Public Risk Management Plan (RMP) Summary

for

Lutathera® (Lutetium (177Lu) oxodotretotide)

Version 1.0 (August 2019)
Based on EU RMP version 1.5 (20/07/2017)
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 minimize them. The RMP summary of Lutathera® 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“ 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 Lutathera® in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch ) approved and authorized by Swissmedic.

Advanced Accelerator Applications is fully responsible for the accuracy and correctness of the content of the here published RMP summary of Lutathera®
Summary of the Risk Management Plan

1 The Medicine and What It Is Used for

Lutathera is authorised for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) in adults. It is administered by intravenous route via slow intravenous infusion and must not be injected as a bolus.

Lutathera is a lutetium-177 (177Lu)-labelled somatostatin analogue peptide conjugated with the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The octreotate moiety binds the somatostatin subtype 2 (sst2) receptors and, therefore, conveys the radioactive moiety Lutetium-177 to the surface of malignant cells overexpressing the receptor. Lutetium-177 (177Lu) is a β-emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumor cells with a limited effect on neighboring normal cells.

It is a ready to use radiopharmaceutical medicinal product for single use only. The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity.

Further information about the evaluation of Lutathera’s benefits can be found in Lutathera’s EPAR, including in its plain-language summary, available on the EMA website under the medicine’s webpage.

2 Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Lutathera, together with measures to minimise such risks and the proposed studies for learning more about Lutathera 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 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 addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report 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 ocrelizumab is not yet available, it is listed under ‘missing Information’ below.

### 2.1 List of Important Risks and Missing Information

Important risks of Lutathera are risks that need special risk management activities to further investigate or minimize 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 Lutathera. 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).

| Important identified risks | • Renal dysfunction (radiation nephropathy, chronic kidney disease, minor renal function deterioration, etc.)  
|                           | • Myelosuppression / cytopenias (immediate hematotoxicity)  
|                           | • Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity)  
|                           | • Hypogonadism, sexual dysfunction  
|                           | • Drug interaction with somatostatin/ somatostatin analogues |
| Important potential risks | • Tumor cell lysis-related hormone release-induced crises (HRIC)  
|                           | • Hepatotoxicity  
|                           | • Radiotoxicity, including occupation exposure and inadvertent exposure |
| Missing information       | • Radiation exposure during breast feeding  
|                           | • Exposure in patients with renal impairment  
|                           | • Exposure in patients with severe hepatic impairment  
|                           | • Secondary malignancies (solid tumors)  
|                           | • Long term safety data |
## 2.2 Summary of Important Risks and Missing Information

### Important identified risk: Renal dysfunction (radiation nephropathy, chronic kidney disease, minor renal function deterioration, etc.)

