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November 14, 2019

Andrea L. Kock, Director
Division of Materials Safety, Security, State
and Tribal Programs
Office of Nuclear Material Safety
and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
(Andrea.Kock@nrc.gov)

Re: Lutetium-177 Licensing Determination (STC-18-042)

Dear Ms. Kock,

On behalf of ITM Medical Isotopes, Inc. ("ITM"), I am writing to provide additional information in support of ITM's letter of October 7, 2019 requesting the Nuclear Regulatory Commission ("NRC" or "Commission") to take certain actions with respect to the medical use and disposal of the radionuclide, Lutetium-177 ("^{177}Lu"). In that letter, ITM indicated that there is unnecessary confusion emerging within the healthcare community about the use and disposal of ^{177}Lu, and that this problem could be easily addressed through clarification of the NRC's June 21, 2018, licensing determination for ^{177}Lu (hereafter "Licensing Determination").[1]

As recognized by the NRC, there are two distinct processes for the production of ^{177}Lu. One of these manufacturing methods produces carrier-added Lutetium-177 (hereafter "c.a.^{177}Lu") and the impurity, Lutetium-177m (hereafter "^{177m}Lu"). A second manufacturing process yields non-carrier-added Lutetium-177 (hereafter "n.c.a.^{177}Lu") and no contaminants such as ^{177m}Lu. While these processes yield two different forms of ^{177}Lu, the Licensing Determination does not reflect these differences and that has led to unnecessary regulatory burdens among licensees using ^{177}Lu.

To address this issue, ITM requested the NRC to revise and reissue the Licensing Determination so as to expressly recognize c.a. ^{177}Lu and n.c.a. ^{177}Lu as separate and distinct forms of ^{177}Lu, with correspondingly different disposal requirements because of the presence and absence of

[1] *See* Memorandum to All Agreement States, Vermont, Wyoming, Licensing of Lutetium-177 (STC-18-042), June 21, 2018. https://scp.nrc.gov/asletters/tech/sp18042.pdf

^{177m}Lu, respectively. In its Licensing Determination, the NRC indicated that licensees should use counters to determine whether ^{177m}Lu is present to ensure it is disposed of as low-level radioactive waste pursuant to 10 CFR Part 20. ITM appreciates the need for flexibility and believes there is an even more efficient and effective approach for licensees to determine whether they need to be concerned about ^{177m}Lu – licensees need only determine whether the product contains n.c.a. ^{177}Lu from its labeling or other specifications.

For example, ITM understands that the only currently approved drug product in the United States containing ^{177}Lu, Lutathera®, uses c.a. ^{177}Lu. This drug product arrives at a licensee's facility in previously filled single-dose vials; it is not mixed with ^{177}Lu at a licensee's pharmacy.[2] Accordingly, any licensee administering this drug product to patients would know that it contains ^{177m}Lu and the NRC's survey and waste disposal measures under 10 CFR Part 20 apply. Moreover, even if it was unclear whether a drug product such as Lutathera uses c.a. ^{177}Lu, ITM believes that the use of counters to determine the presence of ^{177m}Lu would be appropriate unless it is clear from the labeling or other specifications that the drug product uses n.c.a. ^{177}Lu.[3]

The same approach may apply to licensees who receive ^{177}Lu directly from suppliers. Indeed, licensees can easily determine the form of ^{177}Lu from a simple review of the labeling and specifications for the product. As reflected in the figures included with ITM's October 7, 2019 letter, and the materials included with this letter, the specific activity for n.c.a. ^{177}Lu is significantly higher than c.a. ^{177}Lu. Moreover, c.a. ^{177}Lu is labeled as containing ^{177m}Lu, while n.c.a. ^{177}Lu is not because ^{177m}Lu is not applicable. Further, since the labeling protocols for c.a. ^{177}Lu and n.c.a. ^{177}Lu are significantly different, licensees will know which form of ^{177}Lu they are using without the need for counters to detect ^{177m}Lu.

