Summary of the Risk Management Plan (RMP)

LYMPHOSEEK
(Tilmanocept)

RMP version: 4.0

Document date: 30 June 2017

Marketing Autorisation Holder : Norgine AG, 4132 Muttenz

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 LYMPHOSEEK 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 LYMPHOSEEK in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Name of the marketing authorisation holder" is fully responsible for the accuracy and correctness of the content of the published summary RMP of LYMPHOSEEK.

This summary of the risk management plan (RMP) for LYMPHOSEEK, kit for radiopharmaceutical preparation is based on the EU RMP, version 4.0 dated 30 June 2017.

Active substance(s) (INN or common name):	**Tilmanocept**
Pharmaco-therapeutic group (ATC Code):	Diagnostic Radiopharmaceutical (Class 1) ATC **V09IA09**
Name of Marketing Authorisation Holder or Applicant:	Norgine B.V.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Lymphoseek 50 micrograms, kit for radiopharmaceutical preparation

Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication Errors Hypersensitivity Reactions, including Anaphylaxis
Important missing information	Use in patients receiving more than one dose Use in Paediatric Population Use in Pregnancy Use during Lactation Use in Patients with Renal Impairment Use in Patients with Hepatic Impairment

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
NAV3-18: A Prospective, Open-Label, Multicenter Comparison Study of Lymphoseek® and Vital Blue Dye as Lymphoid Tissue Targeting Agents in Paediatric Patients with Solid Tumours (interventional, Phase 3)	To determine the concordance of in vivo detection rates of Lymphoseek and vital blue dye in excised tissue histologically confirmed as lymph nodes.	Use in children under the age of 18 years.	PIP approved. Study ongoing.	Deferred status has been granted for this study. Milestones will be agreed with the Paediatric Committee following approval of the Lymphoseek marketing authorisation application.

VI.1.3 Summary of Post authorisation efficacy development plan

There is no post-authorisation efficacy development plan for Lymphoseek.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication errors	**SmPC:** Sections 4.2 'posology and method of administration, 4.4 'special warnings and precautions', and 12 'instructions for preparation of radiopharmaceuticals' provide clear and detailed instructions for the preparation and use of Lymphoseek. **PIL:** Detailed information has been provided in Section 3 'How to use Lymphoseek' which includes information on the administration of Lymphoseek and conduct of the procedure and duration of the procedure.	None proposed
Hypersensitivity reactions, including anaphylaxis	**SmPC:** Section 4.3 'Contraindications' contraindicates the use of Lymphoseek in patients with a known hypersensitivity to tilmanocept or any of the components of the radiolabelled pharmaceutical. **PIL:** Section 2 'What you need to know before Lymphoseek is used' *"If you are allergic to tilmanocept or any of the other ingredients of this medicine (listed in section 6) or to any of the ingredients of the radiolabelled pharmaceutical."*	None proposed
Use in patients receiving more than one dose	**SmPC:** Section 4.2 "Posology and method of administration" of the SmPC describes the processes for single dosing of each patient. **PIL**:	None proposed

	None proposed	
Use in pregnancy	**SmPC:** Section 4.6 'Fertility, pregnancy and lactation' *"<u>Women of childbearing potential</u> When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.* *<u>Pregnancy</u> There are no data from the use of Lymphoseek in pregnant women. No reproductive toxicity studies in animals were performed, and it is not known if Lymphoseek can cause foetal harm when administered to a pregnant woman.* *Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus."* **PIL:** Section 2 'What you need to know before Lymphoseek is used' *"Warnings and precautions Take special care with Lymphoseek: • if you are pregnant or believe you may be pregnant • if you are breast-feeding".* *"Pregnancy and breast-feeding If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.*	None proposed

	You must inform the nuclear medicine doctor before the administration of Lymphoseek if there is a possibility you might be pregnant, if you have missed your period, or if you are breast-feeding. *When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.* *If you are pregnant, the nuclear medicine doctor will only administer this product during pregnancy if a benefit is expected which would outweigh the risks.* *If you are breast-feeding, breast milk should be discarded for 24 hours after administration of Lymphoseek.* *Please ask your nuclear medicine doctor when you can resume breast-feeding."*	
Paediatric use	**SmPC:** Section 4.2 "Posology and method of administration" of the SmPC includes the following language to ensure that healthcare professionals know there is no available information on the use of Lymphoseek in the paediatric population: *"The safety and efficacy of Lymphoseek in children and adolescents below the age of 18 years has not yet been established. No data are available."* **PIL:** Section 2 'What you need to know before Lymphoseek is used' *"Children and adolescents* *This medicine is not for use in children and adolescents under 18 years of age because it has not been studied in this age group."*	None proposed
Use during lactation	**SmPC:** Section 4.6 'Fertility, pregnancy and lactation' "*It is not known whether technetium Tc 99m tilmanocept is excreted into human milk.* *Before administering radiopharmaceuticals to a*	None proposed

