Part VI: Summary of the risk management plan

Summary of risk management plan for Lymphoseek (technetium Tc 99m tilmanocept)

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

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

This summary of the RMP for Lymphoseek 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 Lymphoseek's RMP.

I. The medicine and what it is used for

Lymphoseek is authorised for imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity. External imaging and intraoperative evaluation may be performed using a gamma detection device. It contains tilmanocept as the active substance and is a kit for radiopharmaceutical preparation. The vial contains a sterile, non-pyrogenic, white to off-white lyophilized powder. Each vial contains 50 micrograms tilmanocept. An additional overfill is included in each vial to ensure that 50 micrograms of tilmanocept can be delivered.

Further information about the evaluation of Lymphoseek's benefits can be found in Lymphoseek's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/lymphoseek

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

Important risks of Lymphoseek, together with measures to minimise such risks and the proposed studies for learning more about Lymphoseek'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.

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

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

II.A List of important risks and missing information

Important risks of Lymphoseek 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 Lymphoseek. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Failure to detect the sentinel lymph node due to medication errors
Missing information	• Use in Patients receiving more than one dose •

II.B Summary of important risks

Important potential risk - Failure to detect the sentinel lymph node due to medication errors	
Evidence for linking the risk to the medicine	Lymphoseek Marketing Authorisation Application, Section 2.5, Clinical Overview. Lymphoseek Marketing Authorisation Application, Integrated Summary of Efficacy Supplemental Tables 111 through 122 A systematic review of the clinical development data from completed studies was performed to identify significant deviations from protocol-required specifications for technetium 99m radiolabelling, injection volume and tilmanocept dose. The results indicated 75% of the technetium 99m radiolabelling deviations were overlabelling, with a maximum injected activity of 370 MBq [10 mCi], or 5-times the maximum recommended activity for radiolabelling Lymphoseek. The remaining 25% representing underlabelling, as compared to the protocol specifications. Overlabelling with technetium 99m represents a tiny fraction of a patient's exposure to ionising radiation from all sources, and is not considered to represent a significant safety concern. Underlabelling is of more concern, as there is potential for

	not identifying metastatic lymph nodes or having a false negative result due to reduced signal from the isotope. Two investigators participating in study NEO3-05 intentionally over-diluted Lymphoseek to volumes in excess of the protocol recommendations. There were no safety issues identified with these incidences. Discordance between the nodes identified by Lymphoseek and the comparator vital blue dye was noted and led to the conclusion that use of large volumes altered the in vivo disposition of Lymphoseek. No other safety or efficacy issues were considered to be associated with any of the deviations described above.
Risk factors and risk groups	Lymphoseek is intended for use by appropriately qualified and experienced personnel. Detailed instructions are provided for its preparation and use in the SmPC. Additionally, use of lymphatic mapping agents is not a new practice and the overall methodology for Lymphoseek is similar to that used for other agents already in common use. It was anticipated that the highest risk of medication errors would be during the launch of Lymphoseek as pharmacists prepared it for the first time and surgeons administered it for the first time, and when new staff are subsequently introduced into the teams experienced in its use.
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC contains wording in Sections 4.2, 4.4, and 12 which provide clear and detailed instructions for the correct preparation and use of Lymphoseek. The PIL contains detailed information in Section 3 which includes information on the administration of Lymphoseek and conduct of the procedure and duration of the procedure. **Additional risk minimisation measures:** None

Missing information - Use in Patients receiving more than one dose	
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC contains wording in Section 4.2 which describes the processes for single dosing of each patient. **Additional risk minimisation measures:** None

II.C Post-authorisation development plan

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

There are no studies required for Lymphoseek.