Advanced Accelerator Applications
A Novartis Company

After first-line somatostatin analog therapy[1]

POWER AGAINST PROGRESSION[2]

LUTATHERA®
Lutetium (^{177}Lu) oxodotreotide

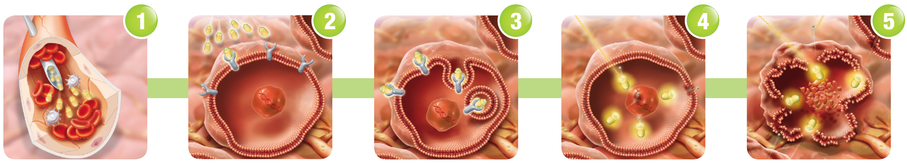
LUTATHERA®: First PRRT approved in GEP-NETs[3]

NOW AVAILABLE in SINGAPORE

- Approved in Singapore in June 2020
- Indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut NETs in adults[2]

How LUTATHERA® works

LUTATHERA® specifically binds to somatostatin receptors overexpressed by GEP-NET cells[2]



1. **LUTATHERA®** is **infused** into the bloodstream
2. **LUTATHERA®** **binds** to **somatostatin receptors** overexpressed by NET cells
3. **LUTATHERA®** is **internalized** into NET cells...
4. ...where it delivers **beta radiation**
5. The radiation **kills targeted tumor cells**, with a limited effect on neighboring normal cells

What LUTATHERA® achieves

In patients with somatostatin receptor-positive GEP-NETs,

82%
Reduction of risk of progression of death[2]

Preliminary evidence of OS benefit**[4]

Manageable safety profile**[4]

28.8 months*
Improved Health-related Quality of Life^[5]

RECOMMENDED
Recommended by ENETS guidelines after 1st line[1]

* Differences in median time to QoL deterioration (TTD) were clinically significant: 28.8 months versus 6.1 months for global health status, and 25.2 months versus 11.5 months for physical functioning.[5]

****Study design:** The NETTER-1 trial is an international phase III study in patients with midgut NETS. 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors were randomised to receive either 177Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (177Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile.[4]

^Study design: European Organisation for Research and Treatment of Cancer quality-of-life questionnaires QLQ C-30 and G.I. NET-21 were assessed during the NETTER-1 trial to determine the impact of treatment on health-related QoL. Patients completed the questionnaires at baseline and every 12 weeks until tumor progression. QoL scores were converted to a 100-point scale according to European Organisation for Research and Treatment of Cancer instructions, and individual changes from baseline scores were assessed. Time to QoL deterioration (TTD) was defined as the time from random assignment to the first QoL deterioration ≥ 10 points for each patient in the corresponding domain scale. All analyses were conducted on the intention-to-treat population. Patients with no deterioration were censored at the last QoL assessment date.[5]

ENETS, European Neuroendocrine Tumor Society; **GEP-NETs**, gastroenteropancreatic neuroendocrine tumours; **HSA**, Health Sciences Authority; **OS**, overall survival; **PFS**, progression-free survival; **PRRT**, peptide receptor radionuclide therapy; **QoL**, quality of life.

References: 1. Pavel M, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172-185. **2.** LUTATHERA® Product Information. July 2021.SIN. **3.** Hennrich U and Kopka K. Lutathera®: The First FDA-and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. Pharmaceuticals. 2019;12(3):114. **4.** Strosberg J, et al. Phase 3 Trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125-135. **5.** Strosberg J, et al. Health-related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors treated with 177Lu-Dotatate in the phase III NETTER-1 Trial. J Clin Oncol. 2018;36(25):2578-2584.

