Taiwan Food and Drug Administration

Assessment Report

Trade Name：鎦治癌注射液 370 百萬貝克/毫升 /
Lutathera 370 MBq/mL solution

Active Ingredient：Lutetium (177Lu) oxodotreotide

License Number： MOHW-PI R00104

Applicant：台灣諾華股份有限公司

Approval Date： 110/02/08

Indication：
用於治療成人無法手術切除或轉移性，分化良好(G1 及 G2)且經體抑素類似物 (somatostatin analogue) 治療無效之體抑素受體 (somatostatin receptor) 陽性的胃腸道胰腺神經內分泌腫瘤 (GEP-NETs)。

Lutathera is indicated for the treatment of unresectable or metastatic, well differentiated (G1 and G2) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) in adults with progressive disease after somatostatin analogue therapy.

Background Information

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Active Ingredient(s)	lutetium (177Lu) oxodotreotide
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	注射劑 370
Indication	用於治療成人無法手術切除或轉移性，分化良好(G1 及 G2)且經體抑素類似物(somatostatin analogue)治療無效之體抑素受體(somatostatin receptor)陽性的胃腸道胰腺神經內分泌腫瘤(GEP-NETs)。 Lutathera is indicated for the treatment of unresectable or metastatic, well differentiated (G1 and G2) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) in adults with progressive disease after somatostatin analogue therapy.
Posology	詳見中文仿單擬稿。
Pharmacological Category **ATC Code**	V10XX04

Lutathera is a radiolabeled somatostatin analogue (SSA) with high affinity for somatostatin subtype 2 (sst2) receptors. It is comprised of the somatostatin peptide analogue Octreotate, coupled to the metal-ion chelating moiety DOTA, labeled with the beta-emitting radionuclide Lutetium-177 (177Lu).

Lutathera® is a sterile, ready-to-use, single-use formulation with a concentration of 370 MBq/mL at the time of calibration. The claimed indication is for the treatment of somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors in adults. Lutatherais intended to be administered at a cumulative dose of 29.6 GBq, provided in 4 administrations of 7.4 GBq with each administration separated by an 8-week interval. The interval can be extended up to 16 weeks due to acute toxicity. The administered dose may also be reduced or withheld in case of persistent toxicity.

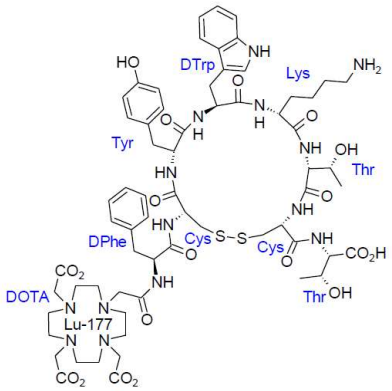
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Lutetium Lu 177 dotatate is used as the drug substance of Lutathera. Lutetium Lu 177

dotatate has the following chemical structure:



Due to its radioactive nature, the drug substance is not isolated. The synthesis of the drug substance and its formulation into the drug product are part of an automated continuous process which does not allow isolation and testing of the pure drug substance.

2.1.2 Drug product

The drug product Lutathera is a sterile ready-to-use solution for infusion with a volumetric activity of 370 MBq/mL at reference date and time. The drug product is presented as a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time. The excipients used in the drug product formulation comply with the compendial monographs or in-house specifications.

Adequate specification has been presented for the drug product. The test items include appearance, identification, pH, assay, chemical purity, radiochemical purity, specific activity, filter integrity test, bacterial endotoxins, sterility and volumetric activity. Analytical methods are described and well validated.

Stability studies of the drug product under refrigerated condition (5 ± 3°C), long-term condition (25 ± 2°C) and accelerated condition (32 ± 2°C) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Lutathera® contains ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate as a Drug Substance comprised of the somatostatin analog Octreotate coupled to the metal-chelating moiety DOTA, and labeled with the β-emitting radionuclide Lutetium-177 (^{177}Lu). Octreotate has a high affinity for somatostatin subtype 2 (sst2) receptors. While the compound binds to malignant cells that overexpress sst2 receptors, the short path length of the β-emission is sufficient to kill targeted tumor cells with fewer effects on the nearby non-target cells.

In vitro, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate demonstrated high-affinity binding for the somatostatin receptor sstr2. *In vivo* studies in rodent sstr2-expressing tumor models, complete regression of the implanted tumors had been shown in animals treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Approx. 50% of the tumor-bearing rats treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate lived a normal life span. Only the highest dose treatment group survivors showed a reduced life span (65% of normal). These studies also showed that kidneys are the target organ of toxicity. Co-administration of 400 mg/kg D-lysine in rats had shown a 40% decrease of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate renal uptake, and therefore the reduced renal toxicity could be expected. Due to no significant pharmacodynamics effect is expected, pharmacodynamics studies of the non-radioactive peptide were not performed. Secondary pharmacodynamics study of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was not performed, either.

