ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ilumira 37 GBq/mL radiopharmaceutical precursor, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 37 GBq lutetium (^{177}Lu) chloride at calibration time (CAL) corresponding to maximum 9 micrograms of lutetium (^{177}Lu) (as chloride).

Each 2 mL vial contains a volume varying from 0.05 mL to 1.2 mL corresponding to an activity ranging from 1.8 to 44.4 GBq at CAL.

Each 10 mL vial contains a volume varying from 0.05 mL to 6.6 mL corresponding to an activity ranging from 1.8 to 244.2 GBq at CAL.

CAL is defined as Tuesday following end of synthesis at 19:00 Central European Time (CET). The minimal specific activity is 3 000 GBq/mg at CAL.

The activity at the date and time ordered by the customer, indicated as ART (activity reference time) is determined by the time elapsed from the CAL and the half-life of lutetium (^{177}Lu).

Lutetium (^{177}Lu) has a half-life of 6.7 days. Lutetium (^{177}Lu) decays by β-minus emission to stable Hafnium (^{177}Hf), with the most abundant β-minus (79.3%) having a maximum energy of 497 keV. 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

Ilumira is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with lutetium (^{177}Lu) chloride.

4.2 Posology and method of administration

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

Posology

The quantity of Ilumira required for radiolabelling and the quantity of lutetium (^{177}Lu)-labelled medicinal product 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 paediatric use of lutetium (^{177}Lu)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

Method of administration

Ilumira is intended for *in vitro* radiolabelling of medicinal products which are subsequently administered by the approved route.

Ilumira should not be administered directly to the patient.

For instructions on preparation of the radiopharmaceutical precursor solution 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 Ilumira, refer to the Summary of Product Characteristics/package leaflet of the 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.

Ilumira is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides, vitamins or other substrates.

Renal impairment and haematological disorders

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. It is recommended to perform individual radiation dosimetry assessments of specific organs, which may not be the target organ of therapy.

Myelodysplastic syndrome and acute myeloid leukaemia
Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with lutetium (^{177}Lu)-based 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, but in some cases patients have required blood and platelet transfusions. In some patients more than one cell line may be affected and pancytopenia requiring treatment discontinuation has been described. 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 including glomerular filtration rate (GFR) should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance of the radiolabelled medicinal product.

Hepatotoxicity

Cases of hepatotoxicity have been reported in the post-marketing setting and in the literature in patients with liver metastases undergoing treatment with lutetium (^{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 lutetium (^{177}Lu)-based 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.

Tumour lysis syndrome

Tumour lysis syndrome has been reported following lutetium (^{177}Lu)-based radioligand therapy. Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.

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 lutetium (^{177}Lu)-labelled 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.

Radiation protection

Point-source approximation shows that the average dose rate experienced 20 hours after administration of a 7.4 GBq dose of lutetium (^{177}Lu)-labelled medicinal product (residual radioactivity 1.5 GBq) by a person at 1 meter distance from the patient's body centre with an abdominal radius of 15 cm is 3.5 µSv/h. Doubling the distance to the patient to 2 meters reduces the dose rate by a factor of 4, to 0.9 µSv/h. The same dose in a patient with an abdominal radius of 25 cm yields a dose rate at 1 meter of 2.6 µSv/h. The generally accepted threshold for discharge of the treated patient from the hospital is 20 µSv/h. In most countries, the exposure limit for hospital staff is set the same as for the general public at 1 mSv/year. When taking the 3.5 µSv/h dose rate as an average, this would allow hospital staff to work approx. 300 hours/year in close vicinity of patients treated with lutetium (^{177}Lu)-labelled medicinal products labeled radiopharmaceuticals without wearing radiation protection. Of course, the nuclear medicine staff is expected to wear standard radiation protection.

Any other person in close vicinity of the treated patient should be informed about possibilities to reduce his/her exposure due to radiation emitted from the patient.

Specific warnings

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

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies of lutetium (^{177}Lu) chloride with other medicinal products have been performed.

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 medicinal product to be radiolabelled.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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. Before the use of lutetium (^{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 due to the risk of ionising radiation to the foetus (see section 4.3).

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, 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

Effects of lutetium (^{177}Lu) chloride on male and female fertility have not been studied in animals. Low exposures could be demonstrated for male and female sexual organs. It cannot be excluded that lutetium (^{177}Lu)-labelled medicinal products lead to reproductive toxicity including spermatogenetic damage in male testes or genetic damage in male testes or female ovaries.