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>The radiation emitted from a radiolabeled peptide bound to a tumor cell may also kill neighboring cells because the path length of $\beta$-particles can extend over several cell diameters and injure / destroy non-tumor tissues.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The major part of conjugated peptides (including radiolabeled somatostatin analogues (RAS)) are eliminated through the kidneys, but a fraction is reabsorbed in the proximal tubule cells</td>
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</tr>
<tr>
<td>− by endocytosis via the megalin / cubulin system [Duncan et al., 1993; Bernard et al., 1997, de Jong et al., 2005; Barone et al., 2005b] and</td>
<td>The major part of conjugated peptides (including radiolabeled somatostatin analogues (RAS)) are eliminated through the kidneys, but a fraction is reabsorbed in the proximal tubule cells</td>
</tr>
<tr>
<td>− by peritubular uptake via somatostatin receptors [Reubi et al., 1993; Balster et al., 2001; Rolleman et al., 2007c; Stahl et al., 2007]</td>
<td>− by endocytosis via the megalin / cubulin system [Duncan et al., 1993; Bernard et al., 1997, de Jong et al., 2005; Barone et al., 2005b] and</td>
</tr>
<tr>
<td>where the radiolabeled somatostatin analogues are retained.</td>
<td>− by peritubular uptake via somatostatin receptors [Reubi et al., 1993; Balster et al., 2001; Rolleman et al., 2007c; Stahl et al., 2007]</td>
</tr>
<tr>
<td>A significant amount of activity accumulates in the whole parenchyma [Christensen &amp; Nielsen, 1991; de Jong et al., 1996; Akizawa et al., 1998], yet the distribution of radioactivity in the human renal cortex and medulla is not uniform and differs significantly from the average dose to the whole kidney:</td>
<td>A significant amount of activity accumulates in the whole parenchyma</td>
</tr>
<tr>
<td>− the inner cortex receives 75% of the highest radioactive density [de Jong et al., 2004];</td>
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<td>− the tubular cells radioresistant than the radiosensitive glomeruli [Pauwels et al., 2005];</td>
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<tr>
<td>− the glomeruli, which form radiation-sensitive functional units for late radiation damage, are not evenly distributed over the cortex in human kidneys: about 85% of the glomeruli are in the outer cortical regions.</td>
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<td>Thus, different effects due to this inhomogeneity can be expected from Peptide receptor radionuclide therapy (PRRT) using radionuclides emitting particles with short ranges, such as $^{177}$Lu. These radionuclides will differentially minimize the dose to the sensitive glomeruli in the outer renal cortex [de Jong et al., 2004]. Because of its lower energy and shorter penetration range, $^{177}$Lu irradiates the renal interstitium and glomeruli less extensively than $^{99}$Y [Bodei et al., 2015].</td>
<td>Thus, different effects due to this inhomogeneity can be expected from Peptide receptor radionuclide therapy (PRRT) using radionuclides emitting particles with short ranges, such as $^{177}$Lu. These radionuclides will differentially minimize the dose to the sensitive glomeruli in the outer renal cortex [de Jong et al., 2004]. Because of its lower energy and shorter penetration range, $^{177}$Lu irradiates the renal interstitium and glomeruli less extensively than $^{99}$Y [Bodei et al., 2015].</td>
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<td>The nature of long-term kidney damage, in fact, reflects the failure to regenerate functional tissue after the initial apoptotic phenomena triggered by the irradiation, and is sustained by radiation-induced late damage to the kidney substructures as detailed above in the section describing the histopathological nature.</td>
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</tr>
<tr>
<td>Risk factors and risk groups</td>
<td>Identified risk factors of kidney injury / disease after PRRT:</td>
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<td>------------------------------</td>
<td>---------------------------------------------------------------</td>
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<tr>
<td></td>
<td>2. Older age (&gt; 60 yrs) [Valkema et al, 2005; Imhof et al, 2011; Bodei et al, 2015]</td>
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<td></td>
<td>3. Diabetes mellitus [Barone et al, 2005a]</td>
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<td></td>
<td>4. Renal morphological abnormalities [Bodei et al, 2008]</td>
</tr>
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<td></td>
<td>5. Low baseline GFR [Imhof et al, 2011; Svensson et al, 2015]</td>
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<tr>
<td></td>
<td>6. Combination of hypertension age, and diabetes mellitus [Valkema et al, 2005]</td>
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<td></td>
<td>7. Previous nephrotoxic chemotherapy or trans-arterial chemoembolization [Barone et al, 2005a; Bodei et al, 2015]</td>
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<td></td>
<td>9. A higher number of concomitant risk factors [Valkema et al, 2005].</td>
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</tbody>
</table>

The variable weighting of risk factors in patients treated with $^{177}$Lu-DOTA-TATE alone:
- According to some series, the risk factors may become relevant only in the presence of a high cumulative or per-cycle kidney absorbed dose [Valkema et al, 2005].
- In counter distinction, the impact of risk factors in patients treated only with $^{177}$Lu-DOTA-TATE was so strong that it masked any possible advantage from, e.g., fractionation [Bodei et al, 2008; Bodei et al, 2011].

Co-dependent associative factors of kidney injury / disease after PRRT:
1. Biological effective dose (BED), with a threshold of nephrotoxicity set at 
   - 28- 30 for patients with risk factors and 40 - 45 Gy [Bodei et al, 2008; Bodei et al, 2015];
2. Hemoglobin toxicity grade, denoting an association between nephrotoxicity and hematotoxicity [Bodei et al, 2015].
3. Short duration of exposure (from first to last cycle) [Bodei et al, 2015].
4. Per cycle kidney absorbed dose > 14 Gy [Valkema et al, 2005]
5. Kidney uptake score (as visualized by nuclear medicine physicians using a four-point scale: score 0, no uptake; score 1, uptake < liver uptake; score 2, uptake similar to liver uptake; and score 3, uptake > liver uptake [Imhof et al, 2011]
The following important determinants of nephrotoxicity emerged from recent recursive partitioning data and regression tree analysis performed in a large retrospective cohort of patients who underwent PRRT (*⁹⁰Y, or *¹⁷⁷Lu, or both) [Bodei et al, 2015]