LUTATHERA® 0.37 GBq/mL solution for infusion
Important note: Before prescribing, consult full prescribing information. Presentation: One mL of solution contains 0.37 GBq of lutetium (177Lu) oxodotreotide at the date and time of calibration. Indications: Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. Dosage and administration: Adults: Adults: •The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7.4 GBq each. The recommended interval between each infusion is 8 weeks. •For renal protection purpose, an intravenous amino acid solution containing lysine and arginine must be initiated 30 minutes before administering Lutathera. The amino acid solution should not be administered in the same arm as Lutathera. The amino acid infusion should continue during, and for at least 3 hours after the Lutathera infusion. The dose of the amino acid solution should not be decreased even if the dose of Lutathera is reduced. •Antiemetics should be administered with sufficient lead time prior to the start of the amino acid solution. Special populations: •Renal impairment: No dose adjustment is recommended in patients with creatinine clearance (CrCl) ≥40 mL/min. Patients with CrCl <40 mL/min should not be treated with Lutathera. The pharmacokinetic profile and safety of Lutathera in patients with severe renal impairment (CrCl <30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied, and treatment with Lutathera in those patients is contraindicated. •Hepatic impairment: Mild or moderate: No dose adjustment is necessary. Severe: careful benefit-risk assessment. •Geriatrics (≥65 years): No dose adjustment is required. •Pediatrics (<18 years): Safety and efficacy have not been established. Contraindications: •Established or suspected pregnancy or when pregnancy has not been excluded. •Severe renal impairment (CrCl < 30 mL/min) Warnings and precautions: •Radiation exposure: Lutathera contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Radiation exposure should be minimized to patients, medical personnel, and household contacts after treatment for at least 7 days. •Hematological toxicity: Hematological evaluation of patients must be performed at baseline and prior to every dose. Treatment initiation in patients with severely impaired hematological function at baseline is not recommended. •Secondary myelodysplastic syndrome (MDS) and leukemia: Late onset MDS and acute leukaemia have been reported after treatment with Lutathera. •Renal toxicity: Renal dysfunction can develop during and after treatment with Lutathera. Cases were reported several years following treatment. Concurrent administration of amino acid solution is recommended to help decrease in the radiation exposure to the kidneys. Treatment with Lutathera in patients with baseline CrCl <40 mL/min is not recommended. Lutathera has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease, and treatment with Lutathera in those patients is contraindicated. More frequent monitoring of renal function is recommended in renally impaired patients with CrCl≥40 mL/min. For patients with CrCl <50mL/min, an increased risk for transient hyperkalemia due to the amino acid solution should also be taken into consideration. •Hepatobiliary toxicity: Patients with severe baseline liver impairment should only be treated with Lutathera after careful benefit-risk assessment. •Endocrine and metabolism: Patients should be monitored for signs and symptoms of tumor-related hormonal release. Somatostatin analogs, fluids, corticosteroids, and electrolytes should be administered as clinically indicated. Overnight hospitalization of patients should be considered in some cases for observation (e.g. patients with poor pharmacologic control of symptoms). Warnings and precautions regarding the renal protective amino acid solution: •Hyperkalemia: Serum potassium levels must be tested before each treatment with amino acid solutions. In case of hyperkalemia, patient's history of hyperkalemia and concomitant medication should be checked, and hyperkalemia must be corrected accordingly before starting the infusion. A second monitoring prior to amino acid infusion must confirm that hyperkalaemia has been successfully corrected. The patient should be monitored closely for signs and symptoms of hyperkalemia. An ECG should be performed prior to patient discharge. •Heart failure: Care should be taken with use of arginine and lysine in patients with severe heart failure. Patients with severe heart failure should only be treated after careful benefit-risk assessment. •Metabolic acidosis: Metabolic acidosis has been observed with complex amino-acid solutions administered as part of total parenteral nutrition (TPN) protocols. Pregnancy, lactation, females and males of reproductive potential: •Pregnancy: Lutathera is contraindicated in