Further information concerning fertility as well as the use of lutetium (^{177}Lu)-labelled medicinal products in women of child-bearing potential, during pregnancy and breast-feeding is specified in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions following the administration of a lutetium (^{177}Lu)-labelled medicinal product prepared by radiolabelling with Ilumira will be dependent on the specific medicinal product being used. Such information will be supplied in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

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.

Tabulated list of adverse reactions

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), not known (cannot be estimated from the available data).

Table 1 List of adverse reactions

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (Myelodysplastic syndrome) (see section 4.4)	Acute myeloid leukaemia (see section 4.4)	
Blood and lymphatic system disorders	Anaemia Thrombocytopenia Leukopenia Lymphopenia	Neutropenia		Pancytopenia
Endocrine disorders				Carcinoid crisis
Metabolism and nutrition disorders				Tumour lysis syndrome
Gastrointestinal disorders	Nausea Vomiting			Dry mouth
Skin and subcutaneous tissue disorders	Alopecia			

Description of selected adverse reactions

Dry mouth
Transient dryness of the mouth has been reported among patients with metastatic castration resistant prostate cancer receiving PSMA-targeted lutetium (^{177}Lu)-labelled medicinal products.

Alopecia
Alopecia, described as mild and temporary, has been observed among patients receiving lutetium (^{177}Lu)-based 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 Ilumira will lead to increased bone marrow toxicity and haematopoietic stem cell damage. Therefore, in case of an inadvertent administration of Ilumira, 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 Ilumira for labelling 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.

One gram 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 radiotoxicity.

The toxicity of 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: Therapeutic radiopharmaceuticals, other therapeutic radiopharmaceuticals, ATC code: V10X

The pharmacodynamic properties of lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with lutetium (^{177}Lu) chloride, 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.

Lutetium (^{177}Lu) emits beta (β^-) particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm. Lutetium (^{177}Lu) also emits low-energy gamma-rays which allow scintigraphic, biodistribution and dosimetry studies with the same lutetium (^{177}Lu)-labelled medicinal products.

5.2 Pharmacokinetic properties

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

Distribution after inadvertent intravenous administration of lutetium (^{177}Lu) chloride

Data from experiments on mice, rats and rabbits indicate that more than half the lutetium (^{177}Lu) entering the systemic circulation is deposited in the skeleton with only small amounts going to the liver and kidneys. Lutetium (^{177}Lu) has a biological half-life of between 10 and 40 days in the soft tissue in mice and rats but has a very long biological half-life in the skeleton. However, these long half-life values in skeleton are not of relevance for lutetium (^{177}Lu) chloride n.c.a., since it completely decays with a half-life of 6.7 days following administration, preventing any accumulation over time. After intravenous injection of lutetium (^{177}Lu) chloride, lutetium (^{177}Lu) is predominantly but slowly excreted in the urine. Some faecal elimination is also observed.

5.3 Preclinical safety data

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

The toxicity of non-radioactive lutetium chloride has been studied in different mammalian species and using different administration routes. The intraperitoneal LD50 in mice was found to be approximately 315 mg/kg. In cats, no pharmacological effects on respiration and cardiovascular function were observed up to a cumulative intravenous dose of 10 mg/kg. A high dose of 10 GBq of lutetium (^{177}Lu) chloride contains 2.4 µg lutetium, corresponding to a human dose of 0.034 µg/kg. This dose is approximately 7 orders of magnitude lower than the intraperitoneal LD50 in mice and more than 5 orders of magnitude lower than the NOEL observed in cats. Therefore, lutetium metal-ion toxicity of Ilumira (^{177}Lu)-labelled medicinal products can be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diluted hydrochloric acid

6.2 Incompatibilities

Radiolabelling of medicinal products, such as monoclonal antibodies, peptides, vitamins 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 lutetium (^{177}Lu)-labelled 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 minimise 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

10 days from the date of manufacture.

Shelf life after first opening

From a microbiological point of view, unless the method of withdrawal from the vial or any insertion into the vial preclude the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in the original package in order to avoid unnecessary radiation exposure.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Clear type I glass 2 mL or 10 mL vial, with a Fluorpolymer coated bromobutyl rubber stopper, closed with an aluminum cap.

The vials are placed into a lead container for protective shielding and packed into an outer carton.

Pack sizes:

2 mL vial: 1, 2, 3 or 4 vials
10 mL vial: 1, 2, 3 or 4 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilumira 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 licenses 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 instructions on extemporary preparation of the radiopharmaceutical precursor solution before administration, see section 12.