Finally, while licensees may easily determine whether they are using c.a. ^{177}Lu or n.c.a. ^{177}Lu in this manner, the survey method proposed by the NRC to allow licenses to draw this distinction may not always be accurate. In the Licensing Determination, the NRC stated that "Lu-177m emits low-energy photons and beta emissions that, even in low quantities, are detectable using standard scintillator detectors and Geiger counters." That may be the case, but much more sophisticated counters may be needed in certain instances to discern the actual presence ^{177m}Lu, which may be confused with the very similar energy peak for ^{177}Lu.

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[2] *See* FDA Approved Labeling for Lutathera, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf

[3] In this regard, it would be very helpful for the NRC to request the FDA to require those seeking approval of drugs, biologics and devices containing ^{177}Lu to specify in the labeling for such products whether they contain c.a. ^{177}Lu or n.c.a. ^{177}Lu. That action would be fully consistent with, and advance the objectives of, the Memorandum of Understanding Between the NRC and FDA. 58 Fed. Reg. 47300, Sept. 8, 1993; 67 Fed. Reg. 78262, Dec. 23, 2002. http://www.nrc.gov/docs/ML0235/ML023520399.pdf

Accordingly, ITM requests the NRC to reissue its Licensing Determination stating that "licensees need not develop and utilize survey methods and safe handling and disposal procedures for ^{177m}Lu, including procedures to comply with 10 CFR Part 20 Subpart K, when using a radiopharmaceutical that contains n.c.a. ^{177}Lu." This action would allow licensees to understand the particular NRC regulatory requirements that apply to both c.a. ^{177}Lu and n.c.a. ^{177}Lu, and that would facilitate administration, handling and disposal of all medical products containing ^{177}Lu.

Thank you for your consideration of the additional information in this letter in support of ITM's October 7, 2019 request for revision of the Licensing Determination. Please do not hesitate to contact me for any additional information that the NRC may require in this connection.

Respectfully submitted,

Bruce S. Manheim

cc: Dr. Said Daibes Figueroa, NRC (Said.DaibesFigueroa@nrc.gov)

Enclosures: as stated

IDB Radiopharmacy bv

European Union
European Regional Development Fund
Investing in your future!

LuMark (^{177}Lu-Lutetiumchloride) Certificate of Analysis

Activity Reference Date : 8th of September 2015
Batch number : 08092015A1
Number of units : 8 vials
Date of analysis : 8th of September 2015
Analysed by : P. Liedorp

Results of analysis

Parameter	Specification	Method	Result	(A)ccept/ (R)eject
Appearance	Clear colourless solution in 10 ml glass vial with rubber stopper, packed in lead container	Visually	Conform	A
Labelling	Date and batch number comply	Visually	Conform	A
Volumetric Activity	72-88 GBq/ml (*)	MvO-09	Not Conform	A
Specific Activity	≥ 500 GBq/mg (*)	MvO-10	803 GBq/mg	A
pH	1 – 2	MvO-02	1.6	A
Chloride test	Positive	MvO-11	Positive	A
Radionuclidic identity ^{177}Lu	Positive	MvO-03	Positive	A
Radionuclidic impurities	^{177m}Lu: ≤ 0.024% (**) Other radioisotopes: ≤ 0.01% (*)	MvO-03	^{177m}Lu: 0.00705 % Other: ≤ 0.01 %	A
Radiochemical identity	Positive	MvO-08	Positive	A
Radiochemical purity	≥ 99% $^{177}Lu^{3+}$	MvO-08	99.92 %	A
Endotoxines	< 10 EU/ml	MvO-07	< 10 EU/ml	A

(*) These values are valid on Activity Reference Time (**) equals ≤ 0.05% at expiry

Administrative controls	
Documents (Charge protocol, Isolator checklist, Sterilization record, Particle counting print, Distribution report, Historical Log Report) are present, complete and signed	

QC Approval

Final result: Approved / ~~Rejected~~
Name QC-operator: P. Liedorp
Signature: P.P.
Date: 9 SEP 2015

Intermediate QP Release for use of LuMark

Name QP: I. UTAMA
Signature:
Date: 9 SEP 2015

IDB Radiopharmacy bv

European Union
European Regional Development Fund
Investing in your future!

