ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lumark 80 GBq/mL radiopharmaceutical precursor, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 80 GBq Lutetium (^{177}Lu) chloride at activity reference time (ART), corresponding to at most a maximum of 160 microgram of Lutetium. The ART is defined as the end of production.

Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq (at ART).

The minimal specific activity is 500 GBq/mg Lutetium (^{177}Lu) at the ART.

Lutetium (^{177}Lu) has a half-life of 6.647 days. Lutetium (^{177}Lu) is produced by neutron irradiation of enriched Lutetium (^{176}Lu). Lutetium (^{177}Lu) decays by β^--emission to stable Hafnium (^{177}Hf), with the most abundant β^- (79.3%) having a maximum energy of 0.497 MeV. Also low gamma energy is emitted, for instance at 113 keV (6.2%) and 208 keV (11%).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lumark is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal must be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.

4.2 Posology and method of administration

Lumark is only to be used by specialists experienced with *in vitro* radiolabelling

Posology

The quantity of Lumark required for radiolabelling and the quantity of the product to be radiolabelled with Lutetium(^{177}Lu) that is subsequently administered will depend on the medicinal product to be radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Paediatric population

For more information concerning the paediatric use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Products Characteristics/package leaflet of the the particular medicinal product to be radiolabelled.

Method of administration

Lumark is intended for *in vitro* radiolabelling of medicinal products, which are subsequently administered by the approved route.
Lumark should not be administered directly to the patient.
For instructions on extemporary preparation of the medicinal product before administration, see section 12.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).

For information on contraindications to particular Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, refer to the Summary of Product Characteristics/package leaflet of each particular medicinal product to be radiolabelled.

4.4 Special warnings and precautions for use

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect. Lumark is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates.

General warnings
Radioactive medicinal products should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official authorities.

Radioactive medicinal products should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For information concerning special warnings and precautions for use of ^{177}Lu-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

Radiation protection
Administration of a high activity (7.400 MBq) of the Lutetium(^{177}Lu)-labelled medicinal product results in an average radiation dose rate at 1 m distance from the patient of 4-11 µSv/h after 24 hours. This is below the threshold considered acceptable for discharge from the clinic (20 µSv/h). For a person in the vicinity of the patient, assuming continuous exposure at 2 m and infinite biological half-life (no disposal by the patient after discharge from the hospital), this dose rate will result in an overall dose of approximately 0.6 mSv, which is approximately one half of the dose limit set for general public (1 mSv/year).

Precautions with respect to relatives, carers and hospital staff are provided in section 6.6.

Renal impairment and haematological disorders

Myelodysplastic syndrome and acute myeloid leukaemia

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment

with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours (see section 4.8). This should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents).

Myelosuppression

Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during radioligand therapy with Lutetium (^{177}Lu). Most events are mild and transient. In some patients more than one cell line may be affected. A blood count should be taken at baseline and monitored regularly during treatment, in accordance with clinical guidance.

Renal irradiation

Radiolabelled somatostatin analogues are excreted by the kidney. Radiation nephropathy has been reported following peptide receptor radionuclide therapy for neuroendocrine tumours using other radioisotopes. Renal function should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance.

Hepatotoxicity:
Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with ^{177}Lu peptide receptor radionuclide therapy for neuroendocrine tumours. Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.

Hormone release syndromes:
There have been reports of carcinoid crisis and other syndromes associated with release of hormones from functional neuroendocrine tumours following ^{177}Lu peptide receptor radionuclide therapy, which may be related to irradiation of tumour cells. Reported symptoms include flushing and diarrhoea associated with hypotension. Observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms). In case of hormonal crises, treatments may include: intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

Extravasation:
There have been reports of extravasation of Lutetium (^{177}Lu) labelled ligands in the post-marketing setting. In case of extravasation, infusion of the medicinal product should be immediately ceased, and the nuclear medicine physician and the radiopharmacist should be promptly informed. Management should be in accordance with local protocols.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies of Lutetium (^{177}Lu) with other medicinal products have been performed. The possible use of chelating therapies could interfere with the use of Lutetium(^{177}Lu)-labeled medicinal products.