If at any time in the preparation of this radiopharmaceutical precursor solution 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 radiopharmaceutical precursor solution 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)-labelled 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 exposition there is no 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 medicinal product or waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SHINE Europe B.V.
Jan Salwaweg 1, 4e verdieping
9641LL Veendam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2018/001
EU/1/26/2018/002
EU/1/26/2018/003
EU/1/26/2018/004
EU/1/26/2018/005
EU/1/26/2018/006
EU/1/26/2018/007
EU/1/26/2018/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The radiation dose received by various organs following intravenous 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 lutetium (^{177}Lu)-labelled medicinal product following administration of the radiolabelled preparation is available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry tables below are 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 Ilumira.

Dose calculations (absorbed normalised doses for target organs [mGy/MBq] and effective normalised doses [mSv/MBq]) were performed using the Medical Internal Radiation Dose (MIRD) S-value method for each organ after administration of 1 000 MBq. Organ doses are listed below for an adult male and female model as well as for 15-year, 10-year, 5-year, 1-year and newborn male and female models.

The results show kidneys and liver as the significant target organs for the biodistribution of lutetium (^{177}Lu) chloride, and red marrow as the dose limiting organ.

Table 2 Estimated organ normalised absorbed doses [mGy/MBq] and normalised effective dose [mSv/MBq] of $^{177}LuCl_3$ in male models as calculated using the Medical Internal Radiation Dose (MIRD) S-value method

Target organ	Adults	15 year old	10 year old	5 year old	1 year old	Newborn
Adipose tissue	1.80E-03	2.12E-03	3.16E-03	5.35E-03	9.06E-03	2.30E-02
Adrenals	2.26E-02	2.43E-02	4.21E-02	7.00E-02	1.30E-01	3.58E-01
Alveolar-interstitial	2.48E-02	2.89E-02	5.06E-02	8.39E-02	1.61E-01	4.73E-01
Bronchioles secretary cells	1.93E-02	1.69E-02	3.03E-02	5.03E-02	1.08E-01	2.96E-01
Brain	4.50E-03	5.59E-03	8.23E-03	1.32E-02	1.98E-02	5.58E-02
Breast	2.27E-03	3.26E-03	4.87E-03	8.83E-03	1.24E-02	4.06E-02
Bronchi basal cells	2.53E-02	1.57E-02	2.78E-02	4.64E-02	1.00E-01	2.65E-01
Bronchi secretary cells	2.50E-02	1.57E-02	2.78E-02	4.64E-02	1.00E-01	2.65E-01
Endosteal cells	8.08E-02	3.93E-02	8.91E-02	2.41E-01	6.76E-01	6.44E-01
ET1 basal cells*	3.85E-03	5.47E-03	1.90E-03	4.62E-03	6.45E-03	1.68E-02
ET2 basal cells**	3.38E-03	1.88E-02	7.96E-03	1.26E-02	1.76E-02	3.72E-02
Lens of the eye	2.00E-03	1.82E-03	2.40E-03	3.27E-03	3.77E-03	8.73E-03
Gall bladder wall	1.67E-02	1.03E-02	1.57E-02	2.34E-02	3.96E-02	8.41E-02
Heart wall	1.77E-02	1.85E-02	3.31E-02	5.45E-02	9.83E-02	2.87E-01
Kidneys	1.03E-01	1.32E-01	2.40E-01	4.06E-01	8.53E-01	2.50E+00
Left colon stem cell layer	1.19E-02	1.50E-02	2.46E-02	4.08E-02	7.09E-02	2.07E-01
Liver	1.74E-01	2.25E-01	4.01E-01	6.78E-01	1.36E+00	3.57E+00
Extrathoracic lymph nodes	1.99E-03	5.93E-03	7.33E-03	1.08E-02	1.39E-02	4.04E-02
Systemic lymph nodes	5.04E-03	3.59E-03	4.98E-03	8.42E-03	1.36E-02	3.36E-02
Thoracic lymph nodes	4.70E-03	5.46E-03	8.95E-03	1.56E-02	2.45E-02	5.42E-02
Muscle	5.23E-03	6.82E-03	1.22E-02	2.16E-02	4.78E-02	9.72E-02
Oral Mucosa	3.32E-03	6.89E-03	8.66E-03	1.50E-02	1.62E-02	4.94E-02
Esophagus	8.72E-03	8.94E-03	1.42E-02	2.30E-02	3.17E-02	1.15E-01
Ovaries	N/A	N/A	N/A	N/A	N/A	N/A
Pituitary gland	3.06E-03	5.35E-03	6.41E-03	1.01E-02	2.16E-02	4.50E-02
Pancreas	1.02E-02	1.50E-02	2.57E-02	4.12E-02	6.95E-02	2.04E-01
Prostate	2.15E-03	2.64E-03	4.88E-03	7.68E-03	1.10E-02	3.56E-02
Red marrow	2.38E-02	3.77E-02	4.11E-02	9.45E-02	2.27E-01	7.13E-01
Right colon stem cell layer	1.32E-02	1.65E-02	2.65E-02	4.39E-02	7.44E-02	2.15E-01
Rectosigmoid Colon stem cell layer	8.74E-03	1.09E-02	1.74E-02	2.80E-02	4.73E-02	1.37E-01
Salivary glands	2.52E-03	5.00E-03	6.26E-03	9.83E-03	1.32E-02	4.51E-02
Small intestine stem cell layer	9.89E-03	2.52E-02	4.32E-02	7.24E-02	1.34E-01	3.80E-01

