

**1 December 2023**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Ruby-Fill, radionuclide generator**

****This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

**1. NAME OF THE MEDICINAL PRODUCT**

Ruby-Fill

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Rubidium (82RbCl) chloride injection is produced by means of a (82Sr/82Rb) generator. The rubidium (82Rb) generator consists of 3.7 GBq of strontium (82Sr) (no carrier added) adsorbed onto a α-stannic acid column in a shielded container. 82Sr decays with a half-life of 25.5 days by electron capture producing the daughter isotope 82Rb. When eluted with sodium chloride 9 mg/ml (0.9 %) solution for injection, the generator provides sterile, non-pyrogenic rubidium (82RbCl) chloride injection. 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 (1.26 min) to stable 82Kr.

The 82Rb activity delivered in a given elution depends on the elution volume, the elution rate, and the 82Sr activity adsorbed on the generator column. The eluted rubidium (82Rb) chloride injection complies with the specifications of the U.S Pharmacopoeia including those for radionuclidic purity (at calibration date: 82Sr ≤ 0.02 kBq/MBq of 82Rb, 83Rb ≤ 0.05kBq/MBq of 82Rb, 85Sr ≤ 0.2kBq/MBq of 82Rb, other gamma-emitting impurities ≤ 0.005kBq/MBq of 82Rb) and chemical purity (assay of tin ≤1 μg per ml of eluate).

For a full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Radionuclide generator

The rubidium (82RbCl) chloride injection obtained by elution of the generator is a clear, colorless, sterile, non-pyrogenic aqueous solution.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

This medicinal product is for diagnostic imaging use only.

Rubidium (82RbCl) chloride injection is used with positron emission tomography (PET) for the assessment of myocardial perfusion and is indicated for the detection and localization of coronary artery disease in adult patients with known or suspected coronary artery disease.

**4.2 Posology and method of administration**

*Posology*

The activity to be injected 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. Typical administered doses of 82RbCl range between 370 to 2220 MBq [10-60mCi] and depend on patient characteristics, imaging equipment, patient evaluation requirements and physician preferences.

*Adults*

The typical recommended administered activity range for an adult weighing 70 kg is 350 to 2100 MBq (5-30 MBq/kg). As noted above, this activity has to be adapted according to the body weight of the patient, the type of camera used and acquisition mode, physician preference and is administered by bolus or continuous activity [over ~15 seconds] intravenous injection. Other activities may be justifiable.

*Elderly population*

The typical recommended administered activity range in adults shall be followed.

*Renal and hepatic impairment*

No adjustments are required for renal and hepatic impairment.

*Paediatric population*

The safety and efficacy of rubidium (82RbCl) chloride injection have not been established in pediatric population. It is not expected that this population will be a potential population for 82Rb-PET myocardial perfusion imaging. Alternative techniques which do not involve ionizing radiation should be considered. Importantly, Rb is present in everyday diets in mg to gram amounts and in a normal component in the circulation in mg % concentrations.

*Method of administration*

For intravenous use.

Generally, both rest and stress injections are required, in either order. Due to the very short half-life of 82Rb, the second test may be done within 10 minutes following the initial test. In some laboratories, a stress test is done first and, if no perfusion defects are seen, the physician may decide to omit the rest test since ischemia or abnormal perfusion at stress has been eliminated. The determination is made by the responsible physician based on their expert judgment and the best patient management decision.

*Precautions to be taken before handling or administering the medicinal product*

The eluate, rubidium (82RbCl) chloride injection should be administered intravenously and directly from the elution system to the patient (see section 6.6 and 12). Only non-pyrogenic, sterile, additive-free sodium chloride 9 mg/ml (0.9 %) solution for injection should be used to eluate the generator (see sections 4.3 and 4.4). The saline confirmation label should be completed, countersigned/verified by a reviewer and .applied to the additive-free 0.9 % sodium chloride injection bag before use

For Instructions on the preparation and the elution of the generator, see section 12.