1. Cumulative *¹⁷⁷Lu activity (> 7 GBq),
2. Mean hemoglobin CTCAE toxicity grade (> 0.4),
3. Number of cycles (> 1.5),
4. Time between diagnosis and PRRT (> 31 months),
5. Age at diagnosis (> 50 years),
6. Leukocyte CTCAE toxicity grade (> 1.5),
7. The use of *⁹⁰Y (in addition to *¹⁷⁷Lu)

The significance of these parameters necessitates further validation in subsequent studies.

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>SmPC sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2 Posology and method of administration</td>
<td>Dose modification</td>
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<tr>
<td>Table 5. Instructions for dose modifications</td>
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<tr>
<td>4.4 Special warnings and precautions for use</td>
<td></td>
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<tr>
<td>4.8 Undesirable effects</td>
<td></td>
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<tr>
<td>Additional risk minimisation measures: none</td>
<td></td>
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</tbody>
</table>

**Important identified risk: Myelosuppression / cytopenias (immediate hematotoxicity)**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>1. Bone marrow uptake mechanisms:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies using *⁸⁶Y-DOTA-TOC and PET showed that somatostatin analogues are taken up in the red marrow but not in the trabecular or cortical bone [Walrand et al, 2002]:</td>
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<tr>
<td></td>
<td>− the mechanisms of the uptake are not entirely elucidated and may include specific binding to SSR, transchelation of the metal label to transferrin, or plasma activity [Pauwels et al, 2005].</td>
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<td></td>
<td>− certain blood cells (lymphocytes, monocytes) and hematopoietic progenitor cells express SST receptors, mainly SST₂ [Reubi et al, 2001; Oomen et al, 2002; Lichtenauer-Kaligis et al, 2004]:</td>
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<td></td>
<td>• somatostatin can modulate lymphocytic functions via its receptors and is likely to play a role during the development of lymphoproliferative diseases [Bhathena et al, 1981; Ferone et al, 1999; Van Hagen et al, 1994];</td>
</tr>
</tbody>
</table>
- this uptake could theoretically result in an underestimation of the absorbed radiation dose to the BM, yet the assumption of specific uptake of RAS into the BM was refuted in a dosimetry study [Forrer et al, 2009].

2. **Mechanism of general radiation-induced myelosuppression:**
   - Repeated administration of PRRT increases the cumulated dose to normal tissues and thereby increases the risk of accumulation of unrepaired DNA damage. This leads to [Denoyer et al, 2015]:
     - apoptosis of cells in the peripheral blood and bone marrow resulting in cytopenias in peripheral blood and myelosuppression, respectively, and
     - in the long term, to genetic instability and, potentially, to leukemogenesis (MDS / AML) (see separate section on this below).
   - The kinetics of radiopharmaceutical-induced DNA damage is more complex than that induced by EBRT, reflecting
     - the nature of radionuclide emissions,
     - biodistribution of the agent within cells and organs, and
     - the time course of radiation delivery determined by physical decay characteristics of the radionuclide and tissue clearance kinetics [Denoyer et al, 2015].

3. **Specific mechanisms of lymphocytotoxicity:**
   - The most sensitive blood cells to radiation damage are the lymphocytes. Possible reasons for the transient lymphocytopenia are:
     - the heterogeneity of expression of SST receptors in lymphoid tissue (which seems to be dependent on the activation state of the cells and on their homing or circulating condition);
     - the variable modulatory functions exerted by somatostatin on immune cells [Ferone et al, 2000a,b].