Target organ	Adults	15 year old	10 year old	5 year old	1 year old	Newborn
Skin	1.77E-03	2.22E-03	3.56E-03	5.57E-03	8.47E-03	2.71E-02
Spleen	1.60E-02	1.98E-02	3.35E-02	5.61E-02	9.85E-02	2.97E-01
Stomach stem cell layer	3.87E-02	4.73E-02	8.48E-02	1.42E-01	2.78E-01	7.53E-01
Testes	1.73E-03	2.43E-03	5.33E-03	6.61E-03	6.68E-03	2.09E-02
Thymus	3.29E-03	3.57E-03	5.92E-03	9.54E-03	1.47E-02	4.89E-02
Thyroid	4.69E-03	5.29E-03	7.67E-03	1.26E-02	1.85E-02	6.96E-02
Tongue	3.02E-03	4.90E-03	6.68E-03	1.05E-02	1.36E-02	4.42E-02
Tonsils	3.88E-03	5.18E-03	6.99E-03	1.05E-02	1.37E-02	5.01E-02
Urinary bladder wall	1.79E-03	2.02E-03	3.00E-03	4.44E-03	8.66E-03	1.90E-02
Ureters	3.03E-03	4.23E-03	6.75E-03	1.25E-02	2.17E-02	6.13E-02
Uterus	N/A	N/A	N/A	N/A	N/A	N/A
Total body	1.80E-03	1.89E-03	2.93E-03	4.52E-03	7.61E-03	1.66E-02
Effective dose	2.26E-02	2.87E-02	4.75E-02	8.34E-02	1.68E-01	4.61E-01

*ET1 basal cells – Endothelin-1 basal cells
**ET2 basal cells – Endothelin-2 basal cells

Table 3 Estimated organ normalised absorbed doses [mGy/MBq] and normalised effective dose [mSv/MBq] of $^{177}LuCl_3$ in female models as calculated using the Medical Internal Radiation Dose (MIRD) S-value method

Target organ	Adults	15 year old	10 year old	5 year old	1 year old	Newborn
Adipose tissue	1.60E-03	2.09E-03	3.13E-03	5.31E-03	9.04E-03	2.29E-02
Adrenals	2.90E-02	2.56E-02	4.21E-02	7.00E-02	1.30E-01	3.58E-01
Alveolar-interstitial	2.85E-02	3.06E-02	5.06E-02	8.43E-02	1.61E-01	4.73E-01
Bronchioles secretary cells	2.17E-02	1.83E-02	3.03E-02	5.06E-02	1.08E-01	2.96E-01
Brain	5.16E-03	5.14E-03	8.55E-03	8.51E-03	1.98E-02	5.58E-02
Breast	2.02E-03	3.06E-03	4.72E-03	8.74E-03	1.23E-02	4.04E-02
Bronchi basal cells	2.98E-02	1.68E-02	2.78E-02	4.64E-02	1.00E-01	2.65E-01
Bronchi secretary cells	2.95E-02	1.68E-02	2.78E-02	4.64E-02	1.00E-01	2.65E-01
Endosteal cells	9.68E-02	4.26E-02	8.91E-02	2.41E-01	6.76E-01	6.44E-01
ET1 basal cells*	3.51E-03	2.16E-03	1.89E-03	4.56E-03	6.37E-03	1.66E-02
ET2 basal cells**	3.43E-03	6.22E-03	7.95E-03	1.25E-02	1.76E-02	3.72E-02
Lens of the eye	1.91E-03	1.59E-03	2.39E-03	3.23E-03	3.73E-03	8.73E-03
Gall bladder wall	1.98E-02	1.16E-02	1.58E-02	2.36E-02	3.97E-02	8.49E-02
Heart wall	2.14E-02	2.00E-02	3.31E-02	5.44E-02	9.86E-02	2.87E-01
Kidneys	1.31E-01	1.50E-01	2.40E-01	4.06E-01	8.53E-01	2.50E+00
Left colon stem cell layer	1.29E-02	1.44E-02	2.46E-02	4.08E-02	7.09E-02	2.07E-01
Liver	2.14E-01	2.49E-01	4.01E-01	6.78E-01	1.36E+00	3.57E+00
Extrathoracic lymph nodes	1.91E-03	5.16E-03	7.32E-03	1.07E-02	1.39E-02	4.04E-02
Systemic lymph nodes	5.08E-03	3.07E-03	4.98E-03	8.42E-03	1.36E-02	3.36E-02
Thoracic lymph nodes	5.32E-03	6.48E-03	8.95E-03	1.56E-02	2.45E-02	5.42E-02
Muscle	6.31E-03	7.34E-03	1.22E-02	2.16E-02	4.79E-02	9.73E-02
Oral Mucosa	6.15E-03	5.68E-03	8.79E-03	1.52E-02	1.66E-02	5.06E-02
Esophagus	9.38E-03	8.30E-03	1.42E-02	2.30E-02	3.17E-02	1.15E-01
Ovaries	4.74E-03	3.17E-03	4.25E-03	7.54E-03	1.47E-02	5.69E-02