For information concerning interactions associated with the use of Lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the radiolabelled medicinal product.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radioactive medicinal products 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. Before the use of ^{177}Lu -labelled medicinal products, pregnancy should be excluded using an adequate/validated test.

Pregnancy
The use of Lutetium (^{177}Lu)-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).

Breast-feeding
Before administering radiopharmaceuticals to a 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 the administration is considered necessary, breastfeeding should be interrupted and the expressed feeds discarded. .

Fertility
According to literature reports and taking a conservative approach (maximum patient dose of 10 GBq, average labeling yield and no additional measures), it may be considered that ^{177}Lu-labelled medicinal products do not lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries.

Further information concerning the use of ^{177}Lu-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

4.7 Effects on ability to drive and use machines

Effects on ability to drive or use machines following treatment by Lutetium (^{177}Lu)-labelled medicinal products is specified in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

4.8 Undesirable effects

Adverse reactions following the intravenous administration of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, will be dependent on the specific medicinal product being used. Such information is supplied in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.
For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Blood and lymphatic system disorders
very common: Anaemia, thrombocytopenia, leukopenia and lymphopenia

Endocrine disorders:
Frequency not known: carcinoid crisis

Gastrointestinal disorders:
very common: Nausea and vomiting

Neoplasms benign, malignant and unspecified (including cysts and polyps):
common: Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)
uncommon: Acute myeloid leukaemia (see section 4.4)

Skin and subcutaneous tissue disorders:
very common: Alopecia

Description of selected adverse reactions:

Dry mouth has been reported among patients with metastatic castration resistant prostate cancer receiving PSMA-targeted Lutetium (^{177}Lu)-labelled radioligands and has been transient.

Skin and subcutaneous tissue disorders: Alopecia, described as mild and temporary, has been observed among patients receiving Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The presence of free Lutetium (^{177}Lu) chloride in the body after an inadvertent administration of Lumark will lead to increased bone marrow toxicity and haematopoetic stem cell damage. Therefore, in case of an inadvertent administration of Lumark, the radiotoxicity for the patient must be reduced by immediate (i.e. within 1 hour) administration of preparations containing chelators like Ca-DTPA or Ca- EDTA in order to increase the elimination of the radionuclide from the body.

The following preparations must be available in medical institutions, which use Lumark for radiolabelling of carrier molecules for therapeutic purposes:
- Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate) or
- Ca-EDTA (Calcium disodium ethylenediaminetetraacetate)

These chelating agents help with the elimination of Lutetium (^{177}Lu) radiotoxicity by an exchange between the calcium ion in the complex and the Lutetium (^{177}Lu) ion. Due to the capacity of the chelating ligands (DTPA, EDTA) of forming water soluble complexes, the complexes and bound Lutetium(^{177}Lu) are rapidly eliminated by the kidneys.

1 g of the chelating agents should be administered by slow intravenous injection over 3-4 minutes or by infusion (1 g in 100-250 mL of glucose, or sodium chloride 9 mg/mL (0,9%) solution for injection).

The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval >1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours.

In any case the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of damage to the blood marrow.

The toxicity of the free Lutetium (^{177}Lu) due to *in vivo* release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned, ATC code: Not yet assigned

Lutetium (^{177}Lu) chloride is produced by irradiation of ^{176}Lu with neutrons. It decays by emission of beta radiation of maximal 498 keV to ^{177}Hf-Hafnium. ^{177}Lu-Lutetium has a half-life of 6.647 days.

The pharmacodynamic properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of the studies with Lumark in all subsets of the paediatric population on grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and on grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for the paediatric patients. This waiver does however not extend to any diagnostic or therapeutic uses of the product when linked to a carrier molecule (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

Distribution
Pharmacokinetics of Lutetium (^{177}Lu) was investigated in rats and mice. The distribution and mineral concentrations in the organs were investigated at low (9-10 mg/kg) and high (19-20 mg/kg) doses administered intravenously to rats. It appeared that more than 78% of the doses was distributed into liver, bone and spleen. For Lutetium (^{177}Lu) the different dose levels did not result in significantly different uptake with 65% appearing in the liver, 5.3% in the spleen and 13% in the bones at one day after administration. With respect to the distribution pattern in blood it appeared that 2 h after administration 15% of the Lutetium as being present in blood, had entered the blood cells with the remaining 85% still being present in the serum.

