Superior Health Council

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Radionuclide Therapy for Symptomatic Prostate Cancer in Castration-Resistant Prostate Cancer Patients with $^{223}RaCl_2$

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1. INTRODUCTION AND ISSUES

The Federal Agency for Nuclear Control (FANC) invokes the Superior Health Council (SHC) for advice on the justification of the use alpha emitting radiotherapy ([^{223}Ra]-$RaCl_2$)[1] as per article 51.1.1, second paragraph a) of the Royal Decree of 20/7/2001 (RD/ARBIS/RGPRI) that states that "for every medical act involving ionizing radiation, the potential benefit for the patient and the society should be considered with regards to the potential detriment to the patient, his environment and the society. This consideration on the use of ionizing radiation should be made in particular if it concerns a medical act introduced in a clinical setting as a general application or when first licensed".

2. CONCLUSION

From the available filed data, there is no doubt that $^{223}RaCl_2$ is efficient (improvement of the overall survival with 3.6 months versus the best standard of care and secondly a delay of clinical events associated with bone lesions) with less myelotoxicity (than currently available beta emitting radiopharmaceuticals) in castration-resistant prostate cancer (CRPC) patients with predominant bone metastases, as was recognized by the relevant US and European authorities.

- The benefit of ^{223}Ra, as an alpha emitter, as compared to previously developed beta emitters is related to the high energy transfer and low range in tissue of the former;
- Considering the lack of data on combined use, it is understood as of now that $^{223}RaCl_2$ should be used as monotherapy, together with the best standard of care;
- Currently, no data are available on the additional or synergic effect of simultaneous administration of $^{223}RaCl_2$ with other therapeutic agents/drugs;
- $^{223}RaCl_2$ may also prove useful in other metastatic cancers, such as breast cancer, that may develop in up to 40 % of the cases as condensing bone metastases (clinical trials ongoing).

This advisory report is not a generic advice for all alpha emitters, it is specifically meant for $^{223}RaCl_2$ in the CRPC patient indication discussed herein.

[1] Further referred to as $^{223}RaCl_2$

3. METHODOLOGY

Keywords

Keywords	Meshterms*	Sleutelwoorden	Mots clés	Stichworte
	Radium/therapeutic use	Radium	Radium	
	Radiotherapy	Radiotherapie	Radiothérapie	
	Prostatic Neoplasms	Prostaatkanker	Cancer de la prostate	
	Bone metastasis	Bot metastases	Métastases Osseuses	
	Metastasis	Metastases	Métastases	
	Humans	Humaan	Humain	

After examining the request, the necessary areas of expertise were identified (expertise in clinical issues, medical technologies, radiation protection and medical physics) and the experts were appointed by the Board and the working group Chair. The working group experts filled in a general and an ad hoc declaration of interest and the potential risk of conflict of interest was assessed within the working group and by the Ethics Commission. The advisory report is based on an overview of the scientific and grey literature as well as on the opinion of the experts. Once the draft advisory report was approved by the working group, it was validated by the Board.

This advice is not intended to give guidance on the registration or reimbursement of the product as such but mainly on the conditions to be followed for optimal use thereof. Given the questions from the FANC were very precise and the deadline for reply rather short, it was agreed to combine discussion and advice in the section ‘advice’, and not to elaborate lengthily in a ‘argumentation section’. The advice is based on experts’ opinion and on the literature and all published information available, including that form the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

4. ADVICE

List of abbreviations

ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer Patients
CHMP	Committee for Medicinal Products for Human Use
CRPC	Castration-Resistant Prostate Cancer
EMA	European Medicines Agency
FANC	Federal Agency for Nuclear Control
FDA	Food and Drug Administration
MIRD	Medical Internal Radiation Dose
MOC	Multidisciplinary Oncology Consultation
NIRAS	Nationale Instelling voor Radioactief Afval en verrijkte Splijtstoffen
HP	Health Physics
RD	Royal Decree of 20 July 2001
RBE	Relative Biological Effectiveness
MPE	Medical Physics Expert
OLINDA	Organ Level Internal Dose Assessment
ONDRAF	Organisme National des Déchets Radioactifs et des matières Fissiles enrichies
SHC	Superior Health Council
SOP	Standard Operating Procedure
[^{153}Sm]Sm-EDTMP	Samarium-153-ethylene diamine tetramethylene phosphonate

4.1. Has the added value for the use of [^{233}Ra]-$RaCl_2$ been sufficiently demonstrated to justify the related radiation exposure to the patient, his family, the staff and the environment?

