# Summary of the EU Risk Management plan for SWAN-PSMA-1007

## Marketing Authorisation Holder (MAH): SWAN Isotopen AG

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| Active substance(s): | $^{18}$F-PSMA-1007 |
| Version number of the RMP public summary: | 1.0 |
| Document date: | 21.06.2024 |
| Based on: | EU RMP version 0.5, 03.02.2023 |

**Disclaimer:**

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of SWAN-PSMA-1007 is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of SWAN-PSMA-1007 in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

SWAN Isotopen AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of SWAN-PSMA-1007.

# PART VI: Summary of the Risk Management Plan

## Summary of Risk Management Plan for Radelumin ([$^{18}$F]Fluor-PSMA-1007)

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

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

Important new concerns or changes to the current ones will be included in updates of Radelumin's RMP.

## I. The Medicine and What is it Used for?

Radelumin is intended for Positron Emission Tomography (PET) for diagnostic use only.

PET after injection of Radelumin is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions in adult patients with a suspected recurrence of prostate cancer after primary curative therapy based on increasing serum prostate specific antigen (PSA) levels (see SmPC for the full indication).

It contains [$^{18}$F]PSMA-1007 as the active substance and it is given by intravenous injection.

## II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Radelumin together with measures to minimise such risks and the proposed studies for learning more about Radelumin'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 Radelumin, these measures are supplemented with additional risk minimization 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.

## II.A List of Important Risks and Missing Information

Important risks of Radelumin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can 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 Radelumin. 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 | |
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| Important identified risks | • None |
| Important potential risks | • PET imaging interpretation errors |
| Missing information | • None |

## II.B Summary of Important Risks

**Important potential risk: PET imaging interpretation errors**

**Evidence for linking the risk to the medicine**

Source of evidence:
Scientific literature

Strength of evidence:
PSMA PET images with false positive or false negative results may be misinterpreted. Literature describes false positive and false negative results with [$^{18}$F]PSMA-1007 and related tracers. Reports on false positives and false negatives associated with [$^{18}$F]PSMA-1007 PET are rare so far, as [$^{18}$F]PSMA-1007 has only recently been introduced into clinical practice. However, given the structural similarity and same mechanism of action of this tracer compared to other PSMA-targeting tracers, it can be assumed that [$^{18}$F]PSMA-1007 might be affected by similar diagnostic pitfalls.
Foley et al.a summarised pitfalls of [$^{18}$F]PSMA-1007 tracer uptake, which may lead to false positive results:

- Ganglia of the sympathetic trunk (coeliac, cervical, sacral);
- Unspecific bone uptake;
- Non-prostatic malignancies (glioblastoma, metastatic breast cancer, renal cell carcinoma, myeloma);
- Benign lesions (thyroid adenoma, rib fractures, Paget's disease, meningioma).

Studies have reported a higher frequency of unclear focal uptake for [$^{18}$F]PSMA-1007 compared to [$^{68}$Ga]-PSMA ligands, particularly in lymph nodes, ganglia, and bones (Grünig et al., 2021)b. Significantly more benign lesions were detected in [$^{18}$F]PSMA-1007 PET compared to [$^{68}$Ga]Ga-PSMA-11. [$^{18}$F]PSMA-1007 PET revealed approximately 5 times more lesions attributed to a benign origin than did [$^{68}$Ga]-PSMA-11 PET. The highest number of benign lesions was found in ganglia (coeliac, cervical and sacral ganglia), the second highest number in lymph nodes, and the third-highest number in bones, predominantly in the ribs (Rauscher et al. 2020). Since bone and lymph node metastases are among the most common sites in metastatic PCa, positive findings in these tissues may affect diagnosis.

Focal unspecific bone uptake (UBU) is a common finding in [$^{18}$F]-PSMA-1007 PET (Grünig et al. 2021b; Arnfield et al. 2021d) and occurs with a higher frequency compared to [68Ga]-PSMA-11 PET (Pattison et al. 2021e; Seifert et al. 2022f). UBU without morphological correlate on anatomical imaging might be misinterpreted as metastasis which may result in over-staging of the patient, leading to inadequate therapy. However, in recent studies, UBUs rarely represented prostate cancer bone metastases (Seifert et al. 2022f; Arnfield et al. 2021d; Grünig et al. 2021b; Vollnberg et al. 2022g). In a study

by Seifert et al.f in patients with biochemical recurrence of prostate cancer the higher rate of UBU for [$^{18}$F]-PSMA-1007 PET compared to [$^{68}$Ga]-PSMA-11 PET did not translate into a more frequent diagnosis of bone metastasis, indicating that experienced readers adjust for UBU findings. The underlying mechanism for UBU in [$^{18}$F]-PSMA-1007 PET remains unclear. Unconjugated fluorine, activated bone marrow granulocytes and PSMA expression in non-prostatic cancer tissue have been discussed. In the study by Vollnberg et al.g no PSMA expression was observed for the UBU foci confirmed as benign by biopsy, suggesting a non-PSMA mediated cause for the [$^{18}$F]-PSMA-1007 uptake. For the interpretation of UBUs, the clinical context and localisation are important. [$^{18}$F]-PSMA-1007 PET should be interpreted by experienced physicians with knowledge of UBU distribution pattern and characteristics (Seifert et al. 2022f). PET-guided biopsy can be useful for clarification (Vollnberg et al. 2022g).

