

Multifactorial Analysis of Radiochemical Purity in High-Activity ^{177}Lu -Labeled Theranostics: Impact of Precursor Source, ^{177}Lu Form, and Production Parameters

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Table S1: Key characteristics of [¹⁷⁷Lu]LuCl₃ obtained from some of the major commercial suppliers.

Characteristic/Test	Supplier Specification				
	ANSTO NCA	Isotopia CA	Isotopia NCA	ITM NCA	IDB CA
Requested Activity	±10%	±10%	±10%	±10%	±10%
Formulation	Lu(III) _{aq} in 0.04M HCl	Lu(III) _{aq} in 0.04M HCl	Lu(III) _{aq} in 0.04M HCl	Lu(III) _{aq} in 0.04M HCl	Undefined
Appearance	“Complies” no description on CoA	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Volume (mL)	0.5	Variable	Variable	Variable	Variable
Radioactivity concentration (GBq/mL)	Variable	-	51.8 ± 10%	36 - 44	-
Specific activity (GBq/mg)	-	>740	>3000	≥3000	≥500
Radionuclide identity (KeV)	-	113 208	113 208	113 208	“Positive”, no emissions listed
Radionuclide purity (%)	99.9 – 100.0	Lu-177m ≤ 0.07 Sum of impurities ≤0.01	Yb-175 ≤ 0.1 Sum of impurities ≤0.01	Yb-175 ≤ 0.1 Sum of impurities ≤0.5	Lu-177 m ≤ 0.05 Sum of impurities ≤0.01
Radiochemical purity (%)	99 – 100	≥99.0	≥99.0	≥99.0	≥99
Chemical purity (µg/ GBq)	-	Fe ≤0.5 Cu ≤1.0 Zn ≤1.0 Pb ≤0.5	Fe ≤0.5 Cu ≤1.0 Zn ≤1.0 Pb ≤0.5 Yb ≤1.0	Fe ≤0.25 Cu ≤0.5 Zn ≤0.5 Pb ≤0.5 Yb-176 ≤0.14 Sum of impurities ≤0.5	-
pH	-	1.0 - 2.0	1.0 – 2.0	1-2	1 – 2
Radiolabelling yield (%)	99 - 100	-	-	≥99.0	-

Bacterial endotoxin (EU/mL)	0 - 140	<35	<35	≤20	<10
Sterility – Retrospective testing	-	Sterile	Sterile	Sterile	-
Other tests/values reported	-	iTLC R _f	iTLC R _f	-	Chloride test

Table S2: Summary of Production and Quality Control Variations in Published Reports on ¹⁷⁷Lu-Labeled Radiopharmaceuticals.

Reference	¹⁷⁷ Lu– product	¹⁷⁷ Lu form and Source	Precursor source	Mass of precursor used per 10 GBq of ¹⁷⁷ Lu	Highest amount of produced ¹⁷⁷ Lu- product	Labelling temp.	Labelling time	Stabiliser*	HPLC Purity (%)
(1)	[¹⁷⁷ Lu]Lu- DOTA- TATE	NCA, ANSTO	Auspep	250 µg	40 GBq	80 °C	20 min	Ascorbic acid	> 97%
(2)	[¹⁷⁷ Lu]Lu- PSMA-I&T	NCA, ITM	ABX	256 – 278 µg	30 GBq	95 °C	30 min	Ascorbic acid and gentisic acid	99.40%
(3)	[¹⁷⁷ Lu]Lu- PSMA-I&T	NCA, ITM	piCHEM	150 – 187 µg	ND	90 °C	15 min	Ascorbic acid	> 96 %
(4)	[¹⁷⁷ Lu]Lu- PSMA-I&T	NCA, ITM	PiChem	135 µg	ND	90 °C	20 min	Ascorbic acid, gentisic acid and EtOH	>95%
(5)	[¹⁷⁷ Lu]Lu- DOTA- TATE	CA, Dhurva (in house)	Pi Chem	270 µg	7.4	90 °C	20 min	None	>99%
(6)	[¹⁷⁷ Lu]Lu- PSMA-617	NCA, NTP + INM	ABX	135 µg	37 GBq	90 °C	30 min	Sodium ascorbate	>98.8

(7)	[¹⁷⁷ Lu]Lu-PSMA-617	CA, BARC (in house)	ABX	~182 µg	5.55 GBq	95 °C	25 min	Gentisic acid	>98.53
(8)	[¹⁷⁷ Lu]Lu-PSMA-617	NCA, ITG	ABX	104 µg	6 GBq	75 °C	45 min	EtOH	≥ 95 %
(9)	[¹⁷⁷ Lu]Lu-PSMA-I&T	NCA, ITG	in house	250 µg	8 GBq	90 °C	30 min	Sodium acetate and gentisic acid	99%
(10)	[¹⁷⁷ Lu]Lu-PSMA-I&T	NCA, ITG	ND	270 µg	15.6 GBq	120 → 105 °C	100 → 800 sec	Ascorbic acid	>98%
(11)	[¹⁷⁷ Lu]Lu-PSMA-I&T	NCA, ITM/Isotopia	piCHEM	~ 139 µg	42 GBq	95 °C	30 min	Ascorbic acid	> 95%

Table S3: Quality Control Tests and Acceptance Criteria for [¹⁷⁷Lu]Lu-Radiopharmaceuticals.