For patient preparation, see section 4.4

*Image Acquisition*

Following the infusion, image acquisition generally starts:

* at 70 to 90 seconds (if LVEF > 50 %); or
* at 90 to 130 seconds if LVEF < 50 %

Image acquisition generally lasts 3 to 8 minutes. Actually imaging parameters must be defined by the responsible physician based on specific patient requirements and/or needs.

If a rest acquisition is performed first, a pharmacologic stress agent infusion can be administered usually within 10 minutes of the end of the rest image acquisition.

**4.3 Contraindications**

Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The eluate must not be used, if the specified generator eluate limits for Strontium have been exceeded (see section 4.4).

Ruby-Fill is contraindicated for use with solutions other than additive-free sodium chloride 0.9 % solution for injection (see section 4.4).

**4.4 Special warnings and precautions for use**

*Individual benefit/risk justification*

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information. The total radiation exposure for 82RbCl evaluations are 1-2mSv which is less than yearly background radiation and <10 % of a Tl-201 or < 20 % of Tc-99m MPI studies.

*Renal impairment Hepatic impairment*

Careful consideration of the benefit risk ratio in ill patients with co-morbid conditions should always occur because the very short T1/2 and significant safety margin for Rubidium-82, evaluations with hepatic or renal impairment may incur if clinically indicated.

*Paediatric population*

For information on the use in paediatric population, see section 4.2 or 5.1.

*Patient Preparation*

Heavy meals should be avoided 4 hours before a stress test. Since pharmacological challenge is part of the rubidium (82Rb) chloride stress myocardial perfusion evaluation, medications that may interfere with responses to a stress test (anti-anginal medicines, theophyllines) should be evaluated for modifications by the physicians, and the patient should abstain from caffeine-containing foods or medicines and beverages for at least 12 hours prior to the test. Failure to respond to pharmacological stress may be due to prolonged caffeine effects or longer serum caffeine clearance which is seen in some individuals.

*Interpretation of Rubidium (82RbCl) Chloride images*

Rb82Cl image evaluation and interpretation should only be performed by those physicians, who by training and experience in Nuclear Medicine, Nuclear Cardiology or other certified medical speciality, can fully evaluate the these images in the context of the patient presentation and clinical history.

*After the procedure*

Close contact with infants and pregnant women should be restricted through ~10-20 minutes after the procedure and administration of the Rb82Cl.

*Specific warnings*

In myocardial scintigraphy investigations imaging under stress conditions, the general contraindications and precautions associated with the induction of pharmacological stress should be considered.

Because of potential tissue irritation, inflammation or damage, extravasation of the injection of this radioactive product should be avoided.

|  |
| --- |
| **Excess radiation exposure with failure to follow quality control testing procedure**Excess radiation exposure occurs when the 82Sr and 85Sr levels in rubidium (82Rb) chloride injection exceed the specified generator eluate limits. To minimize the risk of unintended radiation exposure to patients, strict adherence to a daily eluate testing protocol is required. Stop using the rubidium (82Rb) generator when the expiration limits are reached (see sections 6.3 and 12). Records of the daily quality control test results must be maintained on file. **Risk of high level radiation exposure with the use of incorrect eluent****Only use additive-free sodium chloride 0.9 % solution for injection to elute the generator**. Additives present in other solutions (particularly calcium ions) may expose patients to high levels of radiation by causing the release of large amounts of 82Sr and 85Sr 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 may be present in the eluate, even with the subsequent use of additive-free sodium chloride 0.9 % solution for injection. |

 82Sr and 85Sr impurities are subject to bone sequestration and subsequent accumulation in bone tissue due to their long half-lives (26 days for 82Sr and 65 days for 85Sr). Long-term safety implications of exposure to 82Sr and 85Sr are unknown and therefore the eluate must not be used, if the specified generator eluate limits have been exceeded (see section 4.3).