Target organ	Adults	15 year old	10 year old	5 year old	1 year old	Newborn
Pituitary gland	9.20E-03	4.30E-03	6.90E-03	1.05E-02	2.28E-02	4.99E-02
Pancreas	1.64E-02	1.64E-02	2.57E-02	4.13E-02	6.95E-02	2.04E-01
Prostate	N/A	N/A	N/A	N/A	N/A	N/A
Red marrow	2.65E-02	3.84E-02	4.11E-02	9.45E-02	2.27E-01	7.13E-01
Right colon stem cell layer	1.36E-02	1.53E-02	2.65E-02	4.39E-02	7.44E-02	2.15E-01
Rectosigmoid Colon stem cell layer	9.34E-03	9.95E-03	1.74E-02	2.80E-02	4.73E-02	1.37E-01
Salivary glands	3.18E-03	4.16E-03	6.23E-03	9.74E-03	1.31E-02	4.48E-02
Small intestine stem cell layer	9.21E-03	2.68E-02	4.32E-02	7.24E-02	1.34E-01	3.80E-01
Skin	2.06E-03	2.16E-03	3.56E-03	5.57E-03	8.47E-03	2.71E-02
Spleen	1.91E-02	2.03E-02	3.35E-02	5.61E-02	9.85E-02	2.97E-01
Stomach stem cell layer	4.84E-02	5.17E-02	8.48E-02	1.42E-01	2.78E-01	7.53E-01
Testes	N/A	N/A	N/A	N/A	N/A	N/A
Thymus	3.01E-03	3.63E-03	5.94E-03	9.57E-03	1.48E-02	4.91E-02
Thyroid	4.88E-03	4.65E-03	7.67E-03	1.26E-02	1.84E-02	6.96E-02
Tongue	3.31E-03	4.22E-03	6.73E-03	1.05E-02	1.38E-02	4.46E-02
Tonsils	3.02E-03	4.91E-03	6.94E-03	1.04E-02	1.36E-02	4.97E-02
Urinary bladder wall	2.14E-03	1.93E-03	2.90E-03	4.60E-03	8.83E-03	1.69E-02
Ureters	3.88E-03	5.04E-03	6.82E-03	1.27E-02	2.18E-02	6.20E-02
Uterus	1.88E-03	1.08E-02	1.70E-02	8.36E-03	2.39E-02	6.71E-02
Total body	1.60E-03	1.97E-03	2.88E-03	4.45E-03	7.52E-03	1.65E-02
Effective dose	2.90E-02	3.06E-02	4.75E-02	8.34E-02	1.69E-01	4.64E-01

*ET1 basal cells – Endothelin-1 basal cells
**ET2 basal cells – Endothelin-2 basal cells

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 (β^-)/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.

Usual precautions regarding sterility and radioactivity should be respected.

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the radiopharmaceutical precursor solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

If the integrity of this vial is compromised, the medicinal product should not be used.

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)-labelled radiopharmaceuticals in order to form a complex with free lutetium (^{177}Lu), if present, leading to its rapid renal clearance.

Adequate quality control of the radiochemical purity of ready to use radiopharmaceuticals gained after radiolabelling with Ilumira should be assured. Limits for radiochemical impurities should be set recognising the radiotoxicological potential of lutetium (^{177}Lu). Free nonbound lutetium (^{177}Lu) should be consequently minimised.

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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 responsible for batch release

MIAS Pharma Limited
Suite 1 First Floor, Stafford House, Strand Road,
Portmarnock, D13 WC83,
lreland

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

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ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Ilumira 37 GBq/mL radiopharmaceutical precursor, solution
lutetium (^{177}Lu) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL solution contains 37 GBq of lutetium (^{177}Lu) chloride at calibration time (CAL).