Quality indicator	Test Method	Acceptance Criterion
Activity	Dose calibrator	≤110 GBq
Radioactivity concentration	Dose calibrator	≤3.5 GBq/ml
Volume	Weight balance	10–30 ml
Appearance	Visual inspection	Clear and colourless
pH	Narrow range pH paper	4-8
TLC radiochemical purity	Radiochemical TLC	>98%
HPLC Radiochemical identity	Analytical HPLC	Within 0.2 min of Standard
HPLC radiochemical purity	Analytical HPLC	>90%
Filter integrity test	Pressure hold test	>50 psi
Sterility	Eu. Phar	No Growth
Bacterial Endotoxins	Eu. Phar	≤20 EU/ml

Table S4: Summary of variables and batch production for ¹⁷⁷Lu forms and precursor sources.

Product; Precursor Supplier	¹⁷⁷ Lu-Supplier			
	ANSTO N.C.A.	Isotopia N.C.A.	Isotopia C.A.	ITM N.C.A.
[¹⁷⁷ Lu]Lu-PSMA-617; ABX	52	18	80	19
[¹⁷⁷ Lu]Lu-PSMA I&T; ABX	2	–	–	–
[¹⁷⁷ Lu]Lu-PSMA I&T; Huayi	31	13	12	15
[¹⁷⁷ Lu]Lu-PSMA I&T; Pi CHEM	11	–	–	1
[¹⁷⁷ Lu]Lu-DOTATATE; Auspep	–	–	5	1
[¹⁷⁷ Lu]Lu-DOTATATE ; Huayi	23	14	47	11



Huayi Isotopes Co.

The leading manufacturer of Oxygen 18 Water & PET Precursors

Product Name: PSMA I&T

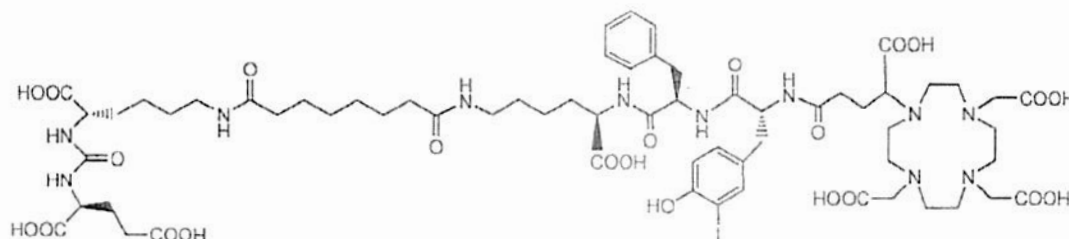
Product Description: Precursor for [$^{68}\text{Ga}/^{177}\text{Lu}/^{90}\text{Y}$] PSMA I&T

Synonyms: (3S,7S,26R,29R,32R)-29-benzyl-32-(4-hydroxy-3-iodobenzyl)-5,13,20,28,31,34-hexaoxo-37-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)-4,6,12,21,27,30,33-heptaazaheptatriacontane-1,3,7,26,37-pentacarboxylic acid

CAS No.: [not yet assigned]

Molecular Formula: $\text{C}_{63}\text{H}_{92}\text{I}\text{N}_{11}\text{O}_{23}$

Molecular Weight: 1498.37



Lot No.: PSMA I&T-T220601-02

Date of Manufacturing: Jun. 2022

Expiry Date: Jun. 2024

Certificate of Analysis

Parameter	Method	Specification	Result
Appearance	Visual inspection	Off-white to white solid	White solid
Chemical Purity	HPLC at 280nm	> 95.0%	98.5%
Chemical impurities	HPLC	< 1.0% single impurity	RT(13.6): 0.2% RT(13.9): 0.4% RT(14.1): 0.3% RT(14.5): 0.2% RT(15.2): 0.3%
		< 3.0% in total	< 3.0% in total
Molecular weight	LC-MS	$m/z[M+2H]^{2+}$, 749.77 ± 0.5	749.9
TFA content	IC	< 20%	8.1%
Bacterial endotoxins	LAL	< 10 IU/Container	< 10 IU/Container
Bioburden	USP	TAMC: < 10^2 CFU/Container	< 1 CFU/Container
		TYMC: < 10^1 CFU/Container	< 1 CFU/Container



Huayi Isotopes Co.

The leading manufacturer of Oxygen 18 Water & PET Precursors

NOTE

Care must be taken when handling this product.

Do not contact skin or eyes.

Do not ingest or inhale.

Protect from light.

For use by qualified personnel only.

From Bulk Lot No.: DL-PSMA I&t-T220601.