False negative results may be caused by high background activity. In study CT-201 background radioactivity of tissues, such as the bone, was shown to interfere with diagnostic interpretation in some cases.

One case of a confirmed positive finding unrelated to prostate cancer was received in an ABX sponsored trial (detection of thyroid tumour). However, neither the investigator nor two blinded readers misinterpreted the uptake as a prostate cancer lesion.

[a] Foley et al. (2020): Fluorine-18 labelled prostate-specific membrane antigen (PSMA)-1007 positron-emission tomography-computed tomography. Normal patterns, pearls, and pitfalls. In: *Clin Radiol* 75 (12), S. 903–913.

[b] Grünig et al. (2021): Focal unspecific bone uptake on (18)F-PSMA-1007 PET. A multicenter retrospective evaluation of the distribution, frequency, and quantitative parameters of a potential pitfall in prostate cancer imaging. In: *Eur J Nucl Med Mol Imaging* 48 (13), S. 4483–4494.

[c] Rauscher et al. (2020): Matched-Pair Comparison of (68)Ga-PSMA-11 PET/CT and (18)F-PSMA-1007 PET/CT. Frequency of Pitfalls and Detection Efficacy in Biochemical Recurrence After Radical Prostatectomy. In: *J. Nucl. Med.* 61 (1), S. 51–57.

[d] Arnfield et al. (2021): Clinical insignificance of (18)FPSMA-1007 avid non-specific bone lesions. A retrospective evaluation. In: *Eur J Nucl Med Mol Imaging* 48 (13), S. 4495–4507.

[e] Pattison et al. (2021): Prospective intra-individual blinded comparison of (18)FPSMA-1007 and (68) GaGa-PSMA-11 PET/CT imaging in patients with confirmed prostate cancer. In: *Eur J Nucl Med Mol Imaging*.

[f] Seifert et al. (2022): Non-specific PSMA-1007 bone uptake evaluated through PSMA-11 PET, bone scan and MRI triple validation in patients with biochemical recurrence of prostate cancer. In: *J Nucl Med*.118.215434.

[g] Vollnberg et al. (2022): Assessment of malignancy and PSMA expression of uncertain bone foci in (18)FPSMA-1007 PET/CT for prostate cancer-a single-centre experience of PET-guided biopsies. In: *Eur J Nucl Med Mol Imaging*.

**Risk factors and risk groups**

- Patients with other types of cancers or non-malignant processes manifesting high PSMA tissue presence (false positive image interpretations);
- Patients with PCa metastases in tissues that show physiological uptake of [$^{18}$F]PSMA-1007 due to naturally expressed PSMA or where [$^{18}$F]PSMA-1007 accumulates in an unspecific manner (false negative image interpretations);
- Patients with low or marginal PSMA-specific tumour burden (false negative image interpretations);
- The diagnostic performance of [$_{18}$F]PSMA-1007 may be affected by serum PSA levels, androgen-receptor-targeting treatments, disease stage and size of malignant lymph nodes;
- Imaging centers and readers with little experience in acquiring and interpreting [$^{18}$F]PSMA-1007 PET.

| Important potential risk: PET imaging interpretation errors | |
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| **Risk minimization measures** | **Routine risk minimisation measures:**<br>SmPC section 4.2, 4.4 and 5.1.<br><br>**Additional risk minimisation measures:**<br>Radelumin educational material in form of reader training programme for physicians. |
| **Additional pharmacovigilance activities** | PASS "A cross-sectional knowledge and understanding survey to evaluate the effectiveness of the Radelumin educational material among physicians qualified to interpret [$^{18}$F]PSMA-1007 PET images." |

## II.C Post-Authorization development plan

### II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of Radelumin.

### II.C.2 Other Studies in Post-authorisation Development Plan

**Study:** A cross-sectional knowledge and understanding survey to evaluate the effectiveness of the Radelumin educational material among physicians qualified to interpret [18F]PSMA-1007 PET images.

**Purpose of the study**:

Rationale: A non-interventional cross-sectional survey is being proposed to evaluate the effectiveness of the Radelumin educational material among physicians who qualified to interpret [18F]PSMA-1007 PET images. The study will be classified as a post-authorisation safety study (PASS), category 3. EU Risk Management Plan 03-Feb-2023/ Version 0.5 Radelumin ([18F]PSMA-1007)

Primary objective: Assessment of effectiveness of Radelumin educational material for physicians qualified to interpret [18F]PSMA-1007 PET images.

Secondary objective: Impact of demographic data (e.g., educational background, years of clinical practice) and training factors (e.g., training method, duration of training, and user baseline training) on knowledge and diagnostic accuracy.