On 19 September 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending to granting a marketing authorization for the medicinal product ^{223}Ra-dichloride (Xofigo®), 1000 kBq/mL[2], solution for injection, intended for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. This product had previously received approval from the Food and Drug Administration (FDA), on May 15, 2013.

Prostate cancer is the most common cancer in men and the second cause of mortality due to cancer in men. 90 % of patients with a metastatic castration-resistant prostate cancer have bone metastases. The morbidity associated with bone metastases is important: pain, impaired mobility, pathological fractures, spinal cord compression, etc. This significantly impacts the quality of life of patients. In addition, pain is a very important predictor of effectiveness, independent of mortality. Therefore, treatments should increase not only the quality of life but also the quantity of life (prolonged survival).

[2] Previously known as Alpharadin®

The ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) study was performed in patients with first line castrate refractory prostate neoplasia, with predominant bone metastases and who had no visceral metastases. The trial compared in a randomized way $^{223}RaCl_2$ *vs* placebo plus best standard of care treatment in both arms[3]; the patients had at least two secondary bone lesions documented (Parker et al., 2013).

The benefits shown in this study were firstly a highly significant improvement of the overall survival for $^{223}RaCl_2$ with 3.6 months versus the best standard of care and secondly a delay of clinical events associated with bone lesions (pain, fractures, compression, etc). The data were further strengthened by a significant improvement of the biological parameters (PSA, alkaline phosphatase).

Compared to radiopharmaceutical containing β^--emitters used in the treatment of bone metastases, $^{223}RaCl_2$ has less myelotoxicity. Indeed, the first three alpha nuclides of the decay chain of ^{223}Ra are issued almost instantly and almost all of the energy emitted will remain concentrated in the area of disintegration of the ^{223}Ra. Alpha particles have a very high relative biological effectiveness (RBE) compared to β^- particles and diffuse very little in the bone (not more than ten cells) whereas the beta particles emitted by strontium-89 diffuse up to 8 mm and can therefore reach and damage a greater proportion of cells in the bone marrow. Therefore $^{223}RaCl_2$ is much less toxic at the hematological level, which is a big advantage. In addition, opposed to $^{223}RaCl_2$, previously used β^--emitting radiopharmaceuticals have shown symptomatic benefit with pain relief (resulting in the reduction of major analgesics use) but no antitumor benefit as expressed as an increase in overall survival.

4.1.1. Mechanisms of action

Beta emitting radiopharmaceuticals have been available for many years for the treatment of pain in castrate-resistant prostate carcinoma patients with painful bone metastases. These include (^{89}Sr)-$SrCl_2$ and [^{153}Sm]Sm-EDTMP which have clearly shown symptomatic benefits including pain reduction. However, due to their relatively high β^- energy, and hence relatively long maximum range (^{89}Sr: 8 mm, ^{153}Sm: 3 mm), their emissions induce bone marrow toxicity. The advantage of ^{223}Ra, and its main alpha emission, is the fact that only ~10 cells receive radiation from the bone cells that accumulate it, resulting in less myelotoxicity. Probably due to this high safety profile, $^{223}RaCl_2$ could be used safely to induce not only symptomatic benefits but probably also antitumor effect with statistically significant improvement of survival.

4.1.2. Potential use

From the preliminary experimental data that lead to the EMA marketing authorization, it appears that patients who are castrate-resistant (i.e. not responding to androgen privation therapy) and who have a predominant bone involvement are the best candidates for treatment with $^{223}RaCl_2$. Because there are now many options for those patients, including chemotherapy with taxols (eg. docetaxel – Taxotere™), it is not clear whether $^{223}RaCl_2$

[3] Best standard of care included local radiotherapy, corticosteroids, antiandrogens, estrogens, estramustine, or ketoconazole and appropriate analgesics (opiate or non opiates). Patients in both groups were to continue androgen deprivation therapy

could be used early on and whether it must be used as a monotherapy or in combination with other therapeutic approaches, such as abiraterone (Zytiga®) or enzalutamide (Xtandi®). Considering the lack of data on combined use, it is understood as of now that $^{223}RaCl_2$ should be used as monotherapy, together with the best standard of care, as previously described in footnote 3.

Studies evaluating this are currently ongoing. Nevertheless, despite its radioactive nature, $^{223}RaCl_2$ needs to be considered in castrate-resistant metastatic patients with predominant bone involvement who are refractory to or not candidates for docetaxel chemotherapy. No, or limited effect can be expected in patients with predominant visceral, including large lymph node metastases. Xtandi® already has a European marketing authorization for patients who prove refractory to chemotherapy with docetaxel, whereas Zytiga® can be used in castrate-resistant patients before chemotherapy.