### Risk factors and risk groups

<table>
<thead>
<tr>
<th>Identified risk factors of myelosuppression / cytopenias after PRRT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Baseline (pre-existent) cytopenias [Sabet et al, 2013];</td>
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<tr>
<td>2. Baseline renal dysfunction (eGFR ≤ 60 ml/min) [Kwekkeboom et al, 2010; Kam et al, 2012].</td>
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</table>

<table>
<thead>
<tr>
<th>Uncertain risk factors of myelosuppression / cytopenias after PRRT (positive correlation detected in most studies, but none in others):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age &gt; 70 years at PRRT onset [Juweid et al, 1999; Kwekkeboom et al, 2010; Kam et al, 2012; Sabet et al, 2013];</td>
</tr>
</tbody>
</table>


Identified co-dependent associative factor of myelosuppression / cytopenias after PRRT:
- Higher whole-body $^{177}$Lu-DOTA-TATE residence time [Svensson et al, 2015].

Uncertain co-dependent associative factor of myelosuppression / cytopenias after PRRT:
- A cumulative injected activity of > 29.6 GBq emerged as a statistically significant co-dependent associative factor [Sabet et al, 2013] and the correlation between myelosuppression and cumulative activity had also been found in previous studies [Lim et al, 1997; Matthay et al, 2009].
- On the other hand, no correlation between cumulated activity and hematotoxicity was found in other studies [Vallabhajosula et al, 2005; Sabet et al, 2014b], probably because of the high inter-patient variability in absorbed red marrow radiation per unit of injected activity, e.g.,
  - mean 0.073 ± 0.01 Gy/GBq (range 0.05 – 0.08) [Kwekkeboom et al, 2001];
  - mean 0.04 ± 0.02 Gy/GBq ((range 0.02 – 0.08) [Wehrmann et al, 2007];
  - mean 0.03 ± 0.014 Gy/GBq (range 0.02 – 0.06) [Bodei et al, 2011].

Protective risk factors of myelosuppression / cytopenias after PRRT:
A high tumor burden acting as an activity sink will lower the blood activity concentration and, if the BM is free of tumor, the BM self-dose, thus this factor is actually a protective factor in the initial stage of therapy. To some extent, this decrease will be counteracted by the higher cross-radiation that, around the large tumors, contributes to the local irradiation of the BM [Sandstrom et al, 2013]
### 4.8 Undesirable effects

**Additional risk minimisation measures:** none

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#### Important identified risk: Myelodysplastic syndrome (MDS) / acute leukemia (AL) (late hematotoxicity)

| Evidence for linking the risk to the medicine | Evidence for radiation-induced MDS or AL comes from radionuclide studies in general, not PRRT in particular: Secondary MDS / AL are considered a rare stochastic event that is without a threshold but with a probability increasing with the absorbed dose [Godely & Larson, 2008]. The induction of secondary malignancies by radiation is a complex process that originates as a result of single or double strand breaks in the DNA and involves errors in the repair mechanisms leading to genetic mutations, with loss of function or oncogene activation. A critical parameter in this process is the different sensitivities of DNA to radiation during the various phases of the cell cycle. Thus, myeloid neoplasms are considered a consequence of mutational events induced by cytotoxic therapies, or to arise via the selection of a myeloid clone with a mutator phenotype that has a markedly elevated risk for mutational events [Boehrer et al, 2009]. Thus, by extrapolation, the pathogenetic mechanism in PRRT-induced MDS is also considered to be mediated by radiation-induced clonal selection followed by genetically induced or regulated proliferative events in the bone marrow [Kayser et al, 2011] |
| Risk factors and risk groups | Identified risk factors of MDS:  
- Prior acute leukemia [Bodei et al, 2015]  
Identified co-dependent associative factors of MDS development:  
- Higher thrombocytopenia CTCAE grade [Bodei et al, 2015];  
- Longer duration of PRRT [Bodei et al, 2015].  
Uncertain risk factors of MDS development (positive correlation in some analyses, none in others):  
Thrombocytopenia > CTCAE grade 1 [Bodei et al, 2015] |
| Risk minimisation measures | Routine risk minimisation measures beyond adverse reactions reporting and signal detection.  
#### Sections in SmPC  
**4.2 Posology and method of administration**  
Dose modification
Table 5. Instructions for dose modifications