LuMark (^{177}Lu-Lutetiumchloride) — Release Certificate

Batch number :	08092015A1	Manufacturing date	: 8th of September 2015
Batch size :	8 Vials	Expiry date	: 16th of September 2015

This is to certify that the above referenced batch was produced according to GMP requirements and IDB Radiopharmacy's quality requirements.

The batch has been manufactured, fully analyzed and meets all the requirements of the current product master file. A copy of the batch certificate of analysis is appended to this document.

Therefore, this batch is accepted for release on the market.

Date of release : 9 SEP 2015

EU Qualified Person : I. UTAMA

Signature :

IDB Radiopharmacy bv

Weverstraat 17
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The Netherlands

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Concerning: Non-conformance Volumetric Activity of the batch containing your product

Baarle-Nassau, 9th of September 2015

Dear valued customer,

This letter is to notify you that the Volumetric Activity of the batch 08092015A1 containing your product does not comply with the Volumetric Activity specification of 72 GBq/ml – 88 GBq/ml at Activity Reference Time (ART) which is the registered specification for our Lumark product.
This is also indicated in the Certificate of Analysis you have received.

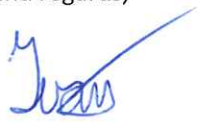
Although not complying with the release specification the batch has been released based on the following rationale:

The specification of 80 GBq/ml ± 10% was put into place during the Lumark registration phase of an EMA Centralised Procedure due to regulations that require a product to have one fixed strength.
Prior to the registration of Lumark, the Volumetric Activity was not fixed at 80 GBq/ml ± 10% and requested activities could be provided in requested volumes.
Although the dispensing system has been modified and tested extensively, occasionally the Volumetric Activity of a product is outside the registered range. We are working on this issue and as of 1 January 2016 the Volumetric Activity has to be within the registered range.

From the information above it can be concluded that a non-conforming Volumetric Activity has no impact on the quality or safety of the product and the product has been provided in various Volumetric Activities in the past.
Radiopharmaceutical products are a special group of medicinal products in the sense that their strength changes in the time due to the radioactive decay. The strength therefore is determined by the moment the activity of the product is measured (ART) and will decrease during the time.
This is very different than more conventional medicinal products where the strength of the product should be guaranteed for at least the full shelf-life and a non-compliance of the strength could lead to wrong dosages and potential harm to the patient.
This product is not for direct use and before use radioactivity should be checked. The Volumetric Activity therefore is not a very relevant parameter.

I hope I have informed you sufficiently.
If you have any questions or comments about this letter, don't hesitate to contact me.

Kind regards,



Ivan Utama
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PASSION FOR PRECISION

endolucin beta

✔ GMP CERTIFIED

✔ REGISTERED

No-carrier-added Lutetium (^{177}Lu) chloride

endolucin beta

EndolucinBeta® 40 GBq/mL radiopharmaceutical precursor, solution.
Active substance: Lutetium (^{177}Lu) chloride.

EndolucinBeta® is an innovative radiopharmaceutical precursor for targeted radionuclide therapies and contains the active substance ^{177}Lu chloride as a no-carrier-added radioisotope.

The use of no-carrier-added (n. c. a.) ^{177}Lu is excellent for the efficacy and quality of therapeutic radiopharmaceuticals. The production route of EndolucinBeta® takes advantage of highly enriched Ytterbium-176 as starting material, thereby providing the highest specific activity and an unprecedented level of radionuclidic purity.