patients with established or suspected pregnancy or when pregnancy has not been excluded. Lutathera, being a radiopharmaceutical, has the potential to cause fetal harm. •Lactation: Women receiving Lutathera should not breastfeed. If Lutathera treatment is started during breastfeeding, breastfeeding should be discontinued permanently. •Females and males of reproductive potential: •Pregnancy testing: The pregnancy status should be verified prior to initiating treatment with Lutathera. •Contraception: Females of reproductive potential should use effective contraception during treatment and for 6 months after the last dose of Lutathera. Males patients with female partners of reproductive potential should use effective contraception during treatment and for 4 months after the last dose of Lutathera. •Infertility: Ionizing radiations of lutetium (177Lu) oxodotreotide may cause temporary infertility in males and females. Adverse drug reactions: Very common (≥10%): Thrombocytopenia, lymphopenia, anaemia, pancytopenia, decreased appetite, nausea, vomiting, fatigue. Common (≥1 to <10%): Refractory cytopenia with multilineage dysplasia (myelodysplastic syndrome), leukopenia, neutropenia, secondary hypothyroidism, hyperglycaemia, dehydration, hypomagnesaemia, hyponatremia, sleep disorders, dizziness, dysgeusia, headache, lethargy, syncope, electrocardiogram QT prolonged, hypertension, flushing, hot flush, hypotension, dyspnoea, abdominal distension, diarrhoea, abdominal pain, constipation, abdominal pain upper, dyspepsia, gastritis, hyperbilirubinaemia, alopecia, musculoskeletal pain, muscle spasms, acute kidney injury, haematuria, renal failure, proteinuria, injection site reaction, oedema peripheral, administration site pain, chills, influenza like illness, blood creatinine increased, GGT increased, ALT increased, AST increased, blood ALP increased, transfusion. Uncommon (≥0.1 to <1%): Conjunctivitis, respiratory tract infection, cystitis, pneumonia, herpes zoster, ophthalmic herpes zoster, influenza, staphylococcal infections, streptococcal bacteraemia, acute myeloid leukaemia, acute leukaemia, chronic myelomonocytic leukaemia, refractory cytopenia with unilineage dysplasia, nephrogenic anaemia, bone marrow failure, thrombocytopenic purpura, hypersensitivity, hypothyroidism, diabetes mellitus, carcinoid crisis, hyperparathyroidism, hypoglycaemia, hypernatraemia, hypophosphataemia, tumour lysis syndrome, hypercalcaemia, hypocalcaemia, hypoalbuminaemia, metabolic acidosis, anxiety, hallucination, disorientation, formication, hepatic encephalopathy, paraesthesia, parosmia, somnolence, spinal cord compression, eye disorders, vertigo, atrial fibrillation, palpitations, myocardial infarction, angina pectoris, cardiogenic shock, vasodilatation, peripheral coldness, pallor, orthostatic hypotension, phlebitis, oropharyngeal pain, pleural effusion, sputum increased, choking sensation, dry mouth, flatulence, ascites, gastrointestinal pain, stomatitis, haematochezia, abdominal discomfort, intestinal obstruction, colitis, pancreatitis acute, rectal haemorrhage, melaena, abdominal pain lower, haematemesis, haemorrhagic ascites, ileus, pancreatic enzymes decreased, hepatocellular injury, cholestasis, hepatic congestion, hepatic failure, rash, dry skin, swelling face, hyperhidrosis, pruritus generalised, leukocyturia, urinary incontinence, glomerular filtration rate decreased, renal disorder, acute pre-renal failure, renal impairment, injection site mass, chest discomfort, chest pain, pyrexia, malaise, pain, death, feeling abnormal, blood potassium decreased, blood urea increased, glycosylated haemoglobin increased, haematocrit decreased, protein urine, weight decreased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood catecholamines, C-reactive protein increased, clavicle fracture, abdominal cavity drainage, dialysis, gastrointestinal tube insertion, stent placement, abscess drainage, bone marrow harvest, polycythemy, physical ability. Interactions: •Long-acting somatostatin analogues should be discontinued at least 4 weeks prior to the administration of Lutathera. If necessary, patients may be treated with short-acting somatostatin analogs up to 24 hours preceding Lutathera administration. •Repeated administration of high-doses of glucocorticosteroids should be avoided during treatment with Lutathera. Patients with a history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during Lutathera administration. Therefore, glucocorticosteroids should be avoided as preventive anti-emetic treatment. Packs and prices: Country-specific.Legal classification: Country-specific. Information issued: Jul 2021.SIN

For Healthcare Professionals Only.

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LUTATHERA®
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