Although 82Rb decays and disappears with 10 minutes, 82Sr and 85Sr have a longer T1/2. Even though these are only present in safe, trivial amounts, these radioactive isotopes may trigger the extremely sensitive radiation detection equipment at border crossings and security check-points at airports up to several weeks after the procedure. It is recommended that if patients intend to travel shortly after the procedure, a physician letter stating the patient’s recent procedure be provided.

Depending on the time when the injection is administered, the content of sodium given to the patient may in some cases be greater than 1 mmol. This additional sodium is negligible but should be taken into account in patient on low sodium diet.

Precautions with respect to environmental hazard are in section 6.6.

**4.5 Interaction with other medicinal products and other forms of interaction**

No interactions studies have been performed in humans. Rubidium is ubiquitous in the environment and food.

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 also likewise be affected.

Medicinal products which affect myocardial function and/or blood flow may cause false negative results in the diagnosis of coronary arterial disease. Particularly beta-blockers and calcium antagonists reduce oxygen consumption and thus also affect perfusion and beta-blockers inhibit the increase of heart frequency and blood pressure under stress. For this reason, conditions and concomitant medication should be taken into consideration when interpreting the results of the myocardial perfusion scan. The recommendations of the applicable guidelines on ergometric or pharmacological stress tests should be followed.

*Paediatric population*

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

*Women of childbearing potential*

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

*Pregnancy*

Radionuclide procedures carried out on pregnant women also involve radiation to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

*Breast-feeding*

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for the half an hour after receiving rubidium (82Rb) chloride injection and the expressed feeds discarded.

Close contact with infants should be restricted during the initial half an hour following injection.

*Fertility*

No studies have been conducted on fertility impact after a Rb82Cl evaluation. Because the absorbed dose in not meaningfully different from background radiation, no significant impact on fertility is expected nor reported.

**4.7 Effects on ability to drive and use machines**

There were no studies performed on the influence of rubidium (82Rb) chloride injection on the ability to drive and use machines. Rb is ubiquitous in the environment and food and no know impact on ability to drive or use machinery has been reported. Because of the radiation used, very sensitive radiation detectors at security point may detect a recent administration.

**4.8 Undesirable effects**

Undesirable effects after the administration of 82Rb have not been observed to date.

Exposure to ionizing radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 1.8 mSv when the maximum recommended administered activity of 2100 MBq is administered, these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It is part of post marketing surveillance and allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

*Paediatric population*

There have been no significant studies of Rb82Cl in the paediatric population. There is no evidence of an unacceptable medical or clinical issue in this population. For patients in this age group the benefits of an MPI imaging must be confirmed compared to the small absorbed dose values calculated in this age group.

**4.9 Overdose**

The administration of a radiation overdose is highly unlikely, as patients can safely be given the maximum available 82Rb activity in the generator. The infuser design does not allow overdose. Similarly, > 50 % of the USP Sr limit on QC will disable the infuser and prevent drug administration well below the USP allow limit.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, ATC code: V09GX04.

*Mechanism of action*

Rb-82 is analogous to potassium ion (K+) in its biochemical behavior and is rapidly extracted by the myocardium proportional to the blood flow. Rb+ participates in the sodium-potassium (Na+/K+) ion exchange pumps that are present in cell membranes. The intracellular uptake of Rb-82 requires maintenance of ionic gradient across cell membranes. Rb-82 radioactivity is increased in viable myocardium reflecting intracellular retention, while the tracer is cleared rapidly from necrotic or infarcted tissue.

*Pharmacodynamic effects*

At the chemical concentrations used for diagnostic examinations, rubidium (82Rb) chloride injection has no pharmacodynamic activity. The normal serum Rb amounts are at least 108 times the administered amounts of Rb82.