Drafted

Reviewed

Approved

Siqing Lv Date: 2022.08.04 Rongyu Sun Date: 2022.08.04 Ping Chu Date: 2022.08.04

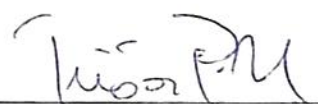
Certificate of Analysis

Product name: PSMA I&T
Article no.: 000.000.CA0.1000.002R
Lot no. / filling no.: CA0-210211/04

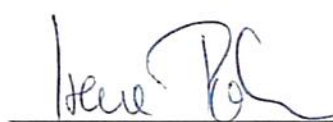
Test parameters	Specifications according to LOS-CA0.07	Results
Impurities		
Peptide purity (RP-HPLC)	≥ 97.0 %	RT(14.3): 98.6 %
Peptide related substances/ impurities	Reporting threshold: ≥ 0.1%	RT(11.0): 0.1 % RRT(0.766) RT(13.2): 0.1 % RRT(0.922)
Identified substances	PSMA(LL-Lys)-I&T ≤ 3.0% PSMA(DD-Lys)-I&T ≤ 3.0%	RT(13.9): 0.1 % RRT(0.971) RT(16.1): 0.1 % RRT(1.127)
Single impurity (RP-HPLC)	Identification threshold: ≥ 2.0% No single unidentified impurity > 2.0%	RT(16.6): 0.2 % RRT(1.163) RT(18.1): 0.1 % RRT(1.263)
		Identified PSMA(DD-Lys)-I&T: RT(14.9): 0.8 % RRT(1.041)
		Identified PSMA(LL-Lys)-I&T: n.d. (RRT: 1.155)
		No single unidentified impurity > 2.0%
Total related substances (sum of all impurities ≥ 0.1 %) (Calculation)	Maximum 3.0 %	1.5 %
Enantiomeric purity (GC-MS)	≤ 3.0 % L-Tyr ≤ 3.0 % L-Phe ≤ 3.0 % D-Glu	< 0.1 % L-Tyr ^a 0.1 % L-Phe ^a 0.2 % D-Glu ^a
Residual organic solvents (GC)	≤ 10 µg CH ₃ CN / container	5 µg CH ₃ CN / container
Specific tests		
TFA content (IC)	≤ 285 µg/ container	52 µg/ container
Bacterial endotoxins (LAL)	≤ 10 EU/ container	≤ 0.05 EU/ container
Microbial contamination/ Bioburden (Microbial enumeration test)	TAMC: ≤ 10 ² CFU/ container TYMC: ≤ 10 ¹ CFU/ container	TAMC: 0 CFU/ container TYMC: 0 CFU/ container

^a data deriving from bulk

Date of issue: December 07, 2021



Quality Control



Quality Assurance

Certificate of Analysis

Product name: PSMA I&T
Article no.: 000.000.CA0.1000.002R
Lot no. / filling no.: CA0-210211/04

Content / container: 1000 µg net peptide
Sequence: Suber-1-oxy-ε-(DOTA-GA-3-iodo-D-Tyr-D-Phe-D-Lys-OH)-8-oxy-ε-(HO-Glu-CO-Lys-OH)
Molecular weight: 1497.5 (m.i.)
 1498.4 (av.)
Molecular formula: C₆₃H₉₂N₁₁O₂₃
Manufacturer: piCHEM Forschungs- und Entwicklungs GmbH
 Parking 3
 8074 Raaba-Grambach, Austria
 +43 (0)316 68 17 11
Date of production: October 07, 2021
Next retest date(s): 24 months after production
 October 2023 (prolongation according to data from stability studies)
Storage conditions: (-20 ± 5)°C
Note:

- Specifications according to Pharm. Eur. 2902 Chemical precursors for radiopharmaceutical preparations
- Temperature excursions to room temperature (25°C ± 2°C) over a period of 10 days do not affect the quality of the product.
- Product soluble in 20 % CH₃CN/ 80 % water (1mg/mL)
- The product may be located not only on bottom but on the whole inner surface of the container.
- This Certificate of Analysis (CoA) reflects analytical data at time of analyses. The quality of the product is certified in the corresponding Certificate of Compliance (CoC). The user shall evaluate both certificates to ensure the suitability of the product for its intended use.

Test parameters	Specifications according to LOS-CA0.07	Results
Primary packaging	2 mL ISO clear type I tubular glass vials 13 mm crimp neck Lyophilisation stoppers, 4023/50/bromobutyl/grey	
Characters		
Appearance (Visual)	White to off-white powder	White powder
Mass spectrometry (MS) Monoisotopic mass	[MH] ⁺ _{m.i.} : 1498.5 ± 0.5 m/z	[MH] ⁺ _{m.i.} : 1498.8
Amino acid analysis (GC)	3-iodo-D-Tyr- as D-Tyr 1 (± 0.2 µmol/ µmol) D-Phe 1 (± 0.2 µmol/ µmol) Glu to be detected Lys to be detected	3-iodo-D-Tyr as D-Tyr 1.0 µmol/µmol * D-Phe 1.0 µmol/µmol * Glu detected * Lys detected *
Confirmation of structure (NMR)	Confirm identity	Identity confirmed *
Assay		
Assay/ Filling quantity (HPLC)	90 % - 110 % 900 µg – 1100 µg	98 % 978 µg

* data deriving from bulk

Date of issue: December 07, 2021



Quality Control



Quality Assurance

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