4.4 Special warnings and precautions for use

4.8 Undesirable effects

**Additional risk minimisation measures:** none

<table>
<thead>
<tr>
<th>Important identified risk: Hypogonadism, sexual dysfunction</th>
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<tbody>
<tr>
<td><strong>Evidence for linking the risk to the medicine</strong></td>
</tr>
<tr>
<td>The best way to evaluate the rate of gonadal toxicity induced by $^{177}$Lu-DOTA-TATE treatment would have been preferable by means of a randomized trial were performed comparing PRRT to no further treatment at all. This however, is presently no longer possible, since PRRT has become available in many medical centers and since the results of such treatment are so impressive that withholding it to the patients in the placebo arm of an experimental setting cannot be ethically justified [Kwekkeboom <em>et al.</em>, 2010]. However, a prevalence of $15 / 35 = 42.9%$ [95% CI: 28.0 – 59.1] hypogonadism in men was documented prior to onset of treatment with $^{177}$Lu-DOTA-TATE in a study of patients with somatostatin receptor-positive tumors [Teunissen <em>et al.</em>, 2009]. Alternative etiologies of sex hormone variations are prior chemotherapy in disseminated cancer [Chlebowski <em>et al.</em>, 1982], as well as weight loss, age, history of alcohol intake, and liver disease have been reported to have deleterious effects on the total testosterone levels in male patients.</td>
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<thead>
<tr>
<th><strong>Risk factors and risk groups</strong></th>
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<tbody>
<tr>
<td>Although no specific data exist, it may be inferred that higher cumulative radioactivity, higher uptake and retention time of radiation in the pelvic area (urinary bladder), and a preponderance of the alternative etiological factors of gonadal dysfunction would constitute commonsensically risk factors.</td>
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<table>
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<tr>
<th><strong>Risk minimisation measures</strong></th>
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<tbody>
<tr>
<td>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</td>
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</table>

**Sections in SmPC**

4.6 Fertility, pregnancy and lactation

**Additional risk minimisation measures:** none

<table>
<thead>
<tr>
<th>Important identified risk: Drug interaction with somatostatin/ somatostatin analogues</th>
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<tr>
<td><strong>Evidence for linking the risk to the medicine</strong></td>
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<tr>
<td>$^{177}$Lu-DOTA$^0$-Tyr$^3$-Octreotate has a high affinity for subtype 2 somatostatin receptors (sst2). It binds to malignant cells which overexpress</td>
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</tbody>
</table>

Advanced Accelerator Applications, s.a. au capital 8 833 315.70 Euros
20, rue Diesel, 01630 Saint Genis Pouilly, France- tel. +33 4 50 99 30 70 – fax +33 4 50 99 30 71 -- www.adacap.com
N° Siret: 441 417 110 00026 - 441417110 RCS Bourg en Bresse - N° TVA: FR 67 441.417.110
sst2 receptors. Somatostatin and its analogues competitively bind to somatostatin receptors.

<table>
<thead>
<tr>
<th>Risk factors and risk groups</th>
<th>Patients receiving somatostatin analogues.</th>
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<td>Risk minimisation measures</td>
<td>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</td>
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<tr>
<td></td>
<td><strong>Sections in SmPC</strong></td>
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<tr>
<td></td>
<td><strong>4.4 Special warnings and precautions for use</strong></td>
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<tr>
<td></td>
<td><strong>4.5 Interaction with other medicinal products and other forms of interaction</strong></td>
</tr>
<tr>
<td>Additional risk minimisation measures</td>
<td>none</td>
</tr>
</tbody>
</table>

**Important potential risk: Tumor cell lysis-related hormone release-induced crises (HRIC)**

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>The exact mechanism of increased hormonal release in the patients developing a hormonal crisis after PRRT has not been fully elucidated. Several factors may have accounted for the HRIC:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1. Tumor lysis because of beta-irradiation from the RSA [de Keiser et al, 2008];</td>
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<td></td>
<td>2. Discontinuation of short-acting SAs before 177Lu-octreotate administration [de Keiser et al, 2008];</td>
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<td></td>
<td>3. Emotional stress response to hospitalization and/or therapy: [Bell et al, 2005; Frojd et al, 2007];</td>
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<td></td>
<td>4. Administration of amino acids (2.5% arginine + 2.5% lysine) [de Keiser et al, 2008].</td>
</tr>
<tr>
<td></td>
<td>Direct receptor-mediated hormonal release by the RSA seems unlikely. SSR binding leads to decrease in hormonal secretion in the majority of patients:</td>
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<tr>
<td></td>
<td>Therapy with SAs in patients with metastatic carcinoid tumors results in symptomatic improvement in more than 70% of the patients and biochemical response in 50 to 60% of the patients [Oberg et al, 2004; Kvols et al, 1985].</td>
</tr>
<tr>
<td>Risk factors and risk groups</td>
<td>Although no specific data exist, it is inferred that a higher cumulative radioactivity, a higher radiation dose received by the scalp, and a history of recent prior chemotherapy would constitute plausible risk factors.</td>
</tr>
<tr>
<td>Risk minimisation measures</td>
<td>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</td>
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<td></td>
<td><strong>Sections in SmPC</strong></td>
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</tbody>
</table>
### 4.4 Special warnings and precautions for use

