# $^{82}$Rb chloride

Rubigen

**1. Indications**

Positron emission tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.
$^{82}$Rb is indicated in adults only. $^{82}$Rb should only be administered intravenously in the immediate vicinity of a suitable PET scanner.

**2. Manufacturing, preparation and administration**

Multiple methods for the preparation of $^{82}$Rb chloride solution for injection have been published, depending on the type of generator. It is essential to read the Summary of Product Characteristics (SmPC )of the specific generator system in use, also for a non-licensed generator system.
It is important to realize that the $^{82}$Rb generator and the required sterile eluens may not be available as licensed products. Following the rules and legislation of the National competent authorities it is possible to use this diagnostic agents for patients.

In this recommendation the composition and preparation method of a new type of $^{82}$Sr/$^{82}$Rb generator system is presented only. This generator system consists of one or more lead shielded columns filled with a specific physical/chemical form of alpha stannic acid to retain the loaded and adsorbed $^{82}$Sr/$^{85}$Sr chloride. The radioactive Strontium solution is accelerator produced and (re)loaded by and under responsability of the manufacturer of the $^{82}$Rb generator system.
$^{82}$Rb is carrier-free, meaning that the rubidium concentration is in the picomolar range.
The generator wagon remains in the PET room during the period of clinical use.
During disinfection and loading the generator wagon is placed in a room dedicated to handling of radioactive agents.
The column(s) are attached to a bottle Sterile Phosphate-Buffered Saline for infusion (pH=7,4) and to an infusion system for immediate intravenous delivery of $^{82}$Rb chloride solution for injection to a patient.
This generator system has an internal radioactive dose calibrator system, the activity of the eluate is measured continuously during the elution time. The generator is used and stored at room temperature.
After elution from the generator the $^{82}$Rb solution is infused directly in the patient intravenously.
Because $^{82}$Rb is radioactive, precautions (gloves, distance to patient, proper shielding) should be taken as prescribed by local regulations. During administration of $^{82}$Rb and during 5 min after administration doctors and technicians should preferably leave the PET room.

**3. Quality control**

$^{82}$Rb chloride for injection is described in the United States Pharmacopeia (USP).
Visual control of the radioactive eluate is not easily possible, the product must be colourless and clear.

The measurement of strontium contamination (breakthrough) should be performed each day the generator is used, just before administration of $^{82}$Rb to the first scheduled patient. At the end of the former day a 1100 MBq $^{82}$Rb chloride sample should be taken from the generator. Let the sample stand overnight. The next day it is measured in a NaI(Tl) well counter for 5 min; a standard $^{85}$Sr source is measured similarly. The $^{82}$Sr/$^{85}$Sr contamination of the eluate is calculated with help of a table of the $^{85}$Sr/$^{82}$Sr ratio at various days after calibration of the generator activity. The result of the break-through measurement should be presented daily to the local pharmacist. Unintended radiation exposure occurs when the levels of $^{82}$Sr or $^{85}$Sr in the $^{82}$Rb chloride injection exceed certain Pharmacopeial limits. Therefore $^{82}$Rb chloride solution should never be administered if the contamination with $^{82}$Sr is higher than 22.300 Bq per 1100 MBq $^{82}$Rb or the contamination with $^{85}$Sr is higher than 223.000 Bq per 1100 MBq $^{82}$Rb.

If the contamination with $^{82}$Sr is within specifications but higher than 6.700 Bq per 1100 MBq $^{82}$Rb or the contamination with $^{85}$Sr is higher than 67.000 Bq per 1100 MBq $^{82}$Rb, the measurement of Strontium contamination should be repeated after four patient tests and before the fifth patient of the day receives $^{82}$Rb.

Before weekly disinfection the absence of endotoxins is measured. The absence of disinfectant is measured after weekly disinfection and flushing.

Tin contamination is very low but is periodically measured through atomic adsorption spectrometry.

Sterility: Incubation or filtration of eluate with Tryptic Soy Broth (TSB) and Thioglycollate Broth at 32°C for two weeks according to the European Pharmacopeia.

Provided that the strontium contamination of the generator eluate meets the specifications, the generator system is properly disinfected and no GMP deviations took place the pharmacist releases the generator for one day of clinical use.

**4. Interactions**

Specific drug-drug interaction studies have not been performed.

**5. Contra-indications**

No absolute contraindications exist. Contra-indications exist for the pharmacological stress agents, and for the infusion of a certain volume of parenteral products (fluid overload). See the SmPC of that products.

In case of pregnancy only administer $^{82}$Rb if clearly needed.

**6. Adverse effects**

No serious adverse effects have been observed so far. Adverse effects are sometimes seen after the administration of pharmacological stress agents during the diagnostic process.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

**7. Biodistribution & pharmacokinetics**

$^{82}$Rb is an analogue to the potassium ion in its physiological behaviour and is rapidly extracted by the myocardium proportional to the blood flow. The rubidium ion ($Rb^+$) is pumped into the myocardial cells by means of the sodium potassium adenosine triphosphatase membrane pump against a concentration gradient. The membrane pump is only active in living cells. $^{82}$Rb radioactivity is increased in viable myocardium, reflecting intracellular retention. $Rb^+$ is cleared rapidly from necrotic or infarcted tissue.

The physical half-life time of 75 sec is the major determinant of the pharmacokinetics of $^{82}$Rb, which is converted by radio-active decay into stable $^{82}$Kr gas. Krypton is exhaled through the lungs. Renal and hepatic excretion do not play an essential role in the elimination of $^{82}$Rb from the body, although some $^{82}$Rb is found in the urinary bladder before radio-active decay.

*Pharmacodynamic effects:* Recommended dose (depending of the type of generator) 1100 MBq $^{82}$Rb in 25-35 ml phosphate-buffered saline (the volume is depending on the age of the generator). An intravenous dose is recommended of 900-1100 MBq $^{82}$Rb in 25-35 ml sterile phosphate-buffered saline with an administration speed of 35 ml/min.

For both the rest and the stress test 900-1100 MBq $^{82}$Rb are administered with a delay of at least 10 min between the two administrations. In human studies, myocardial activity of $^{82}$Rb was observed within the first minute after peripheral intravenous administration. When areas of ischemia or infarction are present, they are visualized within 2-7 min as photon-deficient regions in the myocardial image. In patients with reduced cardiac output/function the appearance of $^{82}$Rb in the myocardium may be delayed. In addition to the myocardium, highly vascularized organs such as the kidneys, the liver, the spleen and the lungs are also visualized after administration of $^{82}$Rb.

**8. Stability**

Using the generator system described here, the shelf life of the generator system is 1 week before periodic disinfection, 1 month until periodic reloading, resp. 3 months cumulated including two times of Strontium reloading.

After 4 weeks of clinical use, the generator should be reloaded and tested, before it can be used clinically for another 4 weeks. The generator should be disinfected and flushed on a weekly schedule to guarantee sterility and absence of pyrogens.

Replace the bottle of sterile PBS on the generator wagon daily.

Each patient gets his own sterile infusion system with sterile membrane filter.

**9. Literature**


- United States Pharmacopeia and NF: USP 39 - NF 34: 2016 Monograph Rubidium Chloride Rb 82 Injection.
- Ziadi MC, deKemp RA, Williams KA et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol. 2011;58(7):740-8.

- Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC) Eur J Nucl Med Mol Imaging 2011;38:201-12.