A more detailed study of the biodistribution of Lutetium (^{177}Lu) chloride in mice confirms the relatively high uptake in the liver, kidneys and bone marrow The results indicated that lutetium (^{177}Lu) chloride is accumulated in the bone marrow and emphasizes the importance of all Lutetium (^{177}Lu) to be peptide-bound at injection, as well as the in-vivo stability of the radionuclide-chelate-complex during therapy.

Pharmacokinetic data on Lumark related to free Lutetium:
When the precursor is bound to a carrier molecule the content of radioactive free Lutetium (^{177}Lu) is supposed to be less than the stated amounts depending on the carrier used. Relevant data is included in the Summary of Product Characteristics of the labeled medicinal products.

5.3 Preclinical safety data

The toxicological properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with Lumark prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

No animal toxicity studies were conducted with Lumark.

The toxicity of Lutetium (^{177}Lu) chloride has been studied in different mammals and using different administration routes. Intraperitoneal administration resulted in generalized peritonitis with adhesion and

accumulation of some ascetic fluid. By intraperitoneal route, the LD50 is approximately 300 mg/kg in mice and rats. By intravenous route, the LD50 in rats and mice ranges between 30 and 60 mg/kg. Intravenously administrated doses resulted in varying effects on the blood pressure and a decreased heart rate. Electrocardiograms showed no irregularities in cardiac rhythm or conduction. Effects of the respiration were slight and variable. No gross differentiating changes were found of the tissues demonstrating no evidence of acute damage resulting from the experiment. The studies suggest that the intravenous toxicity of the ionic compounds of the rare earth elements would decrease with atomic weight resulting in Lutetium (^{177}Lu) being the least toxic of the series.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Water for injections

6.2 Incompatibilities

Radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates, with Lutetium (^{177}Lu) chloride is very sensitive to the presence of trace metal impurities.

It is important that all glassware, syringe needles etc., used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example non-metallic) with proven resistance to dilute acid should be used to minimize trace metal impurity levels.

In the absence of compatibility studies, this medicinal product must not be mixed with medicinal products other than the medicinal products to be radiolabelled.

6.3 Shelf life

8 days from the date of ART (= end of production).

6.4 Special precautions for storage

Store in the original package in order to protect from radiation.
No special storage condition required.
Storage of radiopharmaceuticals should be in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

The radiopharmaceutical precursor solution is packaged in colourless type I glass vial of 10 mL, closed with a bromobutylrubber stopper and aluminium overseal.
Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq at the ART.

The vials are placed in a lead container for protective shielding and packed in a plastic jar.
Each pack contains one vial in a lead container.
For single use only.

6.6 Special precautions for disposal and other handling

Lumark is not intended for direct use in patients.

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instruction on extemporary preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of this container is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients injected with Lutetium (^{177}Lu)-radiopharmaceuticals. The use of television monitor systems to monitor the patients is recommended. Given the long half-life of Lutetium (^{177}Lu) it is specially recommended to avoid internal contamination. For this reason it is mandatory to use protective high quality (latex/nitrile) gloves in any direct contact with the radiopharmaceutical (vial/syringe) and with the patient. For minimising radiation exposure resulting from repeated exposure, there is no specific recommendation except the strict observance of the above ones.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

I.D.B. Holland B.V.
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1013/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2015

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The radiation dose received by the various organs following administration of a Lutetium (^{177}Lu)-labelled medicinal product will be dependent on the specific molecule being radiolabelled.

Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry table below is presented in order to evaluate the contribution of non-conjugated Lutetium(^{177}Lu) to the radiation dose following the administration of Lutetium (^{177}Lu)-labelled medicinal product or resulting from an accidental intravenous injection of Lumark.