The myocardial uptake of 82Rb reflects blood flow through the myocardium. In regions with reduced myocardial perfusion, 82Rb kinetics is different in areas of coronary stenosis because of decreased blood flow and, hence, Rb82Cl delivery. This is also confirmed by varying degrees of coronary flow reserve values. In area of myocardial scar and dead myocardium, there is no uptake of Rb

*Clinical efficacy and safety*

In a pivotal study with 121 patients with suspected coronary artery disease Rubidium chloride [82Rb] injection had a sensitivity of 94 % (CI95 % 86 %- 97 %) and a specificity of 88 % (67 %-97 %) for the diagnosis of coronary artery disease.

In patients with a history of a previous myocardial infarction it has not been demonstrated that imaging using Rubidium chloride [82Rb] can be used to assess the clinical relevance of a stenosis or occlusion in the infarct related artery.

*Paediatric population*

The European Medicines Agency has deferred the obligation to submit the results of studies with Ruby-Fill in all subsets of the paediatric population in the visualization of myocardial perfusion for diagnostic purposes. (See section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

*Distribution*

Following intravenous administration, rubidium (82Rb) rapidly clears from the blood and is extracted by myocardial tissue in a manner analogous to potassium.

*Organ uptake*

82Rb in plasma crosses the capillary membrane relatively freely and is extracted by healthy or viable myocardium in proportion to blood flow. The first-pass extraction of rubidium (82Rb) by the myocardium has been shown to be approximately 60 % at rest.

The pharmacokinetics of 82Rb follows a two-compartment model. In human studies, myocardial activity is noted within the first minute after injection. Uptake is also observed in kidney, liver, spleen, and lung.

*Elimination*

82Rb is primarily eliminated by radioactive decay to stable 82 Kr has which is in turn eliminated by the lungs. Lesser quantities of 82Rb not taken up by the myocardium or other potassium analog uptake are eliminated from the circulation by the kidney.

*Half-life*

As rubidium's biological half-life is very long (31-46 days) in comparison to 82Rb‘s physical half-life of 75 seconds, its effective half-life is not different from its physical half-life.

*Renal/ Hepatic impairment*

The pharmacokinetics in patients with renal or hepatic impairment has not been characterized.

*Paediatric population*

The pharmacokinetics of rubidium (82RbCl) chloride injection have not been established in pediatric population.

**5.3 Preclinical safety data**

The LD50 of intraperitoneally administered 'cold' rubidium chloride in rats is 1.2 g/kg (1.2 x 1012pg/kg). A 10 MBq/kg dose of rubidium (82Rb) chloride corresponds to a mass dose of 0.15 pg/kg of rubidium. The safety factor is therefore approximately 1012 This agent is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Rubidium (82Rb) generator is eluted with a sterile, additive-free sodium chloride 9 mg/ml (0.9 %) solution for injection. Therefore, the eluate, rubidium (82Rb) chloride injection contains sodium chloride.

Rubidium Rb 82 Generator contains tin oxide (alpha-stannic acid) as an absorbent column matrix.

**6.2 Incompatibilities**

In the absence of compatibility studies, rubidium (82Rb) chloride injection must not be mixed with other medicinal products.

**6.3 Shelf life**

The shelf life of the rubidium (82Rb) generator is 60 days from the date of manufacture. The expiry date of the generator is stated on the label.

Due to the 75-second half-life of 82Rb, rubidium (82Rb) chloride injection eluted from the generator should not be stored. It should immediately be administered directly to the patient using the dedicated elution system.

**6.4 Special precautions for storage**

Do not refrigerate or freeze.

Rubidium (82Rb) chloride injection should not be stored but administered immediately.

Storage of radiopharmaceuticals should be stored in accordance with national regulations on radioactive materials.

Store in the original package to minimize the transmission of ionizing radiations.

**6.5 Nature and contents of container**

The generator is encased in a lead shield container.

The generator is supplied with one additional sterile and pyrogen-free set of connectors. The connector set serves to connect the generator to the elution system. At the user site and once the generator is installed, the upper sets of the connectors affixed to the generator are removed using aseptic techniques and replaced with the additional set. For more specific information refer to the Rubidium Elution System User Manual.