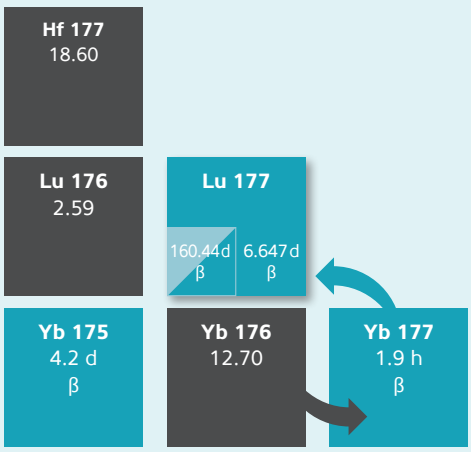
Using ^{177}Lu in its pure form enables the specific radioactivity to be greatly increased by up to 6-times. As a result, the superior performance creates favorable preconditions for efficient radiolabeling of biomolecules such as peptides and antibodies.

With us, you can choose your day of Activity Reference Time (ART) at one of 7 days within shelf life, right according to your needs.

Through our reliable, longstanding partnerships with nuclear reactors we can guarantee security of supply and daily availability of EndolucinBeta® 365 days a year. The ITM Group and its subsidiary ITG strive for excellence in establishing an innovative, fully-integrated n. c. a. ^{177}Lu platform, setting new standards.

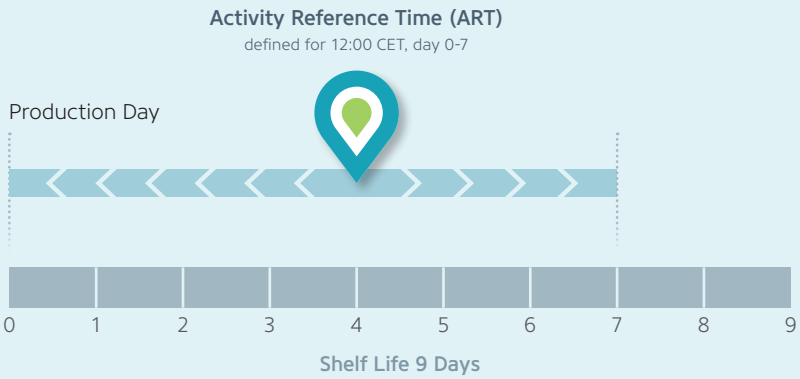
EndolucinBeta® is GMP certified and received EU Marketing Authorization.

PRODUCTION ROUTE



Using the indirect production route by taking ^{176}Yb as starting material we are able to offer no-carrier-added ^{177}Lu with superior characteristics when compared to the carrier-added radioisotope.

DEFINITION OF ART



Choose the day of Activity Reference Time (ART) and get EndolucinBeta® according to your needs, any day of the week.

NO-CARRIER-ADDED VS. CARRIER-ADDED ^{177}Lu

EndolucinBeta® displays **superior characteristics** when compared to the carrier-added radioisotope.

The specific activity of n.c.a. ^{177}Lu is up to **6 times higher** than of the c.a. isotope.

Due to its slower decrease of specific activity EndolucinBeta® offers **favorable preconditions** for an **efficient radiolabeling reaction** over its entire shelf-life of 9 days after production.

Furthermore, EndolucinBeta® provides the **highest achievable radionuclidic purity.** In comparison to the c.a. isotope EndolucinBeta® contains no metastable ^{177m}Lu and does not require any costly logistics and storage of contaminated radioactive waste.

KEY ADVANTAGES

- **EU Marketing Authorization**
- **GMP certification**
- **Highest specific activity at ART ≥ 3,000 GBq/mg**
- **No contamination with long-lived ^{177m}Lu**
- **Availability – 365 days a year**
- **Choose the day of ART according to your needs**
- **Sterile / Endotoxin-tested**
- **Cost effective and environmentally sustainable waste management**

Take advantage of our one-stop-shop offering: Get all components and services from one supplier!

Radioisotopes + Biomolecules

iQS® Ga-68 Fluidic Labeling Module

iQS®–Theranostics Synthesizer

Consumables

Quality Control Solution

PRECISELY FOR ME.

Excipient

Hydrochloric acid solution

Therapeutic indications

EndolucinBeta® 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 authorized for radiolabelling with Lutetium (177Lu) chloride.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Established or suspected pregnancy or when pregnancy has not been excluded.