Safety pharmacology studies performed on the non-radioactive compound ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate showed that the cold peptide did not affect the neuro-behavioral function and body temperature at doses up to 700-fold the intended human dose on an mg/m^2 basis. The cold peptide showed a stimulant effect in rats on several respiratory parameters at doses exceed 5000 μg/kg. The NOEL of this study was equivalent to 40-fold the intended human dose on an mg/m^2 basis. A minimal effect of ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the hERG inhibition was noted. No significant potential risk of QT prolongation in humans could be identified based on the *in vitro* and *in vivo* study results. No ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate-related effects on most of the cardiovascular parameters evaluated in dogs were noted at doses up to 100-fold the intended human dose on an mg/m^2 basis. However, ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate showed a hypertensive effect associated with a reflex mediated bradycardia when administered intravenously, at doses from 5-fold to 100-fold the intended human dose on an mg/m^2 basis. This hypertensive effect was considered to be a pharmacological activity of the peptide.

The non-clinical toxicological profile of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was evaluated in terms of radiotoxicity and also potential toxicity of the non-radioactive compound. Acute radiotoxicity evaluation of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate performed in rats showed a dose-dependent decrease in WBC counts but returned to normal after 1-month post-injection at doses above 163 MBq/kg. Delayed toxicity evaluation in rats showed that high doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (555 MBq/rat) resulted in severe renal damage, which was also indicated by the decrease of ^{99m}Tc-DMSA kidney uptake, a marker of renal tubular damage. This damage was dose-dependent and became evident after more than 100 days post-treatment. Fractionation of the dose significantly demonstrated beneficial effects on kidney function. Co-administration of Lysine also showed reduced renal damage. In terms of toxicology of the non-radioactive ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate, the cold compound was

well tolerated when administered at high single doses up to 700 times and 400 times the intended human dose (on an mg/m2 basis) in rats and dogs, respectively. In the repeated-dose toxicology study in rats and dogs, no overt toxicity signs were shown. Minimal to moderate pancreatic acinar apoptosis, which was not completely reversed by the end of the recovery phase, was noted in the mid- and high-dose groups. The NOAEL in the repeat-dose toxicity study of the non-radioactive peptide was defined to be approx. 40 folds and 400 folds the human dose on an mg/m^2 basis in rats and dogs, respectively.

The cold compound was studied in two *in vitro* genotoxicity studies, and no genotoxic effects were shown. No *in vivo* clastogenicity study report was submitted. Carcinogenicity study and developmental and reproductive toxicology study reports were not submitted as well. Given the nature of the indication and the radioactive product, the lack of these studies is acceptable. Because of the radioactivity's hazard associated with reproductive and embryofetal development, pregnant women are excluded from treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. For patients using Lutathera®, contraceptive measures should be used.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The pharmacokinetics (PK) of lutetium Lu 177 dotatate have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of lutetium Lu 177 dotatate at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36 %]. The mean maximum blood concentration (C_{max}) for lutetium Lu 177 dotatate is 10 ng/mL (CV 50%), which generally occurred at the end of the LUTATHERA infusion.

Distribution

The mean volume of distribution for lutetium Lu 177 dotatate is 460 L (CV 54%). Within 4 hours after administration, lutetium Lu 177 dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid. The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of lutetium Lu 177 dotatate by 36%. The non-radioactive form of lutetium dotatate is 43% bound to human plasma proteins.

Elimination

The mean clearance (CL) is 4.5 L/h (CV 31%) for lutetium Lu 177 dotatate. The mean (± standard deviation) effective blood elimination half-life is 3.5 (±1.4) hours and the mean terminal blood half-life is 71 (± 28) hours.

Metabolism

Lutetium Lu 177 dotatate does not undergo hepatic metabolism.

Excretion

Lutetium Lu 177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu 177 dotatate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA.

2.3.2 Interaction Studies

The non-radioactive form of lutetium is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 *in vitro*. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 *in vitro*.

2.3.3 Special Populations

Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Perform more frequent assessments of renal function in patients with mild to moderate impairment. The safety of LUTATHERA in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of LUTATHERA in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A Phase III study (NETTER-1) was reviewed to evaluate the efficacy of Lutathera (177Lu-DOTA0-Tyr3-Octreotate), indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Study NETTER-1 was a multicenter, open-label, randomized, comparator- controlled, parallel-group trail, comparing treatment with Lutathera to Octreotide LAR 60 mg in patients with inoperable, somatostatin receptor positive, histologically proven midgut carcinoid

tumors.