#### 4.8 Undesirable effects

**Additional risk minimisation measures:** none

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#### Important potential risk: Hepatotoxicity

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

The best way to evaluate the rate of hepatotoxicity induced by $^{177}$Lu-DOTA-TATE treatment would have been preferable by means of a randomized trial were performed comparing PRRT to no further treatment at all. This however, is presently no longer possible, since PRRT has become available in many medical centers and since the results of such treatment are so impressive that withholding it to the patients in the placebo arm of an experimental setting cannot be ethically justified [Kwekkeboom et al, 2010].

However, it is inferred that the prevalence of hepatotoxicity among NET patients is most probably higher than that of the aged-matched general population without NETs, mostly in those patients that have liver metastases and also due to prior cytotoxic treatments such as chemotherapy, external beam radiotherapy (to liver fields), prior radionuclide therapy ($^{131}$I-MIBG).

**Risk factors and risk groups**

The presence of liver metastases transpires as the sole risk factor [Forrer et al, 2007]

**Risk minimisation measures**

Routine risk minimisation measures beyond adverse reactions reporting and signal detection.

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#### Important potential risk: Radiotoxicity, including occupation exposure and inadvertent exposure

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

Exposure to ionizing radiation is linked with cancer induction and can lead to development of hereditary defects

**Risk factors and risk groups**

Health Professionals, patients, others
<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</th>
</tr>
</thead>
</table>

**Sections in SmPC**

6.6 Special precautions for disposal and other handling

**Section 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

**Additional risk minimisation measures:** As a risk minimisation measure for the potential risk - Radiotoxicity, including occupational exposure and inadvertent exposure, an educational program is conducted before launch in each country. The focus of this program is to make the patients educated in understanding the risk of radiotoxicity exposure. The patients will receive a detailed written Patient’s Guide provided by the healthcare professionals. The guide will include guidance related to patients contact with family members and the public to maximize their safety.

### Missing information: Radiation exposure during breast feeding

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</th>
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**Sections in SmPC**

4.6 Fertility, pregnancy and lactation

**Additional risk minimisation measures:** none

### Missing information: Exposure in patients with renal impairment

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures beyond adverse reactions reporting and signal detection.</th>
</tr>
</thead>
</table>

**Sections in SmPC**

4.2 Posology and method of administration
4.4 Special warnings and precautions for use

**Additional risk minimisation measures:** none

### Missing information: Exposure in patients with severe hepatic impairment
2.3 Post-Authorization Development Plan

2.3.1 Studies which are conditions of the marketing authorization

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

2.3.2 Other studies in post-authorisation development plan

Category 3 studies

Study short name and title:

This is a multinational, multicenter, non-interventional, retrospective and prospective study of patients with GEP-NET receiving treatment with Lutathera.

**The objectives of this study are:**

a) To assess the incidence and nature of potential long term second primary malignancies, including solid tumours and haematological neoplasia, occurring over a 7-year follow-up period in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours.

b) To quantify the incidence of other important identified and potential risks specified in the Lutathera Risk Management Plan (RMP) such as: renal dysfunction, myelosuppression/cytopenias, myelodysplastic syndrome, hypogonadism, sexual dysfunction, drug interaction with somatostatin/somatostatin analogues, tumour cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity.

c) To detect potential new risks overall, and potential risks in patients under-represented in the clinical trial, including elderly patients, patients with renal and liver impairment, reduced bone-marrow reserve, exposure in breast-feeding women, accidental foetal and child exposure.

d) To describe the patterns of drug utilisation that may add knowledge about the safety of Lutathera.
Reference