**6.6 Special precautions for disposal and other handling**

General warnings

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organization.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

The Jubilant DraxImage generator should only be used with the dedicated elution system provided by Jubilant DraxImage. The elution system is automated, has a built-in dose calibrator, and capable of accurate measurement and delivery of doses of rubidium (82Rb) chloride injection in one of three modes: constant activity, constant flow, or constant time. The volume administered will be a function of patient weight and generator age. For more specific information about the administered volume, please refer to the elution system user manual.

Care should be taken to not inadvertently introduce air into the generator during the connection to the elution system or during the patient infusion.

If at any time in the preparation of this product the integrity of the container is compromised it should not be used.

Administration procedures should be carried out in a way to minimize risks of contamination of the medicinal product and operators exposure. Adequate shielding is mandatory.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Jubilant Pharmaceuticals NV

Axxes Business Park

Guldensporenpark 22, Block C
9820 Merelbeke
Belgium

**8. MARKETING AUTHORISATION NUMBER(S)**

69449

**9. DATE OF FIRST AUTHORISATION**

1 December 2023

**10. DATE OF REVISION OF THE TEXT**

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**11. DOSIMETRY**

The table below shows the dosimetry as calculated using biokinetic data from a 30-patient study at the University of Ottawa Heart Institute, OLINDA/EXM V 1.1. and ICRP 103 tissue weightings.

Table 1 - Absorbed dose per unit activity administered(mGy/MBq)

|  |  |
| --- | --- |
| *Organ* | ***Adults*** |
| Adrenals | 0.00039 |
| Brain | 0.00011 |
| Breasts | 0.00017 |
| Colon | 0.00058 |
| Gallbladder | 0.00051 |
| Gonads | 0.00024 |
| Heart | 0.0025 |
| Kidneys | 0.0047 |
| Liver | 0.00056 |
| Lungs | 0.0019 |
| Muscle | 0.00017 |
| Pancreas | 0.0016 |
| Red Marrow | 0.00028 |
| Osteogenic Cells | 0.00043 |
| Skin | 0.00028 |
| Small Intestine | 0.00086 |
| Spleen | 0.001 |
| Stomach | 0.00091 |
| Thymus | 0.00035 |
| Thyroid | 0.00077 |
| Urinary Bladder | 0.00039 |
| Uterus | 0.00042 |
| Remainder | 0.00042 |
| Effective dose (mSv/MBq) | 0.00073 |

The effective dose resulting from the intravenous administration of a (maximal recommended) activity of 30 MBq/kg for an adult weighing 70 kg is about 1.5 mSv. For an administered activity of 2100 MBq the typical radiation biologic relevant dose to the target organ, the heart, is 5.3 mGy and the typical radiation dose to the critical organ, the kidney, is 9.9 mGy.

At the limits allowed by the elution system, the following impurities can be contained in the eluate: 185 kBq Rb-83 with an effective dose of 0,35 mSv (absorbed dose to bone surface 0,53 mSv, red marrow 0,44 mSv), 37 kBq Sr-82 with an effective dose of 0,23 mSv (absorbed dose to bone surface 1,0 mSv, red marrow 0,88 mSv), and 370 kBq Sr-85 with an effective dose of 0,41 mSv (absorbed dose to bone surface 0,99 mSv, red marrow 1,0 mSv).

**12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

As with any pharmaceutical product, if at any time in the preparation of this product the integrity of the generator or its accessories is compromised it should not be used.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

*Method of preparation*

**For reliable removal of air bubbles and strontium breakthrough activity, the generator should be flushed each day with 75 ml of additive-free sodium chloride 0.9 % solution for injection (as set in the Rubidium Elution System to be specifically used with Ruby-Fill generator).**

Only RUBY Rubidium Elution System (RbES, the infuser) should be used with the Ruby-FillRubidium RB 82 Generator. The applicable operator’s manual delivered with the infusion system should be consulted for detailed directions on generator installation, daily quality control procedure, elution processes and patient administration.