mother who is breast-feeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If administration is considered necessary, breast-feeding should be interrupted for 24 hours post injection and the expressed feeds discarded."

PIL:

Section 2 'What you need to know before Lymphoseek is used'

"*Warnings and precautions*
Take special care with Lymphoseek:
• if you are pregnant or believe you may be pregnant
• if you are breast-feeding".

"Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.

You must inform the nuclear medicine doctor before the administration of Lymphoseek if there is a possibility you might be pregnant, if you have missed your period, or if you are breast-feeding.

When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

If you are pregnant, the nuclear medicine doctor will only administer this product during pregnancy if a benefit is expected which would outweigh the risks.

If you are breast-feeding, breast milk should be discarded for 24 hours after administration of Lymphoseek.

Please ask your nuclear medicine doctor when you can resume breast-feeding."

Use during renal impairment	**SmPC:** Section 4.2 'Posology and method of administration' of the SmPC states "*Careful consideration of the activity to be administered in these patients is required since an increased radiation exposure is possible. The radiation dose to the patient would not exceed 0.69 mSv even if none of a 74 MBq dose were eliminated.* *Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of technetium Tc 99m tilmanocept in patients with renal or hepatic impairment have not been characterised.*" Section 4.4 'Special warnings and precautions for use' states "*Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. The estimated radiation dose to the patient would not exceed 0.69 mSv even if none of a 74 MBq dose (2.0 mCi) were eliminated*." **PIL:** None proposed	None proposed
Use during hepatic impairment	**SmPC:** Section 4.2 'Posology and method of administration' of the SmPC states "*Careful consideration of the activity to be administered in these patients is required since an increased radiation exposure is possible. The radiation dose to the patient would not exceed 0.69 mSv even if none of a 74 MBq dose were eliminated.* *Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of technetium Tc 99m tilmanocept in patients with renal or hepatic impairment have not been characterised.*" Section 4.4 'Special warnings and precautions for use' states "*Careful consideration of the benefit risk ratio in these patients is required since an increased*	None proposed

	radiation exposure is possible. The estimated radiation dose to the patient would not exceed 0.69 mSv even if none of a 74 MBq dose (2.0 mCi) were eliminated." **PIL:** None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Lymphoseek is a diagnostic medicine used to identify sentinel lymph nodes in patients with breast cancer, melanoma (a skin cancer) and oral squamous cell carcinoma (a cancer of the mouth). Approximately 367,000 new cases of breast cancer, 83,000 new cases of melanoma and 55,000 new cases of head and neck/oral cancer are diagnosed in Europe annually.

VI.2.2 Summary of treatment benefits

Lymphoseek is used to locate lymph nodes known as 'sentinel' lymph nodes, which drain the cancer and are the nodes where the cancer is likely to spread to first. When the sentinel lymph nodes are found, they can be checked for cancer cells or removed to help prevent the spread of the cancer.

The benefits of Lymphoseek were shown in two main studies in which 311 patients with breast or skin cancer had their lymph nodes first located with Lymphoseek and then with another method involving the use of a dye known as 'vital blue dye'. The blue dye is used during surgery to stain the lymph nodes so they can be seen and then checked for cancerous tissue.

In these two studies, doctors were able to detect a higher number of sentinel lymph nodes with Lymphoseek than with the blue dye: almost all of the lymph nodes identified using the blue dye (98% in one study and 100% in the other) were identified using Lymphoseek, while around 70% and 60%, respectively, of the lymph nodes detected using Lymphoseek were detected with the blue dye.

In a third study in patients with cancer of the head and neck including mouth cancer, Lymphoseek was used to detect sentinel lymph nodes before patients had their lymph nodes removed surgically. Almost all the patients (38 out of 39) with cancerous lymph nodes were identified by Lymphoseek.