The dosimetry estimates are based on biodistribution data provided by ICRP-30, showing bone, liver and kidneys as the significant target organs for the biodistribution of lutetium.

Table 1. Absorbed dose per unit activity administered for various tissues

	ICRP-30 data
Target Organ	**Dose / Injected Activity (mGy/MBq)**
Adrenals	0.018
Brain	0.017
Breasts	0.005
Gallbladder Wall	0.012
LLI Wall	0.868
Small Intestine	0.069
Stomach Wall	0.038
ULI Wall	0.327
Heart Wall	0.009
Kidneys	0.210
Liver	0.220
Lungs	0.010
Muscle	0.012
Ovaries	0.015
Pancreas	0.012
Red Marrow	1.090
Osteogenic Cells	7.530
Skin	0.007
Spleen	0.008
Testes	0.006
Thymus	0.007
Thyroid	0.011
Urinary Bladder Wall	0.240
Uterus	0.011
Total Body	**0.185**
Effective Dose (mSv/MBq)	***0.35***

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Lutetium (^{177}Lu) is a beta(-)/gamma emitter. Activity measurements using an ionization chamber are very sensitive to geometric factors and therefore should be performed only under geometric conditions which have been appropriately validated.

For single use only

Usual precautions regarding sterility and radioactivity should be respected.

The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper.

Appropriate aseptic precautions should be taken, in order to maintain the sterility of Lumark and to maintain sterility throughout the labelling procedures.

The complexing agent and other reagents should be added to the vial with Lutetium (^{177}Lu)-chloride. Free Lutetium (^{177}Lu) is taken up and accumulates in the bones. This could potentially result in osteosarcomas. It is recommended to add a binding agent such as DTPA prior to intravenous administration of Lutetium (^{177}Lu)-labeled conjugates in order to form a complex with free Lutetium (^{177}Lu), if present, leading to a rapid renal clearance of Lutetium (^{177}Lu).

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

I.D.B. Holland B.V.
Weverstraat 17
5111 PV Baarle-Nassau
NETHERLANDS

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC JAR and LEAD CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Lumark 80 GBq/mL radiopharmaceutical precursor, solution
Lutetium (^{177}Lu) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL of solution contains 80 GBq Lutetium (^{177}Lu) chloride at activity reference time (ART), corresponding to at most a maximum of 160 microgram of Lutetium. The ART is defined as the end of production.

3. LIST OF EXCIPIENTS

Hydrochloric acid
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.
1 vial contains

Volume: {Z} mL
Activity (at ART): {Y} GBq
Activity Reference Time (ART): {DD/MM/YYYY} {hh:mm} CET
Specific activity (at ART): {YY} GBq/mg
Lu mass:
Client code:
Destination:

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For administration after *in vitro* radiolabelling. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date: {DD/MM/YYYY} hh:mm CET

9. SPECIAL STORAGE CONDITIONS

Store in the original package that provides protection from radiation.
No special storage condition required.
Storage must be in accordance with local regulations for radioactive substances

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

I.D.B. Holland B.V.
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1013/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lumark 80 GBq/mL radiopharmaceutical precursor, solution
Lutetium (^{177}Lu) chloride

2. METHOD OF ADMINISTRATION

For administration after *in vitro* radiolabelling.

3. EXPIRY DATE

EXP: {DD/MM/YYYY}

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Client code:

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lumark 80 GBq/mL radiopharmaceutical precursor solution
Lutetium (^{177}Lu) chloride

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given the medicine combined with Lumark because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lumark is and what it is used for

Lumark is not a medicine and it is not intended to be used on its own.

Lumark is a type of product called a radiopharmaceutical precursor. It contains the active substance Lutetium (^{177}Lu) chloride.

Lumark is used for radiolabelling medicines, a technique in which medicines are tagged (radiolabelled) with a radioactive form of the element lutetium, known as lutetium (^{177}Lu). These medicines can then be used in medical procedures to carry radioactivity to where it is needed in the body such as sites of tumour cells.

Lumark is only used to radiolabel medicines that have been specifically developed for use with the active substance lutetium (^{177}Lu) chloride.