4.1.3. Potential use in association with other treatments or other indications

Multiple clinical trials are ongoing or will be started shortly to evaluate the additive effect of $^{223}RaCl_2$ with other medication. Currently, no data are available on the additional or synergic effect of simultaneous administration of $^{223}RaCl_2$ with other therapeutic agents/drugs. Conceptually, it is clear that targeting two different pathways of progressing disease may be of added value. Especially, if the toxicity profiles of the compounds are different, one could expect additional (if not supplementary, -synergistic-) effects. It is however premature to elaborate on this. Finally, $^{223}RaCl_2$ may also prove useful in other metastatic cancers, such as breast cancer, that may develop in up to 40 % of the cases as condensing bone metastases. This condition is of particular interest as it may lead to predominant if not exclusive bone metastases. Clinical trials in this direction are ongoing.

4.2. If you find that the use of [^{233}Ra]-$RaCl_2$ is justified, we would like to have your advice on the following points:

4.2.1. Medical Specialists

4.2.1.1. Which Medical Specialists should be involved for the justification, the prescription and the planning of the therapy?

The Multidisciplinary Oncology Consultation (MOC) including nuclear medicine physicians, medical oncologists, radiotherapists and urologists.

4.2.1.2. Which Medical Specialists should be involved in the implementation?

Nuclear medicine physicians for administration, according to their license following article 53.4 of the Royal Decree of 20 July 2001, granted by the Medical Jury of the FANC defined in article 54.9 of this RD.

4.2.1.3. Which Medical-Specialists should be present when administrating the [^{233}Ra]-$RaCl_2$?

A nuclear medicine physician (preferably supported by a nuclear medicine technologist/nurse).

4.2.1.4. Which Medical Specialist bears the final medical responsibility for this therapy?

For the practical aspects, the nuclear medicine physician.

Justification of the practice is shared between the physician in charge (ie. nuclear medicine physician as indicated in paragraph 2.2.1.2) and the referring physician, according to article 51.1.1. §c.

The follow up of the patient must ideally be shared between the physicians present in the MOC, involving at the minimum the general practitioner for information.

The nuclear medicine physician will personally check the patient's status during the week before the administration to verify that treatment is still useful. This can ideally be made with the direct contribution of the referring oncologist or urologist, or general practitioner.

4.2.1.5. Should these Medical Specialists follow additional training? If yes, what conditions should meet this training?

As for any other radiopharmaceutical, Nuclear Medicine Physicians must comply with the requirements of art 53.1 (7th paragraph) of the Royal Decree of 20 July 2001:

"De vergunde artsen, tandartsen en dierenartsen zijn ertoe gehouden hun kennis en bekwaamheid op het gebied van de stralingsbescherming op peil te houden en te vervolmaken, in het kader van een permanente vorming op universitair niveau."

"Les médecins, dentistes et vétérinaires autorisés sont tenus d'entretenir et de développer leurs connaissances et leur compétence en radioprotection, dans le cadre d'une formation continue de niveau universitaire.»

4.2.2. Should there always be a medical physics expert (MPE) in radiation physics involved?

Yes. The use of alpha-particle emitting radionuclides, such as ^{223}Ra, requires the involvement of an authorized nuclear medicine medical physics expert (Radiation physicist).

4.2.2.1. If yes, what are the tasks to perform?

In the institution where the patient is treated, the medical physicist should be familiarized with the use and quality assurance of all devices that are used as part of the treatment. The medical physicist verifies at least the correct use of the dose calibrator and supervises the calibration for the determination of the administered activity.

In consultation with the nuclear medicine physician, the medical physicist should help in the establishment of gamma camera imaging parameters, such as correct energy window settings for the used radionuclide. The availability of an appropriate gamma camera imaging protocol might help to visualize and support findings in case of a treatment incident (e.g. misadministration). Systematic imaging is however not useful, hence not mandatory.

The medical physicist needs to be notified if there is a deviation from the treatment protocol.

The medical physicist should maintain his/her knowledge about basic and advanced techniques for radionuclide therapy and internal dosimetry in nuclear medicine. Again, it must be kept in mind that systematic dosimetry assessment is not required since in the case of a low-abundance gamma emission, systematic imaging and formalism based Dosimetry (i.e. MIRD or OLINDA) may be prone to uncontrolled errors.

4.2.2.2. If yes, has the MPE to be present during the administration?

No. He has no role in the administration and is not directly in charge of radiation protection.