Prior to use with patients, a thorough understanding of the use and performance of the system should be established and training successfully completed.

The operator's manual for the infusion system should be read before beginning elution. Additional information concerning eluting the generator follows:

* All tubing used to administer rubidium (82Rb) chloride injection to the patient should be sterile.
* The terminal patient line includes a 0.22 μm sterility filter.
* Change the patient line together with integrated sterile filter, and needle for every patient.
* Change daily the sodium chloride 9mg/ml (0.9 %) solution for injection and the IV solution set.
* Use the provided saline confirmation label to confirm that additive-free 0.9 % sodium chloride injection bag is to be used, have it countersigned/ verified by a reviewer and apply it on the clean side of the additive-free 0.9 % sodium chloride injection bag before use.
* Change all other lines and connectors with each change of generators.
* Wear waterproof gloves during the preparation and elution processes;
* Employ aseptic techniques throughout the preparation and elution processes;
* Elute with additive-free, pyrogen-free, sterile, sodium chloride 9 mg/ml (0.9 %) solution for injection only;
* Discard the first 75 ml of daily eluate. Since the eluate contains radioactivity, it must be handled employing proper safety and radiation protection precautions.

Any unused product or waste material should be disposed of in accordance with local requirements.

*Quality control*

The Ruby-Fill generator has to be used only with Rubidium Elution System (RbES), an elution system specifically designed for use with Ruby-Fill generator and capable of accurate measurement and delivery of doses of rubidium (82Rb) chloride injection. Prior to the first daily use, the elution system will require the user to perform a flush, a calibration, and quality control check for strontium breakthrough activity:

* The flush consists in pumping a precise amount of saline solution through the generator to remove air bubbles from the line and strontium breakthrough from the generator column. The solution is directed to the waste shielded container and can be left there to decay.
* Calibration consists of running a measured amount of solution through the generator into a vial in the dose calibrator to determine the maximum activity available at this point in the life of the generator. This information will be used by the system when performing patient elutions.
* The breakthrough test is conducted on the sample produced during the calibration step. After allowing 30 minutes for decay of 82Rb, the system will assay the calibration sample and determine the amount of 82Sr and 85Sr present in the sample.

Perform the Daily Quality Control test as per detailed instructions contained in the RbES User Manual delivered with the elution system. **The daily quality control is mandatory before any eluates are used for patient administration.**

**Only use additive-free sodium chloride 0.9 % solution for injection for all elutions.** Additives present in other solutions, particularly calcium ions to which strontium ions are chemically analogous, may cause the exchange of the additive for Sr2+ and the release of substantial amounts of 82Sr and/or 85Sr into the eluate regardless of the age or prior use of the generator. **Patients may be exposed to high levels of radiation, if the incorrect eluent is used to elute the generator. Immediately stop any infusion and discontinue the use of the affected rubidium (82Rb) generator.** Evaluate the patient’s radiation absorbed dose and monitor for the effects of radiation to critical organs such as bone marrow.

The assay of rubidium (82Rb) and of strontium (82Sr and 85Sr) breakthrough are determined using an ionization chamber-type dose calibrator and are performed by the user through a daily procedure run by the elution system (RbES). This procedure is mandatory and the system will not operate if it is not performed. As indicated in the RbES User Manual, the user must conduct a flush and a calibration at least once in 24 hours (daily). These runs are intended to remove air bubbles from the lines, prime lines, and remove any breakthrough of 82Sr or 85Sr activity from the generator. Once a flush has been conducted, a calibration run is mandatory to validate the activity counter and to ensure that strontium (82Sr and 85Sr) breakthrough activity is within acceptable fraction of USP limits (0.02 kBq of 82Sr and 0.2 kBq of 85Sr per MBq of 82Rb) for rubidium (82Rb) chloride injection. DO NOT use eluates obtained from the flush or calibration runs for patient administration.