3. LIST OF EXCIPIENTS

diluted hydrochloric acid. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.

1 vial
2 vials
3 vials
4 vials

ART: {DD/MM/YYYY hh:00 CET}

Specific activity at CAL: …GBq/mg

Volume: …mL Activity at ART: …GBq/vial	Volume: …mL Activity at ART: …GBq/vial	Volume: …mL Activity at ART: …GBq/vial	Volume: …mL Activity at ART: …GBq/vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For *in vitro* radiolabelling.
NOT INTENDED FOR DIRECT ADMINISTRATION TO PATIENTS.

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

Radioactive

8. EXPIRY DATE

EXP {DD/MM/YYYY, 19:00 CET}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to avoid unnecessary radiation exposure.

Storage should 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 medicinal product or waste material must be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SHINE Europe B.V.
Jan Salwaweg 1, 4e verdieping
9641LL Veendam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2018/001
EU/1/26/2018/002
EU/1/26/2018/003
EU/1/26/2018/004
EU/1/26/2018/005
EU/1/26/2018/006
EU/1/26/2018/007
EU/1/26/2018/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LEAD CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Ilumira 37 GBq/mL radiopharmaceutical precursor, solution
lutetium (^{177}Lu) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL solution contains 37 GBq of lutetium (^{177}Lu) chloride at calibration time (CAL).

3. LIST OF EXCIPIENTS

diluted hydrochloric acid. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.

1 vial

Volume: …mL

Activity at ART: …GBq/vial

ART: {DD/MM/YYYY hh:00 CET}

Specific activity at CAL: …GBq/mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For *in vitro* radiolabelling.
NOT INTENDED FOR DIRECT ADMINISTRATION TO PATIENTS.

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

Radioactive

8. EXPIRY DATE

EXP {DD/MM/YYYY, 19:00 CET}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to avoid unnecessary radiation exposure.

Storage should 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 medicinal product or waste material must be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SHINE Europe B.V.
Jan Salwaweg 1, 4e verdieping
9641LL Veendam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2018/001
EU/1/26/2018/002
EU/1/26/2018/003
EU/1/26/2018/004
EU/1/26/2018/005
EU/1/26/2018/006
EU/1/26/2018/007
EU/1/26/2018/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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 (2 mL, 10 mL)

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

Ilumira 37 GBq/mL radiopharmaceutical precursor, solution
lutetium (^{177}Lu) chloride

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {DD/MM/YYYY, 19:00 CET}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Volume: …mL

Activity at ART: …GBq/vial

ART: {DD/MM/YYYY hh:00 CET}

6. OTHER

MIAS Pharma Limited

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ilumira 37 GBq/mL radiopharmaceutical precursor, solution
lutetium (^{177}Lu) chloride

Read all of this leaflet carefully before you are given this medicine combined with Ilumira 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 Ilumira is and what it is used for

This medicine is a type of product called a radiopharmaceutical precursor. It contains the active substance lutetium (^{177}Lu) chloride which gives off beta-minus radiation.

Ilumira is not intended to be used on its own, but has to be combined with other medicines (so called carrier medicines) before it can be used. This process, where a carrier medicine is tagged with a radioactive compound, is called radiolabelling.

Carrier medicines are used with a specific compound, in this case lutetium (^{177}Lu) chloride, to achieve a specific goal. They may be substances that have been designed to recognise a particular type of cell in the body. When such a lutetium (^{177}Lu)-radiolabelled carrier medicine is given to a patient, it carries the radiation to where these cells are located, to treat a disease or to obtain images on a screen that are used to diagnose or locate an illness.

The use of a ^{177}Lu- radiolabelled medicine involves exposure to radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit of using ^{177}Lu- radiolabelled medicine outweighs the risk due to radiation.
For more information, refer to the package leaflet of the ^{177}Lu- radiolabelled medicine.

2. What you need to know before Ilumira is used

Ilumira must not be used
- if you are allergic to lutetium (^{177}Lu) chloride or any of the other ingredients of this medicine (listed in section 6);
- if you are pregnant or believe you may be pregnant.

For more information, refer to the package leaflet of the ^{177}Lu- radiolabelled medicine.

Warnings and precautions
Lutetium (^{177}Lu) chloride is not to be administered directly to patients. Of course, the hospital staff is expected to wear standard radiation protection. Any other person in close contact of the treated patient should be informed about possibilities to reduce their exposure due to radiation coming from the patient.

