Part VI: Summary of the risk management plan

Summary of risk management plan for RUBY-FILL®

This is a summary of the risk management plan (RMP) for RUBY-FILL®. The RMP details important risks of RUBY-FILL®, how these risks can be minimised, and how more information will be obtained about RUBY-FILL®'s risks and uncertainties (missing information).

RUBY-FILL®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RUBY-FILL® should be used.

Important new concerns or changes to the current ones will be included in updates of RUBY-FILL®'s RMP.

I. The medicine and what it is used for

RUBY-FILL® generator is authorised for myocardial perfusion scintigraphy for the detection and localisation of coronary artery disease (see SmPC for the full indication). As the active substance, RUBY-FILL® generator contains the parent radionuclide Strontium-82 (^{82}Sr) adsorbed on a tin oxide column bed and which decays into ^{82}Rb, the daughter radionuclide. When eluted with Sodium Chloride 0.9%, the RUBY- FILL® generator provides Rubidium (^{82}Rb) Chloride which is administered intravenously.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of RUBY- FILL®, together with measures to minimise such risks and the proposed studies for learning more about RUBY- FILL®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of RUBY-FILL®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of RUBY-FILL® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of RUBY- FILL® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product be safely administered. Important risks can be regarded as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of RUBY- FILL®.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Radiation exposure to Strontium-82 (^{82}Sr) and Strontium-85 (^{85}Sr), above predefined limits)
Important potential risks	None
Missing information	Safety in paediatric population

II.B Summary of important risks

Important identified risk 1: Radiation exposure to ^{82}Sr and ^{85}Sr (above USP limits)	
Evidence for linking the risk to the medicine	International Commission on Radiological Protection[13] - United States Nuclear Regulatory Commission and Federal Drug Agency [14] In 2018, in Colorado USA, eight (8) patients were administered with excess levels of Sr-82 and Sr-85 through the usage of a compromised $^{82}Sr/^{82}Rb$-Generator from another manufacturer. The event was identified three (3) days after a bag of Lactate Ringer's intravenous fluid was inadvertently used as the eluent. On days two and three, sterile saline was used, but the generator was already compromised and releasing Sr-82 and Sr-85 in the eluate.
Risk factors and risk groups	None. The risk of radiation exposure is independent of any patient factors.
Risk minimisation measures	Routine risk communication: SmPC sections: 4.2; 4.3; 4.4; 4.8; 6.6; 12. Other routine risk minimisation measures beyond the Product Information: Classified as a Prescription Only medicine, hence available only as per physician's prescription and is not freely accessible to patients. The use is restricted to authorised persons in designated clinical settings. Additional Risk Minimisation Measures: • Educational material • Training programme • Saline Confirmation Label

Additional pharmacovigilance activities	• Study: Survey of Nuclear Medicine Professionals Involved in the Use of RUBY-FILL® in Europe to evaluate the Effectiveness of Additional Risk Minimisation Measures. • Study: Evaluation of Calibration and Usage Data Results obtained from the RUBY-FILL® generator in Europe See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information 1: Safety in paediatric population	
Risk minimisation measures	Routine risk communication: SmPC sections 4.2; 5.1 Other routine risk minimisation measures beyond the Product Information: Classified as a Prescription Only medicine, hence available only as per physician's prescription and is not freely accessible to patients. The use is restricted to authorised persons in designated clinical settings. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Paediatric Investigation Plan [EMEA-000882-PIP03-11-M04] See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

There are two ongoing studies and two planned studies in the post-authorisation development plan.

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of RUBY-FILL®.

II.C.2 Other studies in post-authorisation development plan

Study short name (planned): *Survey of Nuclear Medicine Professionals Involved in the Use of RUBY-FILL® in Europe to evaluate the Effectiveness of Additional Risk Minimisation Measures.*
Purpose of the study: To measure the effectiveness of the additional risk minimisation measures put in place in regarding the risk of radiation exposure to Strontium.

Study short name (ongoing): *Paediatric Investigational Plan [EMEA-000882-PIP03-11-M04]*

Purpose of the study: To establish dosimetry, safety and tolerability in paediatric patients from 1 month to less than 18 years of age at high risk of myocardial ischemia.

Study short name (planned): *Evaluation of Calibration and Usage Data Results obtained from the RUBY-FILL® generator in Europe*

Purpose of the study: Collection of calibration data will allow characterisation of the system performance and its most frequent usage in the population. It will also enable evaluation of user compliance in terms of usage within shelf-life and strontium ratio entry at generator's installation.