4.2.3. Physical control

The expert in Health Physics[4] (HP), hereunder identified as PC, according to Belgian denomination, must be informed and must approve the clinical procedures as well as other procedures relevant to the radiation protection of personnel, public and environment.

4.2.3.1. May the expert (PC) delegate this task? If yes, to whom?

No, as this is the law (art.23 §1 5° RD, 2001).

4.2.3.2. Must the Expert (PC) be present during the administration?

No, as he/she is not directly involved with the act of injecting the drug.

4.2.4. Radiopharmacist

4.2.4.1. Must there always be a radiopharmacist present? If yes, what are the tasks to perform?

No, since there is no specific preparation except for withdrawing the necessary volume from the vial(s). As for all ready-to-use radiopharmaceuticals, the delivered vials come with a GMP certificate issued by a certified/qualifies person and need no further certification by a local radiopharmacist. The most important step for the preparation of the to-be-injected syringe, is the calibration and regular check of the dose calibrator, which are tasks described above for the Medical Physicist. The current Belgian legislation prescribes that the final delivery of a radiopharmaceutical is that of an Hospital Pharmacist, that can, but must not, be assisted by a radiopharmacist.

[4] Expert in Health Physics is the official international denomination of the words 'Expert qualifié en Contrôle Physique' and 'Deskundige bevoegd in de Fysische Controle', as per the Belgian legislation.

4.2.5. Staff (Nuclear Medicine unit, nursing units, etc.)

4.2.5.1. Should the involved staff follow additional training? If yes, what conditions should meet this training?

Yes and this applies to all involved nuclear medicine staff members. The activities to be used in individual patients, namely 50 kBq/kg, are unusually low for a therapeutic application. Despite the relatively low activity (with which staff are usually not familiar), major risks for the staff are related to internal contamination because of the high radiotoxicity of the compound. Special measures during manipulation of $^{223}RaCl_2$ should therefore be focused on the minimisation of the risk of both potential contamination and potential cross-contamination. This means that procedures involving $^{223}RaCl_2$ should be accompanied by appropriate measures to avoid internal radiation exposure as a result of ingestion, inhalation and/or skin contact.

The preparation of the dose must be provided by the supplier using a detailed brochure whereas the training for handling and for radiation protection is the responsibility of the institution and must be supervised by the PC. Extension of training in accordance with article 25 of the RD 20 July 2001, needs to be foreseen. Nuclear medicine staff should be able to understand and follow all steps of the SOP.

4.2.5.2. Is extremity dosimetry indicated? If yes, for which categories?

No. The very low β^-/γ emissions are not expected to result in significant extremity doses. All efforts should however be made to ensure that direct skin contaminations are avoided. Very simply, all manipulations (dosing, transport of syringe, injection, management of waste, etc.) must be performed by individuals wearing gloves at all times – gloves have to be changed between different tasks.

4.2.6. Conditions for hospitalization and release of the patient

4.2.6.1. Does the injected patient always need to be hospitalized because of the aspects of radiation protection? If yes, for how long? If yes, has this hospitalization to be foreseen in a FANC-licensed hospital room? If yes, should the faeces and urine be collected separately as radioactive waste?

No, if no treatment contraindication; MOC Patients should be autonomous and not suffer fecal incontinence. From the scientific information available, diarrhea is one of the expected side effects. However, it is expected to occur as a consequence of irradiation to the ileum mucosa and after ^{223}Ra is excreted. Provided normal hygiene measures are taken, there should be no risk for the relatives or caregivers. A statement of the NRC has considered external exposure and internal contamination negligible (Bailey D et al., 2012).

4.2.6.2. What written instructions should be given to the patient leaving the hospital?

Instructions must be handed to the patient in accordance with previous SHC advisory report (SHC n° 7221). The patient should receive written information about radiation protection, hygiene measures, and measures to avoid conception, further potential

hospitalization and modalities about premature death including potential delay for cremation (SHC n° 8416), see 4.2.7.3.

If a patient needs to be hospitalised because of contraindication or socio-economic reasons, special measures should be taken in conformity with the written instructions for ambulatory patients to minimise radiation exposure to other patients, comforters, carers and visiting family members.

4.2.7. Are there other conditions related to radiation protection to be met in the planning and execution of this therapy?

4.2.7.1. Special considerations for staff protection

Due to the presence of the γ-emitting progeny there is no need for special equipment (alpha counters). Geiger-Müller and NaI counters are satisfactory for the detection of contamination but should be approved and checked regularly by the HP officer.