The RbES calibration run serves as a thorough system test, and alerts the user when levels of 82Sr and 85Sr corresponding to 20 % (Alert Limits) or 50 % (Expiration Limits) of the USP limits are reached. In this unlikely event that these limits are observed, the user should refer to the Infuser’s User Manual for additional information. For example, when 82Sr and 85Sr are detected at levels from 20 % and less than 50 % of the USP limits (Alert Limits) the RbES requires an additional calibration run every 8 elutions (generally equivalent to 4 patients). The elution system will not operate if the calibration run is not repeated. In the case 82Sr and 85Sr levels reached 50 % or more of USP limits (Expiration Limits), the Infuser [RbES] will lock (cease to operate) and not allow patient administrations. Depending on the situation the following instructions A or B could then apply:

1. Stop use of the Ruby-Fill generator once any one of the following Expiration Limits is reached.

- 60 days post manufacturing date, or

- An eluate 82Sr level of 0.01 kBq/MBq 82Rb, or

- An eluate 85Sr level of 0.1 kBq/MBq 82Rb.

1. Perform additional daily eluate tests after detecting any of the following Alert Limits:

- 82Sr level reaches 0.004 kBq per MBq 82Rb, or

- 85Sr level reaches 0.04 kBq per MBq 82Rb.

The following describes the mandatory daily RbES testing protocol to perform on eluate to determine the assay of rubidium (82Rb) and of strontium (82Sr and 85Sr) breakthrough activity:

Rubidium Eluate Level Testing:

1. The dose calibrator is automatically set for 82Rb within the RES system.
2. The Daily Quality Control function begins by automatically initiating a flush using 75 ml of Sodium Chloride Injection Ph. Eur. This eluate is by default diverted towards the waste container and is ultimately discarded. Proper safety precautions should be employed since the eluate contains radioactivity.
3. After the generator flush, a complete generator recharge of 12 82Rb half-lives (approximately 15.2 minutes) is accomplished before automatically initiating the next elution for the calibration step.
4. Using the dose calibrator, the system automatically quantifies the activity of 82Rb in the sample eluate (82Rb decay does not need to be corrected for because of a real-time automated measurement).
5. Maintain an on-going record of all eluate volumes (washing, testing, dosing volumes), including a summary of the cumulative volume of eluate from the generator. The system automatically generates a record and saves the data for each generator eluate volume, including waste and test volumes. Total cumulative eluate volumes are also recorded and saved for the life of the generator.

Strontium Eluate Level Testing:

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

|  |  |  |
| --- | --- | --- |
| R =  | [85Sr] | on calibration date X Ratio Factor on the day (post-calibration) of measurement |
| [82Sr] |

1. The system uses a correction factor (F) of 0.478 to compensate for the contribution of 85Sr to the reading.
2. The system calculates the amount of 82Sr in the sample using the following equation:

|  |  |
| --- | --- |
|  82Sr (kBq) =  |  dose calibrator reading (kBq) |
| [1 + (R)(F)] |

Example: dose calibrator reading (kBq) = 0.8

85Sr/82Sr ratio (R) = (1.48)

correction factor (F) = 0.478

|  |  |  |
| --- | --- | --- |
|  82Sr (kBq) =  | 0.8 | = 0.47 |
|  [1 + (1.48)(0.478)] |

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

Example: 0.47 kBq of 82Sr; 50 MBq of 82Rb

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| --- | --- |
| 0.47 kBq 82Sr | = 0.0094 kBq/MBq 82Rb (is above Alert Limit of 0.004 kBq/MBq; additional daily eluate testing must be performed) |
| 50 MBq 82Rb |

1. The system determines if 85Sr in the eluate exceeds an Alert or Expiration Limit by multiplying the result obtained in step 11 by (R) as calculated in step 10 (above).

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

1. Perform the additional daily eluate tests at time points determined by the day’s elution volume. The system will automatically indicate when alert levels have been reached and require that additional tests be performed at a frequency determined by a volume equivalent to 4 patient procedures.