The use of Lutetium (^{177}Lu)-labelled medicines does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

Please refer to the package leaflet of the medicine that is to be radiolabelled with Lumark.

2. What you need to know before the medicine radiolabelled with Lumark is used

The medicine radiolabelled with Lumark must not be used:
- if you are allergic to Lutetium or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or believe you may be pregnant

Warnings and precautions
Take special care with the medicine that is radiolabelled with Lumark:
- If you are breast-feeding

Treatment with Lutetium (177Lu) radioligand therapy may lead to the following side effects
- a reduced number of red blood cells (anaemia)
- a reduced number of platelets in the blood (thrombocytopenia) which are important to stop bleeding
- a reduced number of white blood cells (leukopenia, lymphopenia or neutropenia) which are important for protecting the body against infection

Most of these events are mild and only temporary. Because Lutetium (177Lu) can sometimes affect your blood cells, your doctor will do blood tests before you start and at regular intervals during treatment.

During peptide-receptor radionuclide therapy for neuroendocrine tumours, radiolabelled somatostatin analogues are excreted by the kidneys. Your doctor will therefore take a blood test to measure your kidney function before you start and during treatment.

Treatment with Lutetium (177Lu) may cause disturbances of liver function. Your doctor will take a blood test to monitor your liver function during treatment.

After neuroendocrine tumours are treated with Lutetium (177Lu), patients may experience symptoms associated with release of hormones from the tumour cells, known as carcinoid crisis. Tell your doctor if you feel faint or dizzy or experience flushing or diarrhoea following your treatment.

Before administration of Lumark you should:
- drink plenty of water before being given the radiolabelled medicine in order to urinate as often as possible during the first few hours after the procedure.

Children and adolescents
Medicines radiolabelled with Lumark should not be used in children and adolescents below 18 years of age.

Other medicines and medicines radiolabelled with Lumark
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines since they may interfere with the procedure.
It is not known whether Lutetium (^{177}Lu) chloride may interact with other medicines as specific studies have not been carried out.

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 medicines radiolabelled with Lumark.

You must inform the nuclear medicine doctor before the administration of medicines radiolabelled with Lumark 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.

If you are pregnant
Medicines radiolabelled with Lumark must not be administered if you are pregnant.

If you are breast-feeding
You will be asked to stop breast-feeding if you are treated with medicines radiolabelled with Lumark. Please ask your nuclear medicine doctor when you can resume breast-feeding.

Driving and using machines
The medicines used in combincation with Lumark could affect your ability to drive and to use machines. Please read the package leaflet of that medicine carefully.

3. How to use the medicine radiolabelled with Lumark

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Medicines radiolabelled with Lumark will only be used in special, controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These people will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of medicine radiolabelled with Lumark to be used in your case. It will be the smallest quantity necessary to achieve the appropriate outcome, depending on the co-administered medicine and its intended use.

Administration of the medicine radiolabelled with Lumark and conduct of the procedure
Lumark must be used only in combination with another medicine which has been specifically developed and authorised for being combined with Lumark. It will only be administered as a combination.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure after the administration of the medicine radiolabelled with Lumark.

After administration of the medicine radiolabelled with Lumark has been performed
The nuclear medicine doctor will inform you if you need to take any special precautions after receiving the medicine radiolabelled with Lumark. Contact your nuclear medicine doctor if you have any questions.

If you have been given more medicine radiolabelled with Lumark than you should
Since the medicine radiolabelled with Lumark is handled by a nuclear medicine doctor under strictly controlled conditions, there is only a very small chance of possible overdose. However, in case of an overdose, you will receive the appropriate treatment.

Should you have any further question on the use of Lumark, please ask the nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, the medicine radiolabelled with Lumark can cause side effects, although not everybody gets them.

Dry mouth has been reported among patients with prostate cancer receiving treatment with Lutetium (^{177}Lu) and has been temporary.