The primary efficacy endpoint was progression free survival (PFS), defined as the time from start of study treatment to documented progression according to RECIST Criteria or death due to any cause, as evaluated by the Independent Review Committee, within 76 weeks of start of study treatment.

Results of FAS analysis showed a significantly lower risk for a PFS event with Lutathera treatment compared to Octreotide LAR (hazard ratio of 0.18 [95% CI: 0.11-0.29]，$p<0.0001$). The ORR for the FAS was also statistically significantly different between the treatment groups in favor of Lutathera ($p=0.0141$), 14.7% of patients under Lutathera treatment had PR or CR compared to 4.0% in the Octreotide LAR arm.

The efficacy was supported with retrospective data from the ERASMUS MC study, an investigator-sponsored, open-label, single-arm, single-institution study of 1214 patients with somatostatin receptor positive neuroendocrine tumors conducted at the Erasmus Medical Center (EMC),Rotterdam, the Netherlands on a compassionate use from January 2000 through December 2012. After prospective data cleaning and management, ERASMUS MC study showed GEP-NET demonstrated response to 177Lu-DOTA0-Tyr3-Octreotate similar to the results of Study NETTER-1.

2.4.2 Safety Results

In NETTER-1 study, 98% of the patients in the Lutathera arm and 93% in the Octreotide LAR arm experienced at least one TEAE. 91% of patients in Lutathera group had at least one TEAE related to study medication (ADR), whereas 40.5% of patients had ADR in control arm. Eight patients (7.1%) in the Lutathera arm and 1 patient (0.9%) in the Octreotide LAR arm reported TEAEs related to study medication leading to premature study discontinuation in 16 (7.2%) patients. The incidence of ≧Grade 3 TEAE by patients in Lutathera arm was 57.1% versus 36.9% in Octreotide LAR arm.

The TEAEs by PTs with incidence > 10%experiencing in in Lutathera group(all grades) are ‘nausea’, ‘vomiting’, ‘fatigue’, ‘thrombocytopenia’, ‘lymphopenia’, ‘anemia’ and ‘decreased appetite’. All grade 3 to 5 TEAEs in ‘nausea’, ‘vomiting’, ‘thrombocytopenia’ and ‘lymphopenia’ were in the Lutathera group. There were seven deaths (6.3%) in the Lutathera arm and 9 deaths (8.1%) in the Octreotide arm. Thirty-seven (33.0%) patients in the Lutathera arm and30 (27.0%) patients in the Octreotide LAR arm experienced at least one SAE. The majority of SAEs were ≧grade 3. More than half of events were related to underlying disease. The most frequent reported SAE in the Lutathera group was acute kidney injury (n=4), followed by abdominal pain (n=3) and lymphopenia (n=2).

The TEAEs in ERASMUS study were similar with those in NETTER-1 study. Grade 3/4 lymphopenia, leukopenia, and abnormal liver function may happen in Lutathera treatment and may not recover after the treatment. Patient receiving Lutathera should be monitored for blood cells counts and liver function, especially lymphocytes.

Lutathera has been granted Rare and Severe Disease Drug Designation by TFDA (小兒或少數嚴重疾病藥品審查認定要點). The ethnic difference was evaluated in the NDA review. There was no Asian data of Lutathera for ethnic difference evaluation. Considering the nature of Rare and Severe Disease Drug Designation and the MOA of Lutathera, we determine a postmarketing requirement to collect specific safety data in Taiwan.

2.6 Conclusion

There is an unmet medical need for treating inoperable or metastatic NETs and we agree that Lutathera has shown benefit in controlling disease progression in patients with GEP-NETs without response to Octreotide. However, besides the renal toxicity of radioisotope agents, the peptide receptor radionuclide therapy also causes irreversible lymphopenia and thrombocytopenia. In conclusion, Lutathera demonstrates a favorable risk-benefit profile. We recommend approval of Lutathera for treatment of unresectable or metastatic, well-differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults with progressive disease after somatostatin analogue therapy.

3. Post-Marketing Requirements

1. Collect specific safety data of patients treated with Lutathera in Taiwan
2. Submit the safety reports of USFDA PMR 3326-01(the risk of renal failure) and PMR3326-02 (the risks of myelodysplastic syndrome and acute leukemia).
3. Submit the final clinical report at the time of the final analysis for overall survival (OS) for Trial NETTER-1.