VI.2.3 Unknowns relating to treatment benefits

The usefulness of identifying lymph nodes in patients with head and neck cancer patients (more specifically, mouth cancer) is currently unknown.

VI.2.4 Summary of safety concerns

Important identified risks

There are no important identified risks with the use of Lymphoseek.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Medication errors	Due to the complexity of the process for preparing and using Lymphoseek, Lymphoseek is used by medical personnel experienced in using radiopharmaceuticals to find sentinel lymph nodes and a mistake affecting the outcome for patients is unlikely.

Risk	**What is known (Including reason why it is considered a potential risk)**
Hypersensitivity (allergic) reactions, including anaphylaxis (a severe allergic reaction)	Since many radiopharmaceutical products cause very severe allergic reactions, there is a possibility that Lymphoseek might also cause allergic reactions. So far, the majority of allergic reactions reported in association with Lymphoseek have been mild, and there have been no reports of anaphylactic reactions.

Important missing information

Risk	What is known
Use in patients receiving more than one dose	There have been no studies in patients who might require more than one dose of Lymphoseek.
Use in children	There are no completed studies with Lymphoseek in children. Study NAV3-18 is ongoing.
Use during pregnancy	There have been no studies with Lymphoseek in pregnant women.
Use during breastfeeding	It is not known whether Lymphoseek is excreted in human milk. Therefore breastfeeding should be interrupted for 24 hours post injection and the milk expressed discarded.
Use in patients with reduced kidney function	No studies have been specifically conducted to look at how Lymphoseek works in patients with kidney impairment, or whether it is safe in these patients. However, patients with kidney impairment were included in main clinical studies for Lymphoseek and a review of the data from the studies did not raise safety concerns.
Use in patients with reduced liver function	No studies have been conducted to look specifically at how Lymphoseek works in patients with liver impairment, or whether it is safe in these patients. However, patients with liver impairment were included in the main clinical studies for Lymphoseek and a review of the data from the studies did not raise safety concerns.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Lymphoseek can be found on Lymphoseek's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
NAV3-18: *A Prospective, Open-Label, Multicentre Comparison Study of Lymphoseek® and Vital Blue Dye as Lymphoid Tissue Targeting Agents in Paediatric Patients with Solid Tumours (interventional, Phase 3)*	To determine how well detection rates with Lymphoseek and vital blue dye match in surgically removed tissue confirmed to be lymph nodes.	Use in children under the age of 18 years.	Paediatric Investigation Plan approved. Study is ongoing.	Deferred status has been granted for this study. Milestones to be agreed with EMA's Paediatric Committee.

Studies which are a condition of the marketing authorisation

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Data Lock Point	Description of Changes
1.0	19-Nov-2012	New Document submitted with initial marketing authorisation application.
1.1	19-Feb-2013	Conversion to new EEA RMP template. No submission of version 1.1 of RMP is planned; administrative update only for format conversion - Subject exposure data for NEO3-06 included following completion of study - Approval of Lymphoseek by FDA included

2.0	31-Jul-2013	Updated in response to PRAC Assessment Report – Day 120 of marketing authorisation application procedure. - Addition of epidemiology for head and neck cancer in Module SI. - Addition of two Important Potential Risks: hypersensitivity reactions, including anaphylaxis, and medication errors. - Addition of three new categories of Important Missing Information: Use during lactation, use in patients with renal impairment, use in patients with hepatic impairment.
3.0	12-Nov-2014	Alignment of information in the RMP with the revised SmPC following CHMP recommendation for approval of the marketing authorisation application procedure.
4.0	30-Jun-2017	Version 4 of the RMP created following the MAH transfer to Norgine on the 23-Jan-2017. Alignment of information in the RMP with the revised SmPC following positive opinion on procedure EMEA/H/C/002085/II/0004/G for approval of the reduced mass vial (50 mcg) presentation. Throughout the document the paediatric study (NAV3-18) is updated as on-going and it's category is updated as 2. Exposure for 'Non-study post authorisation exposure' is updated (SV.2.2. Exposure) The objectives for important potential risks and missing information is updated and routine additional PhV activities for use in 'patients receiving more than one dose' is updated to remove targeted ICSR questionnaire. Table of completed studies/activities from the pharmacovigilance is added. Information from PIL is added to section part V: Risk minimisation measures. Table of effectiveness of risk minimisation measures is updated to 'Not applicable' as there are no risk minimisation measures for LYMPHOSEEK.