Very common side effects (may affect more than 1 in 10 people):

- Reduction in blood cell counts (platelets, red or white blood cells)
- Nausea
- Vomiting

Side effects reported among patients treated for neuroendocrine tumors:

Very common (may affect more than 1 in 10 people):

- Mild temporary hair loss

Common (may affect up to 1 in 10 people):

- Bone marrow cancer (myelodysplastic syndrome)

Uncommon (may affect up to 1 in 100 people):

- Bone marrow cancer (acute myeloid leukaemia)

Not known (frequency cannot be estimated from the available data):

- Carcinoid crisis

Bone marrow cancer (myelodysplastic syndrome and acute myeloid leukaemia) has been reported in patients several years after treatment with Lutetium (^{177}Lu) peptide receptor radionuclide therapy for neuroendocrine tumours.

After the medicine radiolabelled with Lumark is administered, it will deliver certain amounts of ionising radiation (radioactivity) which carries a small risk of cancer and development of hereditary defects. In all cases, the risk of the radiation is outweighed by the potential benefit of receiving the radiolabelled medicine.

For more information, refer to the package leaflet of the particular medicine to be radiolabelled.

If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How Lumark is stored

You will not have to store this product. Storing Lumark is the responsibility of the specialist and will be done in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The following information is intended for the specialist only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date and time which are stated on the label after EXP.

Store in the original package to protect from radiation. No special storage condition required.

6. Contents of the pack and other information

What Lumark contains
- The active substance is Lutetium (^{177}Lu) chloride. One mL of solution contains 80 GBq Lutetium (^{177}Lu) chloride at Activity Reference Time (ART), corresponding to a maximum of 160 microgram of Lutetium. The ART is defined as the end of production. (GBq: GigaBecquerel is the unit in which radioactivity is measured).
- The other ingredients are hydrochloric acid and water for injections.

What Lumark looks like and contents of the pack
Lumark is presented as a sterile, clear, and colourless solution in a colourless type I glass vial of 10 mL, closed with a bromobutylrubber stopper and aluminium overseal

Each vial contains a volume varying from 0.1 to 5 mL corresponding to an activity ranging from 8 to 400 GBq (at ART) The volume depends on the quantity of medicines combined with Lumark required for administration by the nuclear medicine doctor.

Each pack contains 1 glass vial in a lead cannister placed in a plastic jar.

For single use only.

Marketing Authorisation Holder
I.D.B. Holland B.V.
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands
Tel: +31(0)13 5079 558
Fax: +31(0)13 5079 912
Email: quality@idb-radiopharmacy.com

Manufacturer
I.D.B. Holland B.V.
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

---------->

The following information is intended for healthcare professionals only:

The complete Summary of Product Characteristics (SmPC) of Lumark is provided as a separate document in the pack of the medicinal product, with the objective to provide healthcare professionals with other additional scientific and practical information about the use of this product.

Please refer to the SmPC.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for lutetium (177Lu) chloride, the scientific conclusions of the CHMP are as follows:

A number of haematological malignancies, most notably myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been reported in clinical studies and in the literature with the use of Lutetium 177. Although patients had received prior chemotherapy in some studies and the clinical studies were mostly uncontrolled, there was no previous chemotherapy in other studies and the reporting frequency is generally consistent. The PRAC also notes that for other Lu-177 containing products, MDS and AML are considered adverse reactions with a frequency of common and uncommon, respectively. In conclusion, the PRAC considers that it would be important for HCPs and for patients to be appropriately informed as to the frequency of these tumours, as it may be a factor in a patient's decision whether or not to receive treatment. An update to the product information to appropriately reflect the frequency of these tumours is therefore recommended.

Two well documented cases of Lutetium 177 extravasation were reported in the literature during the reporting period. The SmPC for other Lutetium-containing products advises that in case of extravasation, the infusion should be immediately ceased. Overall, the PRAC considers that it would be important for HCPs to be reminded of the potential for extravasation and the need to immediately cease the infusion and to promptly implement measures to reduce the potential for harm. As a result, section 4.4 of the SmPC should be updated with the inclusion of a new warning on extravasation.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for lutetium (177Lu) chloride the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing lutetium (177Lu) chloride is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.