Take special care with the ^{177}Lu radiolabelled medicines:
- if you have kidney problems or a haematological condition (problems with your blood or blood-forming tissue, such as bone marrow). Increased exposure to radiation is possible in patients with these conditions leading to a greater risk of certain side effects (see section 4. Possible side effects). Your doctor will consider the expected benefits of the medicine against the possible risks and may stop treatment if certain side effects occur.
- a reduced number of red blood cells (anaemia);
- a reduced number of blood platelets (thrombocytopenia), which are important to stop bleeding;
- a reduced number of white blood cells (leucopenia, lymphopenia or neutropenia) which are important for protecting the body against infection.

Most of these events are mild and temporary. A reduced number of all 3 types of blood cells (red blood cells, platelets, and white blood cells - pancytopenia) has been described in some patients. Treatment has to be stopped in patients with pancytopenia.

Because lutetium (^{177}Lu) can sometimes affect your blood cells, your doctor will do blood tests before you start and at regular intervals during treatment. Talk to your doctor if you experience shortness of breath, bruising, nose bleeds, bleeding from your gums, or if you develop a fever.

When lutetium (^{177}Lu) chloride is used to radiolabel carrier medicines called somatostatin analogues applied to treat cancers called neuroendocrine tumours, the radiolabelled carrier medicine is 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 ^{177}Lu-radiolabelled medicines may affect the way your liver works. In this case, you may experience some of the following symptoms: yellowing of the skin and eyes (jaundice), belly (abdominal) pain (especially in the upper right side of your abdomen) feeling sick / nauseous, vomiting, tiredness, loss of appetite, dark urine, and bleeding or bruising more easily than normal. Your doctor will take a blood test to check your liver function during treatment.

Lutetium (^{177}Lu)-labelled carrier medicines may be given directly into a vein through a tube known as a cannula. There have been reports of leakage of the fluid into the surrounding tissue (extravasation). Tell your doctor if you get any swelling or pain in your arm.

After neuroendocrine tumours are treated with ^{177}Lu-radiolabelled medicines, you may get symptoms associated with release of hormones from the tumour cells, known as a carcinoid crisis. Tell your doctor if you feel faint or dizzy or have flushing (sudden reddening of the skin, usually on the face or neck) or diarrhoea following your treatment.

Treatment with ^{177}Lu-radiolabelled medicines may cause tumour lysis syndrome, a condition resulting from the rapid breakdown of tumour cells. This may lead to abnormal blood test results, irregular heartbeat, kidney failure or seizures within a week of treatment. Your doctor will carry out blood tests to monitor you for this syndrome. Tell your doctor if you have muscle cramping, muscle weakness, confusion, or shortness of breath.

Please refer to the package leaflet of the ^{177}Lu-radiolabelled medicine for additional warnings and precautions.

Children and adolescents
Talk to your nuclear medicine doctor if you are under 18 years old.
^{177}Lu-radiolabelled medicine may be used in children and adolescents under 18 years old. Please refer to the package leaflet of that medicine.

Other medicines and medicines radiolabelled with Ilumira
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
You must inform the nuclear medicine doctor before you are given ^{177}Lu-radiolabelled medicines 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
^{177}Lu-radiolabelled medicines must not be administered if you are pregnant.

If you are breast-feeding
You will be asked to stop breast-feeding during treatment with ^{177}Lu-radiolabelled medicines. Please ask your nuclear medicine doctor when you can resume breast-feeding.

Driving and using machines
There could be effects on your ability to drive and to use machines due to the ^{177}Lu-radiolabelled medicine. Please read the package leaflet of that medicine carefully.

3. How the medicine radiolabelled with Ilumira is used

There are strict laws on the use, handling and disposal of radiopharmaceuticals. ^{177}Lu-radiolabelled medicines will only be used in special controlled areas. This medicine will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this medicine and will keep you informed of their actions.
The nuclear medicine doctor supervising the procedure will decide on the quantity of a ^{177}Lu-radiolabelled medicines to be used in your case. It will be the smallest quantity necessary to achieve the appropriate outcome, depending on the ^{177}Lu-radiolabelled medicines you will be given and what it is used for.

Administration of the medicine radiolabelled with Ilumira and conduct of the procedure
Ilumira must be used only in combination with another medicine (carrier medicine), which has been specifically developed and authorised for being combined with lutetium (^{177}Lu) chloride. The way it is given to you will depend on the type of the carrier medicine. Please read the Package Leaflet of that medicine.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of the medicine radiolabelled with Ilumira
The nuclear medicine doctor will inform you if you need to take any special precautions after receiving the ^{177}Lu-radiolabelled medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more medicine radiolabelled with Ilumira than you should
Since ^{177}Lu-radiolabelled medicine is handled by a nuclear medicine doctor under strictly controlled conditions, there is only a very small chance of possible overdose. However, in the case of an overdose, you will receive appropriate treatment as necessary.