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

Undesirable effects

Adverse reactions following the administration of a Lutetium (177Lu)-labelled medicinal product prepared by radiolabelling with EndolucinBeta® 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.

Special warnings and precautions for use

EndolucinBeta® contains a radioactive substance.

Read the package leaflet before use.

For administration after in vitro radiolabelling. 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.

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

Keep out of the sight and reach of children.

Medicinal product subject to restricted medical prescription.

Marketing Authorization Holder

ITG Isotope Technologies Garching GmbH

Lichtenbergstrasse 1
85748 Garching, Germany

A company of the ITM Group.

endolucin beta

FIXED PARAMETERS

Characteristics	Acceptance Criteria
Element	Lutetium
Nuclide	^{177}Lu
Half-life	6.647 days
Decay mode	Beta decay
Beta max. energy	0.498 MeV
Main gamma radiation	112.9498 keV (6.17 %), 208.3662 keV (10.36 %)
Chemical form	Lu^{3+} in aqueous HCl solution
Solvent	0.04 M HCl solution

Characteristics	Acceptance Criteria
Volume per vial	0.075–3.75 mL
Radiolabeling yield	≥ 99.0 % (based on radiolabeling with ^{177}Lu of DOTA-derivate, molar ratio 1:4)
Packaging	Type I glass vial, closed with fluorotec® coated bromobutyl septum and center hole crimp cap
Shelf-life	9 days from production (filling of product)

PHYSICAL DATA

Characteristics	Description
Content	Range: 3–150 GBq per vial at ART
ART	Specifiable to 12:00 (CET) of days 0–7 after production
Primary Packaging	Options: • **vial 2 mL,** conical bottom (Available for 3–80 GBq) • **vial 10 mL,** flat bottom (Available for 8–150 GBq)

RELEASE PARAMETERS

Characteristics	Acceptance Criteria	Method
Specific activity	≥ 3,000 GBq/mg at ART	ICP-MS
Radionuclidic purity	^{175}Yb: ≤ 0.01 % Sum of others (the total radioactivity due to other radionuclidic impurities): ≤ 0.01 %	Gamma spectrometry, corrected to ^{177}Lu activity at end of shelf life
Activity per vial	90 %–110 % of the declared ^{177}Lu radioactivity at the date and time stated on the label (ART)	Dose calibrator
Radioactivity concentration	36–44 GBq/mL at ART	Dose calibrator / Weighing
Identity ^{177}Lu	113 keV gamma line existing 208 keV gamma line existing	Gamma spectrometry
Identity chloride	White precipitate visible	Chloride detection reaction (Ph. Eur. 2.3.1)
pH	1–2	pH-strip
Appearance	Clear and colorless solution	Visual
Chemical purity	Fe ≤ 0.25 µg/GBq, Cu ≤ 0.5 µg/GBq, Zn ≤ 0.5 µg/GBq, Pb ≤ 0.5 µg/GBq, ^{176}Yb ≤ 0.1 µg/GBq Sum of impurities ≤ 0.5 µg/GBq	ICP-MS, impurities content corrected to ^{177}Lu activity at end of shelf-life
Radiochemical purity	≥ 99.0 % as $^{177}LuCl_3$	TLC (Ph. Eur. 2.2.27)
Radiolabeling yield	≥ 99.0 % (based on radiolabeling with ^{177}Lu of DOTA-derivate, molar ratio 1:4)	TLC (Ph. Eur. 2.2.27)
Bacterial endotoxins	≤ 20 EU/mL	Turbidimetric-kinetic (Ph. Eur. 2.6.14)
Sterility	Sterile (final autoclaving)	Direct inoculation (Ph. Eur. 2.6.1)

About ITM Group

ITM Isotopen Technologien München AG is a privately held group of companies dedicated to the development, production and global supply of innovative diagnostic and therapeutic radionuclides and radiopharmaceuticals.

ITM's main objectives are to significantly improve outcomes and quality-of-life for cancer patients while at the same time reducing side-effects and improving health economics through a new generation of targeted radionuclide therapies in precision oncology.

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itm

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