table with 6 columns: Days, Fraction Remaining, Days, Fraction Remaining, Days, Fraction Remaining

\*Calibration time

To correct for physical decay of 82Rb, 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 82Rb

Table with 6 columns: Seconds after Calibration, Fraction remaining, Seconds after Calibration, Fraction remaining, Seconds after Calibration, Fraction remaining

\* Elution time

INDICATIONS AND CLINICAL USE

RUBY-FILL® (Rubidium Rb 82 Generator) produces a parenteral solution of 82RbCl (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 (t1/2 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.

Carcinogenesis and Mutagenesis

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

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 82Rb 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 82Rb-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. Labeled 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 82RbCl 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 82RbCl 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 82Rb is secreted in breast milk. However, due to the short half-life of 82Rb (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.<sup>2</sup>

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 82RbCl 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 82RbCl. 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 82RbCl.

A standard clinical 82RbCl 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.

82Rb assay and 82Sr breakthrough should be determined each day the generator is used in order to verify the quality of the 82RbCl 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 82Rb 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 ASCN 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 82Rb;
• 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 82Rb and the 82Sr and 85Sr 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)

Table with 5 columns: Organ, Mean, s.d., LL 95%CI, UL 95% CI

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 82Rb chloride. Overdose is highly unlikely, as patients can safely be given the maximum available 82Rb activity in the generator. The effective dose from 3700 MBq injected activity is 2.7 mSv.

ACTION AND CLINICAL PHARMACOLOGY

Following intravenous administration, 82Rb rapidly clears from the blood and is extracted by myocardial tissue in a manner analogous to potassium. The myocardial uptake of 82Rb 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. 82Rb is eliminated from the circulation by the kidney via the urine.

82Rb in plasma crosses the capillary membrane relatively freely and is extracted by healthy myocardium in proportion to blood flow. The first-pass extraction of 82Rb by the myocardium has been shown to be approximately 60% at rest. The pharmacokinetics of 82Rb 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 °C to 25 °C). Due to the short life of 82Rb 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 authorized 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 82Sr adsorbed on a hydrous stannic oxide column with an activity of 3.7 GBq of 82Sr at calibration time.