Should you have any further questions on the use of the ^{177}Lu-radiolabelled medicine, ask your nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, the ^{177}Lu-radiolabelled medicine can cause side effects, although not everybody gets them.

Some side effects could be serious.

If you experience any of the following serious side effects, **tell your doctor right away**.

Very common (may affect more than 1 in 10 people):
- Decreased levels of red blood cells (anaemia)
- Decreased levels of white blood cells (leucopenia)
- Decreased levels of lymphocytes, another type of white blood cell (lymphopenia)
- Decreased levels of blood platelets (thrombocytopenia)

Common (may affect up to 1 in 10 people):
- A type of cancer where the bone marrow does not make enough healthy blood cells or platelets (myelodysplastic syndrome)
- Decreased levels of neutrophils, a type of white blood cell (neutropenia)

Uncommon (may affect up to 1 in 100 people):
- A fast-growing cancer in which too many myeloblasts (a type of immature white blood cell) are found in the bone marrow and blood (acute myeloid leukaemia)

Not known (frequency cannot be estimated from the available data):
- Carcinoid crisis
  Carcinoid crisis is a combination of symptoms caused by the release of serotonin and other substances from carcinoid tumours. Symptoms may include flushing of the face, flat angiomas (small collections of dilated blood vessels) of the skin, diarrhoea, difficulty breathing, rapid pulse, and sudden drops in blood pressure causing dizziness and light headedness.
- Tumour lysis syndrome
  Tumour lysis syndrome is a condition when tumour cells break down and release their contents into the bloodstream, which can damage organs such as the heart, kidneys and liver. Symptoms may include nausea, vomiting, weakness, tiredness, muscle cramps, seizures, or changes in urine output.
- A reduced number of red blood cells, platelets and white blood cells (pancytopenia)

Bone marrow cancers (myelodysplastic syndrome and acute myeloid leukaemia) have been reported in patients several years after treatment with lutetium (^{177}Lu)-labelled carrier medicines for neuroendocrine tumours.

Other possible side effects

Very common side effects (may affect more than 1 in 10 people):
- Feeling sick (nausea)
- Vomiting
- Mild temporary hair loss (alopecia)
  Alopecia has been reported among patients receiving lutetium (^{177}Lu)-based peptide receptor radionuclide therapy for neuroendocrine tumours (tumours that form from cells that release hormones into the blood in response to a signal from the nervous system)

Not known (frequency cannot be estimated from the available data):
- Dry mouth (reported among patients with prostate cancer receiving treatment with lutetium (^{177}Lu) and has been temporary)

After a ^{177}Lu-radiolabelled medicine is given, it will deliver certain amounts of ionising radiation (radioactivity), which means there is a 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 ^{177}Lu-radiolabelled medicine.

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 Ilumira is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist 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.

Ilumira must not be used after the expiry date and time which is stated on the label after EXP. Ilumira will be stored in the original package that provides protection from radiation.

This medicine does not require any special temperature storage conditions.

6. Contents of the pack and other information

What Ilumira contains
- The active substance is lutetium (^{177}Lu) chloride.
  1 mL sterile solution contains 37 GBq lutetium (^{177}Lu) chloride on the activity reference time (CAL), corresponding to maximum 9 micrograms of lutetium (^{177}Lu) (as chloride).
  (GBq: GigaBecquerel is the unit in which radioactivity is measured).
- The other ingredients are hydrochloric acid and water.

What Ilumira looks like and contents of the pack
Ilumira is a radiopharmaceutical precursor, solution. It is presented as a clear and colourless solution in a clear type I glass 2 mL or 10 mL vial either conical or flat bottom, respectively, with a Fluorpolymer coated bromobutyl rubber stopper, closed with an aluminum cap.
The vials are placed into a lead container for protective shielding and packed into a an outer carton.

Pack sizes:
2 mL vial: 1, 2, 3 or 4 vials
10 mL vial: 1, 2, 3 or 4 vials

Not all pack sizes may be marketed.

The volume of one vial ranges from 0.05-6.6 mL solution (corresponding to 1.8-244.2 GBq at activity reference time). The volume depends on the quantity of medicine combined with Ilumira required for administration by the nuclear medicine doctor.

Marketing Authorisation Holder
SHINE Europe B.V.
Jan Salwaweg 1, 4e verdieping
9641LL Veendam

The Netherlands

Manufacturer

MIAS Pharma Limited
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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:
The complete SmPC of Ilumira is provided as a separate document in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC.