NOVARTIS

Regulatory Affairs

Lutetium (177Lu) oxodotreotide

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Lutetium (177Lu) oxodotreotide
Product(s) concerned (brand name(s)):	Lutathera
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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 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 / 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 Lutathera in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Lutathera.

Table of contents

Part VI: Summary of the risk management plan for Lutathera (Lutetium (^{177}Lu) oxodotreotide)

This is a summary of the RMP for Lutathera. The RMP details important risks of Lutathera, how these risks can be minimized, and how more information will be obtained about Lutathera's risks and uncertainties (missing information).
Lutathera's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Lutathera should be used.
This summary of the RMP for Lutathera should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Lutathera's RMP.

I. The medicine and what it is used for

Lutathera is authorized for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSR positive GEP-NETs in adults. It contains lutetium (^{177}Lu) oxodotreotide as the active substance.
The recommended treatment regimen in adults consists of 4 infusions of 7400 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 European Medicines Agency website, under the medicine's webpage: link to the EPAR summary landing page: Lutathera, INN-lutetium (177Lu) oxodotreotide (europa.eu)

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Lutathera, together with measures to minimize such risks and the proposed studies for learning more about Lutathera's risks, are outlined below.
Measures to minimize 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 authorized pack size — the amount of medicine in a pack is chosen so as 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 minimize its risks.

In the case of Lutathera, 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 analyzed, including PSUR assessment (if applicable) so that immediate action can be taken as necessary. These measures constitute routine PV activities.
If important information that may affect the safe use of Lutathera is not yet available, it is listed

II.A: 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).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Renal dysfunction Myelosuppression / cytopenias (immediate hematotoxicity) Myelodysplastic syndrome / acute leukemia (late hematotoxicity) Hepatotoxicity Tumor lysis syndrome Hormone release-induced crises Hypogonadism, sexual dysfunction Drug interaction with somatostatin/somatostatin analogues
Important potential risks	Radiotoxicity, including occupational exposure and inadvertent exposure Secondary malignancies (solid tumors) Embryo-fetal toxicity
Missing information	Radiation exposure during breast feeding Exposure in patients with renal impairment Exposure in patients with severe hepatic impairment Long-term safety data

II B: Summary of important risks

Table 2 Important identified risk: Renal dysfunction

Evidence for linking the risk to the medicine	Evidence is based on clinical trial data and literature. Considering the theoretical potential mechanism as well the number of patients having renal dysfunction in Study AAA-III-01 (NETTER-1) in lutetium (^{177}Lu) oxodotreotide group, and literature data, there is a strong evidence.
Risk factors and risk groups	<u>Identified risk factors of kidney injury / disease after PRRT:</u> • Hypertension • Older age (> 60 years) • Diabetes mellitus • Renal morphological abnormalities • Low baseline GFR • Combination of hypertension age, and diabetes mellitus • Previous nephrotoxic chemotherapy or trans-arterial • chemoembolization • Male gender • A higher number of concomitant risk factors <u>The variable weighting of risk factors in patients treated with ^{177}Lu-DOTA-TATE alone:</u> According to some articles, the risk factors may become relevant only in the presence of a high cumulative or per-cycle kidney absorbed dose. 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. Co-dependent associative factors of kidney injury / disease after PRRT: • Biological effective dose, with a threshold of nephrotoxicity set at • 28 - 30 for patients with risk factors and 40 – 45 Gy • 40 -45 Gy for patients without risk factors • Hemoglobin toxicity grade, denoting an association between • nephrotoxicity and hematotoxicity • Short duration of exposure (from first to last cycle) • Per cycle kidney absorbed dose > 14 Gy • Kidney uptake score (as visualized by nuclear medicine physicians using a 4-point scale: score 0, no uptake; score 1, uptake < liver uptake; score 2, uptake similar to liver uptake; and score 3, uptake > liver uptake 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 (99Y, or 177Lu, or both) • Cumulative ^{177}Lu activity (> 7 GBq) • Mean hemoglobin CTCAE toxicity grade (> 0.4) • Number of cycles (> 1.5) • Time between diagnosis and PRRT (> 31 months) • Age at diagnosis (> 50 years) • Leukocyte CTCAE toxicity grade (> 1.5) • The use of 90Y (in addition to ^{177}Lu) The significance of these parameters necessitates further validation in subsequent studies.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 4.9 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 3 Important identified risk: Myelosuppression / cytopenias (immediate hematotoxicity)

Evidence for linking the risk to the medicine	Evidence is based on clinical trial data and literature.
Risk factors and risk groups	Identified risk factors of myelosuppression / cytopenias after PRRT: 1. Baseline (pre-existent) cytopenias 2. Baseline renal dysfunction (eGFR ≤ 60 ml/min) Uncertain risk factors of myelosuppression / cytopenias after PRRT (positive correlation detected in most studies, but none in others): 1. Age > 70 years at PRRT onset 2. Previous chemotherapy 3. Presence of bone metastases Identified co-dependent associative factor of myelosuppression / cytopenias after PRRT

	• Higher whole-body 177Lu-DOTA-TATE residence time 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 and the correlation between myelosuppression and cumulative activity had also been found in previous studies • On the other hand, no correlation between cumulated activity and hematotoxicity was found in other studies, probably because of the high inter-patient variability in absorbed red marrow radiation per unit of injected activity, e.g., o mean 0.073 ± 0.01 Gy/GBq (range 0.05 – 0.08) o mean 0.04 ± 0.02 Gy/GBq ((range 0.02 – 0.08) o mean 0.03 ± 0.014 Gy/GBq (range 0.02 – 0.06) 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.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8 and 4.9 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 4 Important identified risk: Myelodysplastic syndrome / acute leukemia

Evidence for linking the risk to the medicine	Evidence is based on clinical trial data and literature.
Risk factors and risk groups	Factors such as age > 70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior exposure to chemotherapeutic agents (specifically alkylating agents), and prior radiotherapy.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 5 Important identified risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Evidence is based on clinical trial data and literature. Considering the theoretical potential mechanism as well the number of patients having hepatotoxicity in Study AAA-III-01 (NETTER-1) in lutetium (^{177}Lu) oxodotreotide group, and literature data, there is a strong evidence.

Risk factors and risk groups	Patients with hepatic metastasis or pre-existing advanced hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6 Important identified risk: Tumor lysis syndrome

Evidence for linking the risk to the medicine	Current evidence is based on literature and clinical trial data.
Risk factors and risk groups	Patients with a history of renal insufficiency and high tumor burden may be at a greater risk.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 7 Important identified risk: Hormone release-induced crises

Evidence for linking the risk to the medicine	Current evidence is based on literature and clinical trial data.
Risk factors and risk groups	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.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 8 Important identified risk: Hypogonadism, sexual dysfunction

Evidence for linking the risk to the medicine	Current evidence is based on literature and clinical trial data.
Risk factors and risk groups	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.

Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 PL section 2 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 9 Important identified risk: Drug interaction with

Evidence for linking the risk to the medicine	Evidence is based on literature data.
Risk factors and risk groups	Patients taking short-acting or long-acting SAs while receiving lutetium (^{177}lu) oxodotreotide.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.5 PL section 2 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 10 Important potential risk: Radiotoxicity, including occupational exposure and inadvertent exposure

Evidence for linking the risk to the medicine	Evidence is based on literature data.
Risk factors and risk groups	Health professionals, patients, caregivers, relatives.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.6, 4.9, 6.6, 11 and 12 PL sections 1, 2 and 3 Additional risk minimization measures: Patient guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 11 Important potential risk: Secondary malignancies (solid tumors)

Evidence for linking the risk to the medicine	Evidence is based on literature and clinical trial data.
Risk factors and risk groups	Patients with a history of chemotherapy.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 PL sections None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS)

	See Section II.C of this summary for an overview of the post-authorization development plan.

Table 12 Important potential risk: Embryo-fetal toxicity

Evidence for linking the risk to the medicine	Evidence is based on literature data.
Risk factors and risk groups	Pregnant women and women of child-bearing potential (female patient or female partner of a male patient).
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3 and 4.6 PL sections 2 and 3 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13 Missing information: Radiation exposure during breast feeding

Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 PL sections 2 and 3 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 14 Missing information: Exposure in patients with renal impairment

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 15 Missing information: Exposure in patients with severe hepatic

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 16 Missing information: Long-term safety data

Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 PL sections None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A-LUT-T-E02-402 (SALUS) See Section II.C of this summary for an overview of the post-authorization development plan.

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 authorization or specific obligation of Lutathera.

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

Table 17 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study A-LUT-T-E02-402 (SALUS)	This study is being conducted to assess the long-term safety profile of lutetium (^{177}Lu) oxodotreotide when used according to the label indication. <u>Primary research objective:</u> To assess the incidence and nature of potential long-term second primary malignancies, including solid tumors and hematological neoplasia, occurring over a 7-year follow-up period in patients with unresectable or metastatic, well-differentiated, SSR positive GEP-NETs. <u>Secondary research objectives:</u> • To quantify the incidence of other important identified and potential risks specified in the lutetium (177Lu) oxodotreotide RMP such as: renal dysfunction, myelosuppression/cytopenias, MDS, hypogonadism, sexual dysfunction, drug interaction with somatostatin/SAs, tumor cell lysis-related hormone release-induced crises, hepatotoxicity, radiotoxicity. • 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 BM reserve, exposure in breast-feeding women, accidental fetal and child exposure. • • To describe the patterns of drug utilization that may add knowledge about the safety of lutetium (177Lu) oxodotreotide.