4.2.7.2. Special environmental conditions

The activity levels of ^{227}Ac, as a potential contaminant in commercial batches of [^{223}Ra]-$RaCl_2$, are expected to be very low, if not inexistent (Jalota D et al., 2012). Information provided by Bayer mentions that the potential contamination will in no case exceed 240 Bq/vial at calibration date. This information refers to radiochemical purity but does not allow drawing any guidance about radiation protection issues. Indeed, there is no accurate data on these levels currently available. Given the very low regulatory clearance level of ^{227}Ac (10 Bq/kg) (Table a in appendix 1b RD), these uncertainties should be subject to caution during waste management after the use of [^{223}Ra]-$RaCl_2$. In view of the above, nuclear medicine departments are allowed to store the vials but are not allowed to directly discharge unused or residual vials as non-radioactive waste after decay storage, ie. at least ten half-lives, and ideally 20, of ^{223}Ra (viz,114 to 228 days). They can of course discharge directly through contracting with ONDRAF/NIRAS. Since Bayer is not licensed for collecting used vials, the SHC recommends that the supplier (i.e. Bayer) takes care of contracting an independent study to demonstrate that no ^{227}Ac is present (or below the clearance level). If this proves to be the case, than, disposal of vials after at 10-20 physical half-lives (depending on the residual activity) will be accepted.

This is proposed as a conservatory measure and the supplier is strongly advised by the SHC to collect scientific data on the potential contaminant and its level. These measures shall be alleviated if consistent independent data demonstrate that the regulatory clearance levels are not exceeded.

4.2.7.3. Considerations about disposal of corpses following premature death after treatment with ^{223}Ra

Recommendations as published in SHC advice 8416: based on file data from Bayer, that were transmitted to EMA, FDA and FANC, cremation of a patient recently treated with ^{223}Ra-dichloride can be authorized without restriction after a precaution period of 3 weeks. Within this precaution period, all recommendations cited above apply, which means that the relevant authorities, and in particular the FANC may consider each individual case, on the basis of physical and biophysical data, after thorough discussion with the treating physician and responsible medical physicist.

4.2.7.4. Patient and public information

A patient card in a convenient format with actual treatment data is advisable, as currently evaluated by the FANC and other European authorities. This card should better be developed by the FANC, together with the supplier and the scientific society for Nuclear Medicine (SBMN-BGNG).

4.2.7.5. The SOP guidelines, validated by HP, should include:

<u>Elements related to:</u>

- Receipt, unpacking and storage;
- Correct determination of the administered activity;
- Special precautions to limit contamination risk;
- Preparation of patient doses;
- Waste collection and management, including inventory;
- Instructions to provide to patients;
- Measures to counteract potential treatment incidents;

5. REFERENCES

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SHC - Superior Health Council. Avis du Conseil Supérieur de la Santé relatif à l'assurance de qualité et radioprotection en médecine nucléaire. Bruxelles : SHC; 2003. Advice n° 7221

6. RECOMMANDATIONS FOR FURTHER RESEARCH

The SHC recommends that the supplier (i.e. Bayer) takes care of contracting an independent study to demonstrate that no ^{227}Ac is present (or below the clearance level). If this proves to be the case, than, disposal of vials after at 10-20 physical half-lives (depending on the residual activity) will be accepted.
This is proposed as a conservatory measure and the supplier is strongly advised by the SHC to collect scientific data on the potential contaminant and its level. These measures shall be alleviated if consistent independent data demonstrate that the regulatory clearance levels are not exceeded.

The SHC also recommends to collect information about contamination and waste outside the hospital environment in particular at home of patients. This could be undertaken by the FANC together with university hospitals that can make use of appropriate (sensitive) detector equipment.

7. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity.*** The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up the advice:

Name	Expertise	Affiliation
BAETE Kristof	Medical Physics	UZ Leuven, KU Leuven
COVENS Peter*	Health Physics	VUB, UZ Brussel
DE SPIEGELEER Michel	Health Physics	UCL
JAMAR François*	Nuclear Medicine	UCL
LUMEN Nicolaas	Urology	UZ Gent
MUYLLE Kristoff	Nuclear Medicine	Jules Bordet Institute, ULB
PAULUS Patrick*	Nuclear Medicine	Hôpital de la Citadelle, Liège
PIRLET Vera	Health Physics	ULg

The administration was represented by:

VANDECAPELLE Marleen, Federal Agency for Nuclear Control (FANC)

The working group was chaired by Patrick PAULUS, the scientific secretary was Veerle MERTENS.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be